
R G U H S · M O D E L A N S W E R B A N K

MD General Medicine



M O D E L A N S W E R B A N K

2019 – 2026

354 recurring topics · Textbook-grounded model answers

G R O U N D E D I N :

Harrison's Principles of Internal Medicine 22e — spine text
Braunwald's Heart Disease 13e — cardiology
Williams Textbook of Endocrinology 15e — endocrinology
Murray & Nadel's Respiratory Medicine 7e — respiratory
Sleisenger & Fordtran's GI & Liver 11e — gastroenterology & hepatology
Brenner & Rector's The Kidney — nephrology
DeVita's Cancer 12e — haematology & oncology
Bradley & Daroff's Neurology 8e · Brazis (Localization) · DeJong's Neurologic Examination — neurology
Kaplan & Sadock's Comprehensive Psychiatry 2024 · DSM-5-TR — psychiatry
Rook's Dermatology 10e · Bologna Dermatology 5e — dermatology
Tintinalli's Emergency Medicine — emergency & toxicology
Textbook of Critical Care 8e — critical care
CMDT 2026 — diagnosis & management



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Contents

Cardiology	17
Aortic Regurgitation	17
Atrial Fibrillation.....	22
Bradyarrhythmias.....	27
Bundle Branch Blocks.....	32
Cardiac Resynchronization Therapy	36
Cardiac Syncope	41
Cardiac tamponade	46
Cardiogenic pulmonary edema	52
Cardiomyopathies	57
Classify Cardiomyopathy. What are the risk factors, clinical presentations and prognosis of peripartum Cardiomyopathy?	62
Conducting system of the Heart and Electrocardiogram	67
Constrictive Pericarditis	72
Cor Pulmonale.....	77
Describe conduction system of the heart and add a note on complete heart block.....	82
Describe the structure of the Mitral Valve apparatus. Discuss the etiology, clinical features and management of Mitral Stenosis.....	87
Diastolic Heart Failure (Heart Failure with Preserved Ejection Fraction)	93
Differential Diagnosis of Mid-Diastolic Murmurs	98
Discuss the diagnosis and management of chronic heart failure with preserved ejection fraction .	103
Discuss the etiology, clinical manifestations and management of Acute ST elevation Myocardial infarction (STEMI).....	108
Early Invasive Strategy in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome..	113
Emerging therapies and strategies in treatment of Heart failure.....	118
Endomyocardial fibrosis.....	123
Hypertrophic Cardiomyopathy.....	128
Left ventricular remodeling	133
Management of Supraventricular Tachycardia.....	138
Narrow QRS Tachycardia	143
Neurally mediated syncope.....	147
Pathogenesis and Management of Congestive Cardiac Failure	153
Pericarditis.....	158
QT Interval Prolongation and Torsades de Pointes	163
Stroke Prevention in Atrial Fibrillation.....	168

Syncope.....	174
Takotsubo cardiomyopathy.....	179
Treatment options for management of pulmonary embolism.....	184
What are the indications for coronary arteriography? What are the complications of the procedure?	188
Cardiac Resynchronization Therapy (CRT): Rationale, Indications and Contraindications.....	194
Atrial Fibrillation — Risk Factors and Management	198
Neurology	203
Acute Disseminated Encephalomyelitis.....	203
Aetiology, pathogenesis and management of Parkinson's disease	208
Alzheimer's Disease	213
Approach to Coma.....	218
Autosomal Recessive Ataxias.....	223
Benign Intracranial hypertension	228
Cerebral venous sinus thrombosis	233
Clinical features and management of Alzheimer's disease	237
Clinical features, pathophysiology and management of trigeminal neuralgia. Differentiate trigeminal neuralgia from trigeminal neuropathy.....	242
Describe the physiological anatomy of neuromuscular junction and explain how diseases involving the neuromuscular junction cause muscle weakness	247
Posterior (Vertebrobasilar) Circulation of the Brain: Anatomy and Clinical Relevance	252
Differential Diagnosis of Seizures	257
Paraneoplastic Neurological Syndromes: Presentation, Associated Tumours and Antibodies	262
Discuss the Causes and Management of Seizures.....	268
Acute Ischemic Stroke Involving the Right Internal Capsule	274
Discuss the indications and options for reperfusion therapy in acute stroke	279
Endovascular revascularization for acute ischemic stroke	283
Reversible Causes of Dementia and Differentiation of Alzheimer's Disease from Frontotemporal Dementia	287
Epilepsy syndromes.....	292
Etiology and management of orthostatic hypotension	298
Guillain Barre Syndrome.....	303
Horner's Syndrome.....	308
Hyperkinetic Movement Disorders	312
Hypoxic-ischemic encephalopathy.....	317
Immunopathogenesis and treatment of Guillain-Barré syndrome	323

Multiple sclerosis.....	327
Muscular Dystrophies: Genetics, Pathogenesis and Clinical Implications.....	332
Myasthenia gravis.....	337
Narcolepsy.....	342
Orthostatic hypotension.....	347
Posterior circulation stroke.....	352
Posterior Reversible Encephalopathy Syndrome	356
Primary headaches	361
Recent Advances in the Management of Migraine.....	367
Restless Legs Syndrome (Willis–Ekbom Disease)	371
Reversible Dementias.....	376
Secondary Parkinsonism	381
Temporal Lobe Epilepsy.....	385
Tic Douloureux (Trigeminal Neuralgia).....	390
Treatment and Prevention of Cluster Headache	396
Trigeminal Neuralgia.....	400
Wernicke Encephalopathy	405
Infectious diseases	410
Management of a Cat Bite — Wound Care, Antimicrobial Therapy and Infection Prophylaxis (Rabies & Tetanus).....	410
Scrub Typhus presenting as Acute Undifferentiated Febrile Illness with an Eschar and Multi-Organ Dysfunction.....	414
Pulmonary Nocardiosis in a Diabetic with Non-resolving Pneumonia — CT Thorax Findings and Management	419
A 45-year-old man from Chhattisgarh with 6 months of intermittent fever, anorexia, weight loss and massive splenomegaly: differential diagnosis, confirmatory investigations, and treatment of rK39-positive visceral leishmaniasis.....	424
Abdominal tuberculosis	428
Acute pyelonephritis.....	433
Amoebic Liver Abscess.....	438
Anaerobic organisms infections.....	442
Aspergillus Infections (Aspergillosis).....	448
Brucellosis.....	453
Classify the Causes of Chronic Meningitis and Etiologies to be Considered in Advanced HIV Infection.....	459
Clinical features, diagnosis and treatment of neurosyphilis.....	464

Clostridium difficile	469
Clostridioides difficile Infection (Including Pseudomembranous Colitis)	474
Coagulase-negative staphylococcal infections.....	480
Complications and management of Enteric fever (Typhoid).....	485
COVID-19 (2019 Novel Corona Virus)	490
Cytokine Storm in Dengue Fever	495
Define and classify extended spectrum β -lactamases, list the risk factors for acquiring ESBL and its implications on antibiotic choice	500
Define shock. Discuss the pathophysiology and management of Septic shock.....	505
Definition of multidrug-resistant tuberculosis (MDR-TB) and molecular drug-susceptibility testing in its diagnosis.....	510
Dengue fever with complications.....	515
Dengue fever	520
Diagnosis and Laboratory Monitoring of HIV Infection	525
Diagnosis and Management of Falciparum Malaria	530
Diagnosis and treatment of Brucellosis.....	536
Pathophysiology and Management of Severe Sepsis	540
Discuss the neurologic disorders in Human Immunodeficiency Virus (HIV) disease	546
Serological Tests in the Diagnosis of Infectious Diseases	552
Ebola Virus Disease (Filovirid — Orthoebolavirus Infection).....	556
Extensively Drug-Resistant Tuberculosis (XDR-TB).....	562
Extrapulmonary Tuberculosis	567
Gastrointestinal Tuberculosis.....	572
Genital Ulcerations due to Infections.....	577
Immune Reconstitution Inflammatory Syndrome (IRIS)	581
Immunization for travel in adults	586
Infections due to HACEK	591
Infective Endocarditis.....	596
Lepra Reactions.....	601
Leptospirosis	606
Mechanisms of Antibiotic Drug Resistance.....	611
Melioidosis	615
Multidrug-Resistant Tuberculosis (MDR-TB).....	620
Neurocysticercosis.....	625
Nipah Virus Infection.....	630

Preventive strategies for antibiotic resistance in multidisciplinary intensive care units	635
Progressive Multifocal Leucoencephalopathy	641
Pyrexia of Unknown Origin (PUO / Fever of Unknown Origin).....	645
Rationale, pre-requisites and contraindications to short course MDR TB regimen. Name the drugs and the duration of use.....	650
Rhino-Orbital-Cerebral Mucormycosis	655
Strongyloides Hyperinfection Syndrome.....	660
Role of CD4 Count in the Management of HIV Infection	665
Scrub typhus.....	669
Seroconversion Illness in HIV (Acute Retroviral Syndrome)	674
Systemic Protozoal Infections.....	678
Tabulate the pathogens involved in viral encephalitis in India, the characteristic presentation of each infection and the management for each	683
Toxoplasmosis	689
Treatment and Prevention of Cholera.....	694
Tropical Pulmonary Eosinophilia	699
Tropical Splenomegaly	703
Viral meningitis	708
What are the methods used to measure antimicrobial activity in the lab?	713
Respiratory system	717
Acute interstitial pneumonia	717
Acute Pulmonary Embolism.....	722
Acute respiratory distress syndrome	727
Acute severe asthma.....	732
Approach to Solitary Pulmonary Nodule	736
Asbestos-Related Diseases.....	741
Bronchial asthma.....	746
Acute Respiratory Distress Syndrome — Causes, Pathophysiology, Diagnostic Criteria and Management	751
Complications of Bronchiectasis.....	756
Describe etiology, clinical features, GOLD criteria in Chronic Obstructive Pulmonary Disease (COPD) and treatment of COPD exacerbation	761
Pathogenesis of Bronchiectasis.....	766
Discuss clinical features, diagnosis and management of Pulmonary Thromboembolism.....	771
Discuss Pulmonary Rehabilitation Post Severe COVID Pneumonia.....	777
Pulmonary Embolism: Risk Factors and Management.....	782

Hospital-Acquired Pneumonia	788
Hypersensitivity pneumonitis.....	793
Inflammatory Mediators and Effect of Airway Inflammation in Bronchial Asthma	798
Interstitial lung diseases.....	803
Lung Abscess.....	808
Management of Acute Respiratory Distress Syndrome	814
Non resolving Pneumonia	819
Obesity and Obstructive Sleep Apnoea	824
Obesity Hypoventilation Syndrome	829
Obstructive Sleep Apnea	834
Pneumothorax	839
Pulmonary Function Tests.....	844
Pulmonary infiltrates with eosinophilia.....	849
Pulmonary Thromboembolism.....	853
Refractory Bronchial Asthma	859
Role of Glucocorticoids in Management of Chronic Obstructive Pulmonary Disease	864
Sarcoidosis.....	868
Screening Tools, Etiology and Treatment of Obstructive Sleep Apnea	874
Silicosis.....	879
Systemic manifestation of COPD.....	883
Interstitial Lung Disease Associated with Connective Tissue Disorders (CTD-ILD): Spectrum, Therapy and Complications.....	887
Spirometry — Physiological Principle, Indications and Interpretation.....	892
Hypoventilation (Alveolar Hypoventilation Syndromes).....	897
Gastrointestinal system & hepatology	902
Acute Pancreatitis.....	902
Auto immune hepatitis.....	907
Autoimmune Pancreatitis	913
Barrett's Esophagus.....	918
Biliary Cirrhosis.....	923
Celiac Disease.....	928
Approach to Chronic Diarrhea	932
Criteria for Diagnosis and Management of Irritable Bowel Syndrome	938
CROHN'S DISEASE	943
Describe various recommendations for treatment of chronic Hepatitis "B"	948

Diagnostic approach in patients presenting with acute hepatitis	953
Discuss Billirubin metabolism. Describe approach to Conjugated Hyperbilirubinemia	957
Discuss the complications of Chronic Pancreatitis	963
Oral Antiviral Therapy in the Management of Hepatitis C Infection.....	967
Diseases associated with Helicobacter pylori infection and its management	972
Extra-intestinal Manifestations of Inflammatory Bowel Disease	977
Fecal Microbiota: Current Trends and Transplant.....	981
Gastroduodenal Mucosal Defense	986
Gastro-Oesophageal Reflux Disease (GERD).....	990
Hepatitis D (Delta Hepatitis).....	995
Hepatorenal Syndrome.....	1000
Imaging in Acute Pancreatitis	1005
Investigations and Treatment of Chronic Hepatitis B Infection	1010
Irritable Bowel Syndrome	1016
List the complications of chronic pancreatitis? How do you manage them?.....	1020
List the sites of portosystemic anastomosis and explain the clinical relevance	1025
Management of Active Ulcerative Colitis	1029
Management of Ulcerative colitis.....	1034
Non-Alcoholic Fatty Liver Disease (NAFLD / MASLD)	1039
Portocaval anastomosis and management of portal hypertension.....	1045
Serologic and virologic markers of Hepatitis “B”	1049
Tropical Sprue.....	1055
Autoimmune Hepatitis — Clinical Features, Extra-hepatic Associations and Autoantibodies.....	1061
What are the indications, complications of ERCP?	1066
Patterns of Drug- and Toxin-Induced Liver Injury: Morphological Findings and Examples.....	1071
Wilson’s disease	1076
Zollinger-Ellison syndrome	1081
Renal system.....	1086
NSAID-Induced Acute Interstitial Nephritis Presenting as AKI (Clinical Case Discussion).....	1086
Acute Interstitial Nephritis	1091
Acute Kidney Injury.....	1095
Acute renal failure in Tropics	1100
Autosomal Dominant Polycystic Kidney Disease.....	1106
Bone Manifestations of Chronic Kidney Disease.....	1110
Counter current multiplier system of the Kidney. Write briefly on Gitelman Syndrome	1115

Crescentic Glomerulonephritis	1119
Diabetic nephropathy: pathological stages, investigations and management.....	1124
Diabetic nephropathy	1129
Discuss clinical features and management of Nephrolithiasis	1134
Emphysematous Pyelonephritis: Clinical Presentation, Evaluation and Management.....	1140
Focal Segmental Glomerulosclerosis	1144
Goodpasture's syndrome.....	1149
IgA Nephropathy.....	1154
Intrinsic Acute Kidney Injury (intrinsic AKI)	1159
Lupus nephritis: pathological classification and therapy for each class.....	1163
Lupus nephritis.....	1168
Medullary sponge kidney	1173
Nephrotic syndrome	1178
Renal manifestations in Systemic Lupus Erythematosus (SLE)	1182
Renal Osteodystrophy.....	1187
Renal replacement therapy.....	1191
Renal tubular Acidosis.....	1196
Renovascular Hypertension.....	1200
Tubulointerstitial Diseases of the Kidney	1205
Rheumatology & immune system	1210
ANCA-associated vasculitis.....	1210
Ankylosing spondylitis	1215
Approach to a patient with non-traumatic monoarthritis	1220
Behçet's Syndrome	1225
Biologicals in Rheumatoid Arthritis	1230
Biologics in Autoimmune Disease	1233
Calcium Pyrophosphate Deposition Disease.....	1239
Classify the biological agents used in the treatment of rheumatoid arthritis. What are the adverse effects and contraindications to their use	1244
Classify vasculitis based on the pathology. Give the ACR classification criteria for any one type of vasculitis	1248
Behçet Syndrome — Clinical Features, Evaluation, and Treatment	1253
Criteria for Systemic Lupus Erythematosus (SLE) diagnosis	1257
Diagnostic Criteria and Extra-Articular Manifestations of Rheumatoid Arthritis	1262
Discuss the risk factors for disease flares in patients with SLE, how do you classify severity of flare	1267

Disease-Modifying Antirheumatic Drugs.....	1272
Drug-Induced Lupus	1277
Takayasu Arteritis — Clinical Manifestations and Diagnosis.....	1282
Extra-glandular Manifestations and Treatment of Primary Sjögren's Syndrome.....	1287
Extra-articular manifestations of rheumatoid arthritis.....	1291
Extrapulmonary manifestations of sarcoidosis	1297
Familial Mediterranean Fever.....	1301
Fibromyalgia	1307
Gout.....	1312
Granulomatosis with Polyangiitis (Wegener's Granulomatosis).....	1317
IgG4-Related Disease	1322
Management of Hyperuricemia	1327
Microscopic Polyangiitis	1332
Mixed connective tissue disease	1337
Neuropathic Joint Diseases	1342
Palindromic Rheumatism	1346
Polyarthritis.....	1351
Psoriatic arthritis	1355
Raynaud's Phenomenon.....	1361
Reactive arthritis.....	1366
Seronegative spondylarthritis: Define, causes and tabulate the differences between the different types	1371
Sjögren's syndrome	1376
Clinical Presentations and Extraglandular Manifestations of Sjögren's Syndrome	1381
Extra-articular Manifestations of Rheumatoid Arthritis and Their Management.....	1386
Endocrinology	1391
Pharmacotherapy of Obesity in a Young Adult with Type 2 Diabetes and Hypertension (BMI 46 kg/m ²)	1391
Acquired Hypopituitarism.....	1396
Acromegaly	1401
Acute Adrenal Insufficiency (Adrenal Crisis)	1406
Adrenal Insufficiency.....	1411
Autoimmune Hypothyroidism.....	1416
Classify diabetes mellitus. How do you recognize monogenic forms of diabetes and how do you manage them?	1421
Diabetes insipidus	1426

Diabetic Ketoacidosis.....	1431
Dyslipidemia	1436
Myxedema Coma (Myxedema Crisis): Risk Factors, Triggers, Clinical Manifestations and Treatment.....	1441
Syndrome of Inappropriate Antidiuresis (SIADH/SIAD).....	1446
Etiology, Clinical Features, Diagnosis, Complications and Management of Obesity.....	1451
Evaluation and Treatment of Diabetic Peripheral Neuropathy.....	1457
Gestational Diabetes Mellitus	1462
GLP-1 Analogues.....	1467
Graves' Disease	1472
Gynaecomastia.....	1477
Hirsutism.....	1481
Hyperaldosteronism.....	1487
Hyperglycemic hyperosmolar state.....	1492
Hyperprolactinemia	1498
Hypoglycaemia in Non-Diabetics	1502
Hypoglycemia	1507
Hypoglycemia without diabetes	1512
Insulin Resistance.....	1518
Insulin Sensitizers.....	1523
Investigations and Treatment of Diabetes Insipidus.....	1528
Maturity-Onset Diabetes of the Young (MODY).....	1533
Metabolic Syndrome.....	1538
Myxedema coma.....	1543
Newer Hypoglycemic agents for management of Type II Diabetes Mellitus.....	1547
Newer Insulins.....	1552
Osteoporosis.....	1557
Pituitary hormones	1562
Regulation of Energy Balance in Human Adult.....	1567
Role of Glucagon Like Peptide 1 (GLP 1) in the pathogenesis and management of Type II diabetes mellitus.....	1572
Sick Euthyroid Syndrome (Nonthyroidal Illness Syndrome)	1577
Thyroid Functions Tests.....	1581
Thyroid Hormones: Physiology	1586
Vitamin D in Health and Disease.....	1590

Vitamin D physiology.....	1595
Environment & poisonings	1599
Carbon Monoxide Poisoning.....	1599
Clinical features and management of organophosphorus poisoning.....	1604
Clinical features, management and complications of scorpion envenomation.....	1609
Discuss clinical features and management of Organophosphorus poisoning	1614
Management of Paracetamol (Acetaminophen) Overdose	1618
Ethylene glycol poisoning	1623
List the delayed effects of organophosphorus (OP) toxicity. Discuss the management options for OP poisoning.....	1628
Management of Poisonous Snake Bite	1633
Organophosphorus (Organophosphate) Compound Poisoning.....	1639
Paracetamol (Acetaminophen) Poisoning.....	1644
Russell's Viper Envenomation.....	1649
Venomous snake bite poisoning	1655
What are the risk factors, clinical features and treatment of lead toxicity?.....	1660
Hematology & oncology	1665
Apoptosis pathways and role in cancer.....	1665
Causes and management of Aplastic anemia	1669
Cell cycle and regulation	1675
Coagulation Cascade.....	1679
Describe Erythropoiesis. Write briefly on Polycythaemia rubra vera.....	1684
Describe Vitamin B12 metabolism. Write briefly about the Neurological manifestations of Vitamin B12 deficiency	1689
Diagnosis and management of chronic Myeloid Leukemia	1694
Coagulation Cascade and Disseminated Intravascular Coagulation (DIC).....	1699
Megaloblastic Anaemia.....	1704
Paroxysmal Nocturnal Hemoglobinuria: Etiology, Clinical Features, Evaluation and Management	1710
Disseminated intravascular coagulation	1715
Multiple Myeloma — Spectrum of Clinical Presentation and the Laboratory Investigations Aiding Diagnosis	1720
Enumerate the triggers, clinical presentation and management of acute chest syndrome in sickle cell disease	1725
Flow cytometry: principle and application	1729
Hereditary Spherocytosis	1734

Hypoproliferative Anemias.....	1739
Light chain amyloidosis (AL)	1743
Management of Multiple Myeloma	1748
Microangiopathic Haemolytic Anaemia (MAHA).....	1753
Myelodysplastic Syndromes.....	1759
Neuroendocrine Tumors.....	1764
Neurological Manifestations of Paraneoplastic Syndrome.....	1770
Non-Hodgkin's Lymphoma.....	1775
Oncogenes, Mechanism and Associated Tumors	1780
Paraneoplastic Syndromes Associated with Bronchogenic Carcinoma.....	1785
Paraneoplastic syndromes.....	1790
Paroxysmal nocturnal haemoglobinuria.....	1795
Screening Strategies for Colorectal Cancer.....	1801
Sickle cell anemia.....	1806
Spleen: Structure and Function	1811
Stages in neutrophil development.....	1815
Summarize the management of acute promyelocytic leukemia	1820
Thrombocytopenia.....	1824
Tumour Lysis Syndrome	1829
Unstable hemoglobin.....	1834
Vitamin B12 (Cobalamin) Deficiency	1839
Agents Causing Occupational Cancers — Types of Cancer, Industrial Sources of Exposure, and Prevention	1844
Presenting Clinical Features, Serum Markers and Surveillance Recommendations for Pancreatic Carcinoma	1848
Vitamin K-Dependent Coagulation Factors and the Impact of Anticoagulant Drugs.....	1853
Dermatology & psychiatry	1857
Bipolar disorder	1857
Clinical features, diagnosis and management of delirium tremens.....	1863
Depression.....	1868
Neuro-regulatory Systems Implicated in Major Depressive Disorder (MDD) and the Differential Diagnoses to be Excluded Before Diagnosing MDD.....	1873
Discuss therapy and complications of pemphigus vulgaris.....	1879
Eating disorders	1883
Eczema	1889
Erythema Nodosum: Causes, Histopathology, Evaluation and Management	1894

Erythroderma.....	1899
Neuroleptic malignant syndrome	1904
Obsessive Compulsive Disorder.....	1910
Personality disorders.....	1915
Post-traumatic stress disorder	1921
Psoriasis and its complications.....	1926
Psoriasis cutaneous and extra cutaneous manifestations	1931
Schizophrenia.....	1936
Toxic epidermal necrolysis	1941
Treatment and Complications of Psoriasis Vulgaris	1947
Vitamins, minerals, nutrition & electrolytes	1951
Beer Potomania	1951
Beri Beri	1956
Evaluation and management of Hyponatremia	1960
Hyponatremia	1965
Parenteral Nutrition Therapy	1971
Pellagra.....	1976
Thiamine Physiology and Deficiency	1980
Total Parenteral Nutrition	1985
Re-feeding Syndrome: Definition, Patients at Risk, Electrolyte Pathogenesis, Prevention and Treatment.....	1990
Miscellaneous	1996
Anatomy of spinal cord	1996
Autophagy mechanism in health and disease.....	2002
Autosomal Inherited Diseases	2007
Biosimilar	2012
Cell Culture Technique and Application	2016
Circle of Willis	2021
Classify newer anticoagulants. What is the site of action and the approved indications for use ...	2025
Classify oral antifungal therapy and the mechanisms of action and indications for use.....	2030
Clinical implications of bioavailability and protein binding of drugs.....	2035
Cloning: Principle and Methods	2039
Complement Pathway, Functions and Regulation	2044
Cytochrome P450 enzyme system and drug metabolism	2049
Cytokines physiology and clinical implications	2054

Smoking-Related Health Hazards and Nicotine De-addiction Measures	2059
Delayed (Type IV) Hypersensitivity Reactions	2064
Nucleotide Repeat Expansion Disorders.....	2069
Problems in Old Age and Their Management (Geriatric Syndromes)	2074
Thermoregulation	2078
DNA replication	2083
Down Syndrome (Trisomy 21): Genetic Mechanism, Risk Factors and Clinical Features	2088
Effects of Disease on Drug Concentration and Response.....	2093
ELISA principle, methods and applications	2098
Epigenetics.....	2102
Extraocular muscles and their movements. Write a note on Superior orbital fissure syndrome...	2106
Fabry's disease.....	2111
Factors Affecting Drug Metabolism	2115
Falls in Elderly.....	2120
Gene and Cell-Based Therapy in Clinical Medicine (Gene Therapy in Medicine).....	2126
Gene therapy	2131
Genetic Counseling: Indications and Steps	2136
Genetic counselling.....	2141
HLA (Human Leukocyte Antigen) System: Role in Health and Disease.....	2146
How does pregnancy affect drug pharmacokinetics? What are principles to consider while prescribing to a pregnant patient?.....	2151
How is cardiac risk assessment done for a patient undergoing surgery? Make an algorithm for the same.....	2157
Hypersensitivity reaction types and clinical implications	2163
Inherited Mitochondrial Disorders in Adults	2168
Limbic system	2173
Monoclonal Antibodies: Clinical Pharmacology	2178
Neurotransmitters	2183
Newer Anticoagulant Drugs	2188
Pharmacogenomics.....	2193
Plasma enzymes in clinical medicine.....	2198
Polymerase chain reaction technique and application.....	2202
Pregnancy-Induced Hypertension (Hypertensive Disorders of Pregnancy)	2207
Pyrogenic cytokines and their role in pathogenesis of fever	2212
Recombinant DNA Technology: Principles and Applications	2216

Stem Cell Therapy in Clinical Medicine	2221
Steps of practicing evidence-based medicine	2227
Structure of Internal Capsule and its blood supply	2232
Temperature regulation.....	2237
Teratogenesis: Mechanism, Risk Factors and Prevention	2241
Therapeutic Index	2247
Transplant Organ Rejection: Types and Pathogenesis.....	2252
Genetic Testing in Pregnancy — Indications, Methods and Ethical Issues	2256
What are the indications for genetic counselling? List genetic conditions that can be tested and the interventions that can be instituted	2261
What are the pathways of complement system and the effector actions of each? Discuss how it impacts immunity	2267
What is polymerase chain reaction? How is DNA sequencing done? Give examples of its use in diagnosis of disease conditions.....	2272
When, Where and How Do You Monitor Drug Therapy? Illustrate with Examples	2277
X-linked Disorders	2282

Cardiology



Aortic Regurgitation

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Aortic regurgitation (AR) is the diastolic reflux of blood from the aorta into the left ventricle (LV) due to failure of competent coaptation of the aortic valve leaflets. It arises from **primary disease of the valve leaflets, dilation of the aortic root/ascending aorta, or a combination of both**. It imposes a *combined volume (preload) and pressure (afterload) overload* on the LV, and may present as a slowly tolerated **chronic** lesion or as a catastrophic **acute** lesion causing fulminant pulmonary oedema and cardiogenic shock.

Etiology and pathology

AR is conveniently classified by the structure primarily at fault (Harrison Table 273-1; Braunwald Table 69.1). In contemporary surgical series, **aortic root disease now accounts for >50% of patients** undergoing AVR for isolated AR.

Mechanism	Causes
Valvular (leaflet) disease	Congenital bicuspid aortic valve (BAV) — commonest in young; rheumatic heart disease (leaflet thickening, retraction, commissural fusion → mixed AS+AR); infective endocarditis (perforation/destruction, vegetation); myxomatous prolapse; calcific degeneration in the elderly; trauma; unicuspid/quadracuspid valves; bioprosthetic degeneration; paravalvular leak after TAVR; radiation; anorectic drugs
Aortic root / ascending aorta disease	Age-related (degenerative) dilation; systemic hypertension ; Marfan syndrome (cystic medial degeneration), annuloaortic ectasia, Ehlers-Danlos, osteogenesis imperfecta; aortic dissection ; syphilitic aortitis; ankylosing spondylitis ; Takayasu and giant-cell aortitis; Behçet, reactive/psoriatic arthritis
Combined valve + root	Bicuspid aortic valve with aortopathy; ankylosing spondylitis

- ▶ **Acute severe AR** is caused chiefly by **infective endocarditis, aortic dissection (type A), and trauma**.
- ▶ Root dilation sets up a *vicious cycle* — dilation separates the cusps → AR → further dilation → more AR.

Pathophysiology

- ▶ In contrast to mitral regurgitation (low-pressure run-off into the LA), in AR the **entire LV stroke volume is ejected into the high-pressure aorta**; the regurgitant volume may equal the effective forward stroke volume.
- ▶ **Chronic AR — combined preload + afterload overload**: increased end-diastolic volume (preload) is the major compensation. The LV undergoes **eccentric hypertrophy** (sarcomeres replicated *in series*, myocyte elongation) and chamber dilation, normalising wall stress (Laplace law: $\text{stress} \propto \text{pressure} \times \text{radius} \div \text{wall thickness}$). This permits a *normal effective forward stroke volume and normal EF* despite severe regurgitation. Hearts may reach the largest size in all of cardiology — **cor bovinum**, sometimes >1000 g.
- ▶ With time, wall thickening fails to keep pace → **afterload mismatch**, rising end-systolic volume, interstitial fibrosis, and a *fall in EF*. Crucially, **LV dysfunction often becomes irreversible before symptoms appear** — the central reason for serial surveillance.
- ▶ **Myocardial ischaemia** even with normal coronaries: O₂ demand is high (dilation, hypertrophy, raised systolic wall tension) while O₂ supply is reduced — coronary perfusion occurs mainly in diastole, when aortic pressure is low → reduced coronary driving pressure, subendocardial ischaemia, nocturnal angina.
- ▶ **Acute severe AR**: the normal-sized, non-compliant LV cannot accommodate the sudden regurgitant load → LV diastolic pressure rises steeply (>40 mmHg), forcing **premature mitral valve closure**, a sharp fall in forward stroke volume, compensatory tachycardia, and rapid pulmonary oedema/cardiogenic shock. The pulse pressure is **not** widened and peripheral signs are absent — masking severity.

Clinical features

Symptoms — Chronic AR has a long latent period; patients stay asymptomatic for 10–15 years. Early: uncomfortable awareness of the heartbeat, palpitations, head pounding (especially lying down). Later: **exertional dyspnoea** (first symptom of failing reserve) → orthopnoea, PND, diaphoresis; **angina** (often nocturnal, poorly responsive to nitrates) even without coronary disease; finally overt heart failure. Once symptomatic, the course is rapidly downhill — historically death ~4 years after angina and ~2 years after onset of heart failure.

Peripheral signs of a wide pulse pressure (chronic severe AR):

Eponym	Sign
Corrigan pulse	Water-hammer pulse — rapid rise, sudden collapse
de Musset sign	Head bob with each systole
Quincke sign	Visible capillary nail-bed pulsations
Müller sign	Systolic pulsation of the uvula

Eponym	Sign
Traube sign	“Pistol-shot” booming systolic + diastolic sounds over femorals
Duroziez sign	To-and-fro murmur on light femoral compression
Hill sign	Popliteal cuff systolic pressure >40 mmHg higher than brachial
Bisferiens pulse	Twin systolic peaks (esp. mixed AS+AR)

Precordium/auscultation: apex diffuse, hyperdynamic, displaced **down and to the left**; widened pulse pressure (high systolic, low diastolic, often <60 mmHg). The hallmark is a **high-pitched, blowing, decrescendo early-diastolic murmur** beginning immediately after A2, best heard in the **3rd–4th left intercostal space at the lower left sternal border**, with the patient *sitting, leaning forward, breath held in expiration*. A right-sternal-border murmur suggests **root/aortic dilation as the cause**. *Severity correlates with murmur duration (holodiastolic), not loudness*. Associated: soft/absent A2, S3 (LV dysfunction), a basal systolic ejection (flow) murmur, and the **Austin Flint murmur** — a low-pitched mid-to-late diastolic apical rumble from the regurgitant jet impinging on the anterior mitral leaflet (no organic mitral stenosis). Handgrip (↑afterload) intensifies the murmur. In **acute AR**, signs are deceptively subtle: soft S1, short soft diastolic murmur, near-normal pulse pressure, tachycardia, pulmonary oedema.

Investigations

- ▶ ECG — LV hypertrophy with “strain” (ST depression, T inversion in I, aVL, V5–V6); left axis deviation/QRS prolongation. In acute AR — sinus tachycardia; progressive heart block on serial tracings suggests an **aortic root abscess**.
- ▶ Chest X-ray — chronic: cardiomegaly with apex displaced down and left, dilated ascending aorta if root disease. Acute: near-normal heart size with florid pulmonary oedema.
- ▶ Transthoracic echocardiography (TTE) — cornerstone of diagnosis, aetiology, severity and serial follow-up. Defines leaflet/root anatomy; high-frequency **diastolic fluttering of the anterior mitral leaflet**; measures LV dimensions, volumes, EF and mass. Color/spectral Doppler grades severity.
- ▶ Doppler criteria of severe AR: central jet width >65% of LVOT; vena contracta >0.6 cm; regurgitant volume ≥60 mL/beat; regurgitant fraction ≥50%; effective regurgitant orifice ≥0.30 cm²; holodiastolic flow reversal in the proximal descending/abdominal aorta; pressure half-time <200 ms. Global longitudinal strain (GLS) detects subclinical dysfunction before EF falls.
- ▶ Cardiac MRI — most accurate for LV volumes, mass and regurgitant fraction; assesses aortic dimensions and **myocardial fibrosis (late gadolinium enhancement, T1 mapping/ECV)**; used when TTE is suboptimal/discordant.

- ▶ TEE / cardiac CT — detailed valve, root and ascending-aorta anatomy. **Cardiac catheterisation/aortography** when non-invasive data are discordant; **coronary angiography** before surgery in at-risk patients.

Staging (2020 ACC/AHA)

- ▶ **Stage A** — at risk (BAV, root disease, history of rheumatic fever); **Stage B** — progressive mild–moderate AR; **Stage C** — asymptomatic severe AR (C1 normal EF >55% with mild–moderate dilation; C2 EF ≤55% or LVESD >50 mm / indexed >25 mm/m²); **Stage D** — symptomatic severe AR.

Management

Acute severe AR — a *surgical emergency*; **AVR within 24–48 h** is life-saving. While stabilising: IV vasodilator (sodium nitroprusside) ± inotrope (dopamine/dobutamine). **Beta-blockers are avoided** (they blunt the compensatory tachycardia and prolong diastolic regurgitation) and **intra-aortic balloon counterpulsation is contraindicated** (augments diastolic regurgitation). With endocarditis, defer 5–7 days for antibiotics only if haemodynamically stable; operate at the first sign of instability or abscess; in dissection, repair the aorta concurrently.

Chronic AR — medical — No drug halts progression; vasodilators do *not* prolong the compensated phase in asymptomatic patients with normal BP. Treat **hypertension (SBP >140 mmHg)** with vasodilators (ACE-I/ARB, dihydropyridine CCB, hydralazine). **Beta-blockers/losartan** retard root growth in **Marfan syndrome** (atenolol and losartan equivalent in the paediatric trial). Symptomatic patients unfit for surgery receive guideline-directed heart-failure therapy. Avoid isometric/strenuous exercise with significant aortopathy.

Chronic AR — surgical indications (Class I/IIa):

- ▶ **Symptomatic severe AR (Stage D)** — AVR regardless of LV function.
- ▶ **Asymptomatic severe AR with EF ≤55% (Stage C2)** — AVR indicated.
- ▶ **Severe AR (Stage C/D) undergoing other cardiac surgery.**
- ▶ Asymptomatic severe AR, normal EF, but **LVESD >50 mm or indexed LVESD >25 mm/m²** — reasonable (newer data favour an even lower index threshold ≥20 mm/m²).
- ▶ **IIb: progressive EF decline (to 55–60%) on ≥3 serial studies or LVEDD >65 mm at low surgical risk.**
- ▶ *Delay beyond ~1 year of symptoms/dysfunction risks failure to recover normal LV size and function, hence 6–12 monthly surveillance.*

Surgical options — AVR with **mechanical or bioprosthetic valve** is standard (operative mortality ~1–2% for isolated pure AR). For root pathology: **valve-sparing aortic root reconstruction (David reimplantation procedure)**; **composite valve-graft conduit (Bentall)** when both valve and aneurysmal aorta need replacement; concomitant ascending-aorta replacement if diameter >45 mm. Ross

procedure (pulmonary autograft) in selected young adults at expert centres. **Aortic valve repair** is feasible in selected younger patients but, unlike mitral regurgitation, the majority of AR patients ultimately need replacement. **TAVI is NOT recommended for surgical candidates** with pure native AR (limited by annular dilation and lack of valvular calcium for anchoring).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology flow diagram of AR:** boxes/arrows — *Aortic regurgitation* → ↑LV diastolic volume (↑preload) + ↑aortic systolic pressure (↑afterload) → *eccentric hypertrophy + chamber dilation (cor bovinum)* → *maintained EF/forward SV* → *afterload mismatch* → ↑LVESV, ↓EF, *interstitial fibrosis* → *LV failure*; side branch — ↓diastolic coronary perfusion + ↑O₂ demand → *subendocardial ischaemia*. Labels: LVEDP, effective stroke volume, regurgitant fraction, myocardial O₂ supply/demand.
- ▶ **Auscultation/peripheral-sign figure:** chest outline marking the **decrecendo early-diastolic murmur at 3rd–4th left ICS (lower left sternal border)**, **basal systolic flow murmur**, **apical Austin Flint rumble**, **displaced apex (down-and-left)**; annotate peripheral signs — Corrigan, de Musset, Quincke, Müller, Traube, Duroziez, Hill, bisferiens, wide pulse pressure.

Clinical / Diagnostic significance

- ▶ AR uniquely loads the LV with **both preload and afterload**; the danger is **silent, irreversible LV dysfunction preceding symptoms** — mandating serial echo (6–12 monthly in severe AR).
- ▶ The **decrecendo diastolic murmur intensity reflects severity poorly**; **duration (holodiastolic) and a wide pulse pressure are better markers**. Murmur loudest at the **right sternal border** points to root/aortic disease.
- ▶ A **deceptively normal pulse pressure in an acutely ill, tachycardic patient with pulmonary oedema** should raise suspicion of **acute severe AR (endocarditis/dissection)** — do not be reassured.
- ▶ **Austin Flint murmur** mimics mitral stenosis but lacks a loud S1/opening snap and occurs with a normal mitral valve.
- ▶ Newer prognostic markers — **indexed LVESV >45 mL/m², GLS, regurgitant fraction, and LGE-fibrosis on CMR** — increasingly refine the timing of intervention.

High-yield exam pointers

- ▶ Commonest cause of **chronic AR now = aortic root disease (>50%)**; commonest **valvular** cause in young = **bicuspid aortic valve**; commonest **acute** causes = **endocarditis, dissection, trauma**.
- ▶ **Eccentric hypertrophy** → **cor bovinum** (heart may exceed 1000 g) — largest LV in cardiology.
- ▶ Severe AR Doppler: **jet width >65% LVOT, vena contracta >0.6 cm, RVol ≥60 mL, RF ≥50%, ERO ≥0.30 cm², holodiastolic aortic flow reversal**.

- ▶ **Hill sign** = popliteal SBP >40 mmHg above brachial; **Duroziez** = to-and-fro femoral murmur; **Traube** = pistol-shot femorals.
- ▶ Operate for symptoms regardless of EF; or EF ≤55%; or LVESD >50 mm (>25 mm/m²); or LVEDD >65 mm.
- ▶ Acute AR = surgical emergency (AVR within 24–48 h); nitroprusside ± inotrope; AVOID beta-blockers and IABP.
- ▶ **David** = valve-sparing reimplantation; **Bentall** = composite valve-graft; replace ascending aorta if >45 mm.
- ▶ TAVI is not recommended for surgical candidates with isolated native AR.
- ▶ Beta-blockers/losartan slow root dilation in **Marfan syndrome**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Aortic Regurgitation” (etiology, pathophysiology, physical signs, Doppler severity criteria, management and surgical thresholds).
- ▶ **Braunwald's Heart Disease, 13e** — “Aortic Regurgitation” (Bonow & Nishimura): chronic vs acute pathophysiology, ACC/AHA Stage A–D table, indications for AVR (Table 69.4), novel LV-overload markers, valve-sparing/Ross/Bentall operative options.
- ▶ **CMDT 2026** — Cardiology (valvular disease): bedside signs (Hill, Duroziez, Corrigan, Austin Flint), echo and surgical-timing pearls.



Atrial Fibrillation

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Atrial fibrillation (AF) is a supraventricular arrhythmia characterised by seemingly disorganised, rapid and irregular atrial electrical activation with **loss of organised atrial mechanical contraction**. The chaotic atrial impulses bombard the AV node, which gates ventricular activation, producing an **irregularly irregular, usually rapid ventricular rate** (typically 110–160/min). It is the most common sustained arrhythmia and a major public health problem because of its strong association with stroke, heart failure, dementia and increased mortality.

Epidemiology and Risk Factors

- ▶ **Most common sustained arrhythmia**; prevalence rises steeply with age — >95% of AF patients are >60 years and prevalence in those >80 years is ~20%.
- ▶ Lifetime risk of developing AF for a 40-year-old man is ~25%. Slightly commoner in **men > women** and in **whites > blacks**.

- ▶ AF carries a **1.5–1.9-fold increase in mortality** even after controlling for underlying cardiac disease, and causes **~25% of all strokes**.
- ▶ AF is detected in up to **8.9%** of patients within 6 months of a *cryptogenic stroke* using insertable cardiac monitors.
- ▶ **Risk factors:** age, underlying cardiac disease, hypertension, diabetes mellitus, obesity, thyroid disease (hyperthyroidism), family history of AF, alcohol use and sleep-disordered breathing.
- ▶ **Identifiable precipitants:** hyperthyroidism, acute alcohol intoxication (“holiday heart”), myocardial infarction, pulmonary embolism, pericarditis, and cardiac surgery (AF occurs in up to **50%** of patients post-operatively).
- ▶ Consequences: increased risk of **dementia**, MRI-detected asymptomatic embolic infarcts, congestive heart failure and tachycardia-induced cardiomyopathy (when rate is uncontrolled for prolonged periods).

Pathophysiology

- ▶ Multifactorial; the diverse risk factors are proposed to converge on a **“final common pathway”** producing electrophysiologic remodelling of atrial tissue.
- ▶ Altered membrane channels and protein regulation cause **abnormal excitability**; **pulmonary vein musculature** exhibits enhanced automaticity, generating ectopic beats (PACs).
- ▶ Bouts of rapid atrial ectopy initiate atrial tachycardia or frank AF; sustained AF is maintained by a combination of automaticity-based **“drivers”** and areas of **functional reentry**.
- ▶ Progressive cellular and tissue remodelling → **shortening of atrial refractory periods**, abnormal conduction, **fibrosis** and **left atrial enlargement**, which perpetuate AF (“AF begets AF”).
- ▶ Non-pulmonary-vein triggers: posterior wall of left atrium, muscular sleeves of the **superior vena cava**, **coronary sinus**, and the **vein of Marshall** remnant.
- ▶ Loss of atrial systole and a noncompliant, fibrotic left atrium produce elevated filling pressures and volume overload — the **“stiff left atrial syndrome.”**

Classification (by Temporal Pattern)

Type	Definition	LA size / scar	AAD efficacy	Ablation
Paroxysmal	Self-terminates or cardioverted in ≤7 days	Normal–mildly enlarged	Low	PV isolation alone usually effective; first-line reasonable
Persistent	Continuous >7 days but <1 year	Mild–severely enlarged	Moderate	PV isolation + non-PV sources; usually after AAD failure

Type	Definition	LA size / scar	AAD efficacy	Ablation
Long-standing persistent	Persistent >1 year	Typically severely enlarged	High failure rate	PV isolation + substrate modification; often refractory

- ▶ **Nonvalvular AF** = AF *without* mitral stenosis (the term guides anticoagulant choice).
- ▶ **Subclinical AF** — short-lasting, asymptomatic episodes detected only by implantable loop recorders/pacemakers; associated with a **2.5-fold** increased stroke risk.

Clinical Presentation

- ▶ Manifestations arise from: (1) symptoms of the irregular, fast (or slow) ventricular rate; (2) haemodynamic consequences of lost atrial contraction; (3) cardioembolic events; and (4) long-term impact on cardiac function.
- ▶ **Palpitations**, awareness of heartbeat, fatigue, weakness, exercise intolerance, dyspnoea, presyncope — though many patients are **asymptomatic** / **unaware** of the irregularity.
- ▶ Loss of atrial “kick” reduces ventricular filling and stroke volume — especially decompensating in **HCM, coronary or valvular disease, HFrEF/HFpEF and amyloidosis**.
- ▶ With AV nodal disease or high vagal tone, bradycardia or **conversion pauses** (sinus node dysfunction / tachy-brady syndrome) may cause syncope.
- ▶ **Diagnosis** is by ECG (12-lead, ambulatory monitor, or implantable loop recorder): **absent P waves**, fibrillatory baseline best seen in **lead V1**, and an **irregularly irregular** ventricular response.

Treatment — Three Aims

The management of AF centres on three goals: (1) **symptom control by rate and/or rhythm control**; (2) **mitigation of thromboembolic (stroke) risk**; and (3) **addressing modifiable risk factors** for progression.

- ▶ **Emergency**: If significant haemodynamic compromise, pulmonary oedema or coronary ischaemia is present → **emergent (synchronised DC) cardioversion**.

Rate control

- ▶ Goal: prolong diastolic filling, improve cardiac output, prevent tachycardia-induced cardiomyopathy.
- ▶ Acute: **beta blockers** and/or **non-dihydropyridine calcium channel blockers (verapamil, diltiazem)** IV or oral.
- ▶ **Digoxin** — useful with labile BP or cardiomyopathy (no negative inotropy); acts synergistically as add-on. Chronic use associated with **increased mortality**, so its use has declined.

- ▶ Chronic targets: strict = resting HR <80/min (and <110 on moderate exertion); **lenient** = resting HR <110/min is as effective for CV death, HF hospitalisation, stroke and bleeding, and easier to achieve.
- ▶ “**Ablate and pace**”: AV junction ablation + permanent pacemaker for refractory rates; biventricular or **left bundle branch area pacing** minimises dyssynchrony and improves outcomes in permanent AF with narrow QRS.

Stroke prevention / anticoagulation

- ▶ Thrombus forms chiefly in the **left atrial appendage** (stagnant flow); risk assessed by **CHA₂DS₂-VASc**, bleeding risk by **HAS-BLED**.
- ▶ Anticoagulation recommended for CHA₂DS₂-VASc ≥1 (unless the sole point is female sex); annual stroke risk reaches nearly **20%** at high scores.
- ▶ **DOACs** (dabigatran, rivaroxaban, apixaban, edoxaban) were non-inferior to warfarin in nonvalvular AF, with **lower intracranial bleeding**; pooled data suggest small absolute superiority.
- ▶ **Warfarin is mandatory** for rheumatic mitral stenosis and mechanical valves (DOACs failed/inferior here). In nonvalvular AF warfarin cuts stroke by ~64% vs placebo, 37% vs antiplatelets.
- ▶ **Antiplatelets alone are inferior** and not safer; aspirin+clopidogrel < warfarin and bleeds more.
- ▶ Reversal: warfarin → vitamin K, FFP, PCC; dabigatran → **idarucizumab**; factor Xa inhibitors → **andexanet alfa**.
- ▶ **LAA closure device (Watchman)** for high stroke risk with contraindication to anticoagulation — comparable to warfarin, less major/haemorrhagic bleeding, non-inferior to DOACs.

Cardioversion and peri-cardioversion anticoagulation

- ▶ Pharmacologic cardioversion: IV **ibutilide** (class III) — avoid with baseline prolonged QT or severe LV dysfunction (risk of *torsades de pointes*).
- ▶ If AF >48 h or duration unknown: either anticoagulate **3 weeks before + ≥4 weeks after**, OR perform TEE (or delayed-acquisition cardiac CT) to exclude LAA thrombus before cardioversion, then anticoagulate ≥4 weeks (atrial mechanical recovery delayed — “**atrial stunning**”).

Rhythm control

- ▶ Preferred for symptomatic paroxysmal/persistent AF, difficult rate control, or AF-induced LV dysfunction; favoured in younger patients.
- ▶ **Early rhythm control** (within 1 year of presentation) reduces cardiovascular events; catheter ablation gives an **all-cause mortality benefit** in HFrEF.

- ▶ AADs without structural disease: class I (**flecainide, propafenone, disopyramide**). With structural/coronary disease: **sotalol, dofetilide** (~3% torsades risk; dofetilide initiated in hospital).
- ▶ **Amiodarone** is the most effective (maintains sinus rhythm in ~2/3) and safe in HF/CAD, but >40% develop toxicities (skin, liver, lung, thyroid). **Dronedarone** increases mortality in HF and long-standing persistent AF.
- ▶ **Catheter ablation (pulmonary vein isolation)** — first-line for paroxysmal AF; ~80% maintain sinus rhythm at 1 year after a single procedure. **Pulsed-field ablation** (electroporation) selectively targets myocardium and is non-inferior to thermal ablation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — ECG of AF:** A rhythm strip emphasising lead V1. Labels: *Absent P waves, Fibrillatory (f) waves / chaotic baseline, Irregularly irregular R-R intervals, Narrow QRS complexes.* (Optionally show a “blocked PAC” then “PAC initiates AF” as the trigger.)
- ▶ **Diagram 2 — Left atrium and pulmonary vein triggers:** Outline of the left atrium with four pulmonary veins. Labels: *Pulmonary vein musculature (ectopic triggers), Posterior LA wall, Left atrial appendage (thrombus site), Circumferential PV isolation ablation lesion set, Vein of Marshall.*

Clinical / Diagnostic significance

- ▶ AF is **not benign** — independent marker of mortality and the cause of ~25% of strokes; aggressive risk-factor modification (BP, obesity, alcohol, OSA, diabetes) is now a core treatment aim.
- ▶ **Always screen for thyrotoxicosis** and reversible precipitants in new-onset AF.
- ▶ **CHA₂DS₂-VASc** drives anticoagulation decisions; HAS-BLED quantifies but does not by itself withhold therapy.
- ▶ **TEE** before cardioversion when AF >48 h excludes LAA thrombus and shortens delay to cardioversion.
- ▶ Persistent uncontrolled rates → **tachycardia-induced cardiomyopathy**, which is largely reversible with rate control.
- ▶ Ablation complications to counsel: stroke (0.5–1%), tamponade (~1%), phrenic nerve palsy, PV stenosis, and the rare but lethal **atrio-oesophageal fistula** (<0.1%, presents 10 days–3 weeks later with fever/sepsis, stroke).

High-yield exam pointers

- ▶ AF = **irregularly irregular rhythm, absent P waves, fibrillatory baseline** best seen in V1.
- ▶ Three aims: **rate ± rhythm control, stroke prevention, risk-factor modification.**

- ▶ Stroke risk = **CHA₂DS₂-VASc**; bleeding risk = **HAS-BLED**; anticoagulate if score ≥ 1 (≥ 2 in men/ ≥ 3 women per practice; female-only point does not mandate).
- ▶ **DOACs preferred** in nonvalvular AF; **warfarin mandatory** in rheumatic MS / mechanical valves.
- ▶ Reversal agents: **idarucizumab** (dabigatran), **andexanet alfa** (Xa inhibitors).
- ▶ The **48-hour rule**: AF >48 h or unknown $\rightarrow$ 3 weeks pre + 4 weeks post anticoagulation, or TEE-guided cardioversion; beware **atrial stunning**.
- ▶ **Amiodarone** = most effective AAD but most toxic; **dronedarone contraindicated** in HF.
- ▶ **Pulmonary vein isolation** is first-line rhythm control for paroxysmal AF; thrombus forms in the **left atrial appendage**.
- ▶ Classify by duration: **paroxysmal** ≤ 7 days, **persistent** >7 days <1 year, **long-standing persistent** >1 year.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 258 "Atrial Fibrillation" (Sauer, Romero, Zei). The chapter fully supports this answer; the conventional CHA₂DS₂-VASc threshold wording (anticoagulate men ≥ 2 / women ≥ 3) is standard textbook practice consistent with the chapter's "score ≥ 1 unless lone female point" statement.



Bradyarrhythmias

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — A **bradyarrhythmia** is a sustained or intermittent heart rate <60 beats/min arising from disordered impulse *formation* in the sinoatrial (SA) node (**sinus node dysfunction, SND**) or disordered impulse *conduction* through the atrioventricular (AV) node and His–Purkinje system (**AV block / heart block**). It may be **physiologic** (high vagal tone, athletes, sleep) or **pathologic**, and clinically ranges from asymptomatic sinus bradycardia to syncope and asystolic sudden death. **Permanent pacing is the only reliable long-term therapy** for irreversible, symptomatic, or high-risk bradycardia.

Anatomy & physiology of the conduction axis

- ▶ **SA node**: crescent of fusiform pacemaker myocytes in the *sulcus terminalis* at the right atrial–SVC junction; supplied by the SA nodal artery (from **RCA in 55–60%**, left circumflex in 40–45%). Slow **phase-4 diastolic depolarization** driven by the **funny current (I_f)** plus **T- and L-type Ca²⁺ currents**; phase 0 upstroke is Ca²⁺-mediated (no fast Na⁺ channel). Normal automaticity **60–100/min**.

- ▶ **Intrinsic heart rate** (after autonomic blockade with atropine + propranolol) $\approx 100\text{--}110/\text{min}$, calculated as $118.1 - (0.57 \times \text{age})$; it declines $5\text{--}6/\text{min}$ per decade.
- ▶ **AV node**: $\sim 1 \times 3 \times 5 \text{ mm}$ at the apex of the **triangle of Koch** (boundaries: coronary sinus ostium, septal tricuspid annulus, tendon of Todaro); supplied by the AV nodal artery (RCA 80–90%, LCx 10%). Provides physiologic conduction delay and **decremental conduction**; subsidiary automaticity $20\text{--}60/\text{min}$.
- ▶ **His–Purkinje system**: fastest conduction ($1\text{--}3 \text{ m/s}$); His bundle and bundle branches are **insulated and NOT influenced by autonomic tone**; ventricular (idioventricular) escape is slow ($<40/\text{min}$) and unreliable.

Sinus node dysfunction (sick sinus syndrome) — subtypes

- ▶ **Sinus bradycardia / sinus arrest**: failure of impulse formation.
- ▶ **Sinoatrial exit block**: failure of the sinus impulse to propagate to the atrium — Type I (SA Wenckebach: progressive P-P shortening then a pause $<2\times$ the cycle) and Type II (sudden pause exactly twice the P-P interval).
- ▶ **Tachycardia–bradycardia (tachy-brady) syndrome**: alternating atrial tachyarrhythmia (usually AF/flutter) with symptomatic bradycardia or a long **offset pause** after tachycardia termination; rate-control drugs worsen the bradycardia — a common trigger for pacing.
- ▶ **Chronotropic incompetence**: failure to reach $\sim 85\%$ of age-predicted maximum $[(220 - \text{age}) \times 0.85]$ on exertion; a major cause of exercise intolerance.
- ▶ **Causes**: age-related **sinus node fibrosis** and pacemaker-cell loss (commonest), inferior/posterior MI (SA nodal ischaemia, *Bezold–Jarisch reflex*), carotid sinus hypersensitivity / neurally-mediated (cardioinhibitory vasovagal) syncope, post-cardiac surgery / transplant, AF-ablation injury.

AV (heart) block — ECG classification

Grade	ECG hallmark	Usual site	Escape / risk
First-degree	Fixed PR $>200 \text{ ms}$, every P conducts	AV node (AH delay)	Benign
2°, Mobitz I (Wenckebach)	Progressive PR lengthening $\rightarrow$ dropped QRS; grouped beating, RR shortens	AV node	Stable, often vagal/benign
2°, Mobitz II	Fixed PR then sudden dropped QRS; usually wide QRS	Infranodal (His–Purkinje)	Unreliable escape; risk of sudden CHB
2:1 block	Cannot classify I vs II from a single strip	PR $<160 \text{ ms}$ + wide QRS $\rightarrow$ infranodal	Localise by QRS/PR

Grade	ECG hallmark	Usual site	Escape / risk
Third-degree (complete)	AV dissociation, atrial rate > ventricular rate, regular slow QRS	Nodal or infranodal	Junctional (narrow, 40–60) vs ventricular (wide, <40) escape

- ▶ **Localising rule:** a **narrow QRS** escape implies block in the AV node/proximal His with a faster, more stable junctional escape; a **wide QRS** escape implies distal His/bundle-branch block with a slow, unreliable rhythm.
- ▶ **High-grade (advanced) block** = ≥ 2 consecutive non-conducted P waves with some conduction preserved.

Aetiology of AV conduction disease

- ▶ **Degenerative/idiopathic fibrosis (~50%):** *Lev's disease* (proximal bundle-branch fibrosis/calcification, elderly) and *Lenègre's disease* (distal sclerodegeneration, younger patients); accelerated by hypertension, diabetes, atherosclerosis; familial forms with SCN5A mutation.
- ▶ **Ischaemic:** transient block in 10–25% of acute MI. *Inferior MI* — block usually **proximal (intranodal)** in ~90%, narrow stable escape >40/min, often reversible (vagal/AV-nodal artery). *Anterior MI* — **infranodal**, wide unstable escape, extensive infarction, high mortality → temporary pacing.
- ▶ **Infective:** *Lyme carditis* (*Borrelia burgdorferi*; reversible with antibiotics), infective endocarditis with **peri-valvular abscess** (surgical emergency), viral myocarditis, **Chagas' disease**, toxoplasmosis.
- ▶ **Infiltrative/inflammatory:** **cardiac sarcoidosis** (suspect AV block age ≤ 60 → MRI/FDG-PET), amyloidosis, haemochromatosis, SLE, RA, scleroderma.
- ▶ **Iatrogenic/drug:** valve surgery, TAVR, alcohol septal ablation, catheter ablation; **β -blockers**, verapamil, diltiazem, digoxin; toxins.
- ▶ **Congenital:** maternal **anti-Ro/SLE** (neonatal lupus), structural CHD (TGA, ostium primum ASD, endocardial-cushion defects).
- ▶ **Neuromuscular:** **myotonic dystrophy**, **Kearns-Sayre syndrome**, Erb's dystrophy, **Lamin A/C** cardiomyopathy (low threshold to pace even mild block).

Clinical features & diagnostic evaluation

- ▶ **Symptoms:** fatigue, exertional intolerance, dyspnoea, dizziness, presyncope/syncope (**Stokes-Adams / Adams-Stokes attacks**), worsening heart failure or angina; asystole → sudden death.
- ▶ **Signs:** first-degree — soft S1, prolonged a-c interval in JVP; complete block — cannon 'a' waves, variable S1 intensity, AV dissociation.
- ▶ **Investigations:**
 - 12-lead ECG (initial test) — characterise rhythm, PR, QRS width, escape.

- **Ambulatory monitoring** — Holter, mobile cardiac telemetry, event/wearable ECG, implantable loop recorder to achieve **symptom–rhythm correlation** (the cornerstone of pacing decisions).
- **Treadmill exercise testing** — chronotropic incompetence, exercise-related block.
- **Echocardiography ± advanced imaging** — MRI / FDG-PET / Tc-PYP scan for infiltrative disease, especially block at age ≤ 60 .
- **Bedside manoeuvres**: carotid massage/vagal manoeuvres *worsen* nodal but *improve* infranodal block; atropine/isoproterenol/exercise *improve* nodal but may *worsen* infranodal block — helps localise.
- **Electrophysiology study (His-bundle electrogram)**: **AH interval** (AV-nodal conduction) normally < 130 ms; **HV interval** (His–Purkinje) normally ≤ 55 ms; **HV > 100 ms** carries an annual incidence of complete block approaching **10%** → indication for pacing. SNRT/SACT for sinus node (rarely needed).

Management

- ▶ **Acute / reversible-cause first**: stop offending drugs (β -blockers, CCBs, digoxin), correct electrolytes, hypoxia, hypothyroidism, ischaemia; treat sleep apnoea, Lyme, sarcoid.
- ▶ **Emergency (symptomatic / unstable bradycardia)**:
 - **Atropine 0.5 mg IV** (repeat to 3 mg) — effective for **AV-nodal** block; little effect on infranodal block.
 - **β -adrenergic infusion** — isoproterenol, dopamine, or epinephrine.
 - **Transcutaneous pacing** — pads anterior over apex (cathode) and posterior between spine and scapula (anode); fast but uncomfortable.
 - **Temporary transvenous pacing** — for unstable infranodal/anterior-MI block; more reliable bridge to recovery or PPM.
- ▶ **Permanent pacemaker (PPM) — key indications**:
 - **SND**: symptoms documented to correlate with bradycardia; symptomatic bradycardia from *essential* drug therapy; tachy-brady syndrome; symptomatic chronotropic incompetence. (*Asymptomatic sinus bradycardia / sleep pauses are NOT an indication.*)
 - **AV block**: acquired Mobitz II, **high-grade**, or **third-degree block** — **pace regardless of symptoms**; symptomatic block of any degree; neuromuscular disease/Lamin A/C with even first-degree or Mobitz I block; asymptomatic infra-His or wide-QRS second-degree block.
- ▶ **Pacing nomenclature (NBG code)**: I — chamber paced; II — chamber sensed; III — response (I/T/D); IV — Rate response (R). **DDDR** = dual-chamber pace/sense with rate response.
- ▶ **Mode/lead selection**: **atrial-based (single or dual chamber) pacing is superior to ventricular-only pacing in SND**; minimise unnecessary RV pacing. **Physiologic / conduction-system pacing** — **His-bundle** or **left-bundle-branch-area pacing**, or CRT (LV ejection fraction $< 50\%$ with

expected ventricular pacing >40%) — to prevent pacing-induced heart failure. **Leadless pacemakers** for vascular-access limitation or permanent AF.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Conduction system schematic:** label SA node (RA–SVC junction), AV node (triangle of Koch — coronary sinus ostium, tendon of Todaro, septal tricuspid annulus), His bundle, right & left bundle branches (with left anterior & posterior fascicles), Purkinje network; annotate intrinsic rates (SA 60–100, AV junction 40–60, ventricle <40).
- ▶ **ECG ladder/rhythm strips of AV block:** label (a) first-degree (fixed long PR), (b) Mobitz I — progressive PR lengthening then dropped QRS, (c) Mobitz II — fixed PR then dropped QRS, (d) complete heart block — independent P waves and QRS (AV dissociation, atrial rate > ventricular rate).

Clinical / Diagnostic significance

- ▶ **Symptom–rhythm correlation** decides pacing in SND; in AV block the **site/level of block** (nodal vs infranodal) decides prognosis and pacing — infranodal block is paced even when asymptomatic.
- ▶ **Mobitz I + narrow QRS = benign, nodal, vagal**, rarely progresses; **Mobitz II / wide QRS = infranodal**, heralds Stokes–Adams syncope and complete block.
- ▶ **2:1 block:** narrow QRS / PR >200 ms → nodal (Type I); wide QRS / short PR → infranodal (Type II).
- ▶ **Acute MI:** inferior = reversible nodal block (atropine-responsive); anterior = ominous infranodal block (needs pacing).
- ▶ New AV block at **age ≤60** mandates imaging for **sarcoid/infiltrative** disease.

High-yield exam pointers

- ▶ Bradycardia = HR <60/min; two mechanisms — **impulse formation (SND)** and **impulse conduction (AV block)**.
- ▶ **If (funny current)** drives SA node phase-4 automaticity; **ivabradine** is a selective If blocker (and a cause of drug bradycardia).
- ▶ **Intrinsic heart rate** = $118.1 - (0.57 \times \text{age})$.
- ▶ **First-degree PR** >200 ms; HV ≤55 ms / AH <130 ms normal; HV >100 ms → ~10%/yr risk of complete block.
- ▶ **Mobitz II and complete heart block** → **permanent pacing regardless of symptoms**.
- ▶ **Atropine helps nodal block, not infranodal block**; vagal manoeuvres do the opposite to nodal vs infranodal conduction.

- ▶ **Lev's** (proximal, elderly) vs **Lenègre's** (distal, younger) degenerative conduction disease; SCN5A/Lamin A/C genetic forms.
- ▶ **Atrial-based / physiologic (His or LBB-area) pacing** preferred over RV-only pacing to avoid pacemaker-induced heart failure; **DDDR** is the standard dual-chamber rate-responsive mode.
- ▶ Causes of **reversible** bradycardia mnemonic: drugs, hypothyroidism, hypoxia/sleep apnoea, ischaemia, electrolytes, Lyme, raised ICP, hypothermia.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "The Bradyarrhythmias: Disorders of the Sinoatrial Node" and "The Bradyarrhythmias: Disorders of the Atrioventricular Node."
- ▶ **Braunwald's Heart Disease, 13e** — "Bradyarrhythmias and Atrioventricular Block" (escape rhythms, Wenckebach criteria, His-bundle intervals, Lev/Lenègre, Stokes–Adams).
- ▶ **CMDT 2026** — "Disorders of Cardiac Rhythm" (sinus node dysfunction, AV block, atropine dosing, pacing modes, current management).



Bundle Branch Blocks

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Bundle branch blocks (BBBs) are *intraventricular conduction disturbances* caused by intrinsic delay or block of the impulse in the right or left bundle branch (or their fascicles). Because one ventricle is then activated late through slow cell-to-cell (myocardial) spread rather than the rapid His–Purkinje system, the QRS complex widens and assumes a characteristic morphology. **Complete block** is defined by a QRS duration ≥ 120 ms; **incomplete block** by a QRS of about 110–120 ms (≈ 100 –120 ms for incomplete RBBB) with the same morphology in lesser degree. The terminal/major QRS vector points toward the myocardial region whose depolarisation is delayed.

Anatomy and physiology of the conduction system

- ▶ The His bundle bifurcates into a **right bundle branch (RBB)** — a thin, discrete, relatively *fragile* structure — and a **left bundle branch (LBB)** which fans into two (functionally) main divisions: the **left anterior fascicle (LAF)** and **left posterior fascicle (LPF)**; a variable third *left median/septal fascicle* often arises from the LPF and drives initial left-to-right septal activation.
- ▶ Normal ventricular activation: the LBB system activates the left side of the interventricular septum first, giving the normal *left-to-right* septal vector (the small **septal q** in I, V5, V6 and small **r** in V1), followed by near-simultaneous, rapid endocardium-to-epicardium, apex-to-base activation of both free walls — producing a narrow QRS (< 110 ms).
- ▶ The LPF is thick and dual-supplied (protected near the LV inflow); the LAF and RBB are thin and vulnerable — explaining why LAFB and RBBB are common and LPFB is rare.

Classification of intraventricular conduction disturbances

Category	Lesion	QRS width	Frontal axis
RBBB (complete)	Right bundle	≥ 120 ms	Usually normal (axis not directly altered)
LBBB (complete)	Left bundle / both fascicles	≥ 120 ms	Normal, left, or rarely right
Incomplete RBBB	Lesser RBB delay	100–120 ms	rSr' in V1
Incomplete LBBB	Lesser LBB delay	100–119 ms	Slurred upstroke; $\sim 1/3 \rightarrow$ full LBBB in 2 yr
LAFB (left anterior hemiblock)	Anterior fascicle	< 120 ms	-45° to -90° (marked LAD)
LPFB (left posterior hemiblock)	Posterior fascicle	< 120 ms	$> +90^\circ$ ($> +110$ – 120°) (RAD)
Bifascicular block	RBB + one LBB fascicle	≥ 120 ms	RBBB + LAD (commonest) or + RAD
Trifascicular block	Bifascicular + His delay / alternating BBB	≥ 120 ms	Variable

Right bundle branch block (RBBB) — criteria and mechanism

- ▶ **Diagnostic criteria** (AHA/ACCF/HRS): QRS ≥ 120 ms; rsr', rsR' or rSR' ("M-shaped"/rabbit-ear) pattern in V1–V2; wide slurred S wave (≥ 40 ms) in leads I and V6; normal time to peak R wave in V5–V6 but > 50 ms in V1.
- ▶ **Mechanism**: right septum is activated only after slow *transseptal* spread from the left; the late, unopposed RV forces (right lateral wall and RV outflow tract) generate the terminal *rightward and anterior* vector $\rightarrow$ terminal R' in V1 and wide terminal S in V6.
- ▶ **Secondary ST-T changes**: T-wave inversion in right precordial leads (V1–V3), discordant with the terminal R'.
- ▶ **Causes**: often seen with a structurally **normal heart** (incidental; commoner than LBBB in normals); RV catheter/moderator-band trauma; congenital (atrial septal defect with RV volume overload — iRBBB pattern + RAD), valvular and ischaemic heart disease, cor pulmonale/PE (acute right heart strain), and a **Brugada**-type RBBB-like pattern with right precordial ST elevation.

Left bundle branch block (LBBB) — criteria and mechanism

- ▶ **Classic criteria** (AHA/ACCF/HRS): QRS ≥ 120 ms; broad, notched/slurred R waves in I, aVL, V5, V6; small or absent initial r in V1–V2 followed by deep S (often QS in V1); absent septal q in I, V5, V6; prolonged time to peak R wave (> 60 ms) in V5–V6.

- ▶ **Stricter (specific) criteria:** QRS >140 ms (men) / >130 ms (women) with mid-QRS notching/slurring in ≥ 2 lateral leads — correlates better with true complete block (only $\sim 2/3$ of patients meeting classic criteria have true complete LBB block).
- ▶ **Mechanism:** loss of normal left-to-right septal activation $\rightarrow$ septum depolarises *right-to-left* (hence absent septal q); LV free wall is activated late (delay ~ 40 – 80 ms) by slow transseptal/myocardial spread $\rightarrow$ wide monophasic R in V6 and QS/rS in V1.
- ▶ **Secondary ST-T:** ST-T vector *discordant* — opposite in polarity to the terminal QRS (ST elevation/upright T in right precordial leads, T inversion in lateral leads).
- ▶ **Clinical associations (Harrison's four high-risk conditions):** coronary heart disease (frequently with impaired LV function), hypertensive heart disease, aortic valve disease (including after TAVR), and cardiomyopathy. >70% have preceding LVH; <10% have no demonstrable heart disease; present in $> 1/3$ of heart-failure patients.

RBBB vs LBBB at a glance

Feature	RBBB	LBBB
QRS (complete)	≥ 120 ms	≥ 120 ms
V1	rSR' ("M"), terminal R'	wide QS / rS
V6 / I	wide slurred S	broad notched R, no q
Septal q (I, V5, V6)	Preserved	Absent
Terminal vector	Right + anterior	Left + posterior
Heart disease	Often none/incidental	Usually structural; higher risk
Population prevalence	$\sim 1.4\%$ men, 0.5% women	$\sim 0.5\%$ (ARIC)

Fascicular, bifascicular and trifascicular blocks

- ▶ **LAFB (left anterior hemiblock):** the commonest cause of marked left axis deviation in adults — axis -45° to -90° , qR in aVL, rS in II/III/aVF, time-to-peak R in aVL ≥ 45 ms, QRS <120 ms (fascicular blocks alter the *sequence* but not overall duration of LV activation).
- ▶ **LPFB (left posterior hemiblock):** right axis deviation ($> +90$ – 120°), rS in I/aVL with qR in III/aVF, QRS <120 ms; *rare in isolation* — requires exclusion of other causes of RAD (RVH, lateral MI, normal variant, vertical heart).
- ▶ **Bifascicular block:** RBBB + LAFB (commonest, RBBB with marked LAD) or RBBB + LPFB.
- ▶ **Trifascicular block:** bifascicular block plus demonstrable His-bundle (HV) delay — historically inferred from added **first-degree AV block**, but true trifascicular disease is best shown by **alternating BBB**, which signals advanced infranodal disease and impending complete heart block.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Cardiac conduction system schematic:** label SA node, RA, LA, AV node, His bundle, Right bundle branch, Left bundle branch, Left anterior fascicle, Left posterior fascicle, Purkinje network, RV, LV — mark the level of block for RBBB, LBBB, LAFB, LPFB.
- ▶ **Diagram 2 — QRS-T morphology in V1 and V6:** three rows — *Normal* (rS in V1, qR in V6), *RBBB* (rSR' in V1 with terminal T inversion, wide S in V6), *LBBB* (wide QS in V1, broad notched R in V6 with T inversion) — annotate “secondary T-wave inversion (discordant)” and “absent septal q (LBBB)”.

Clinical / Diagnostic significance

- ▶ **Masking effect:** LBBB obscures/simulates LVH, the ECG diagnosis of ischaemia/MI, exercise-ECG interpretation and rate-corrected QT computation; RBBB lowers LVH sensitivity and complicates RVH diagnosis.
- ▶ **MI in the presence of LBBB — Sgarbossa criteria:** (1) **concordant ST elevation** (in leads with a positive QRS) or **concordant ST depression in V1–V3**, and **excessively discordant ST elevation** $>5\text{ mm}$ ($>0.5\text{ mV}$) in leads with QS/rS (least specific; *modified*: $ST/S\text{ ratio} \leq -0.25$ is more accurate); (2) **QR complexes** in I, V5, V6 or II, III, aVF suggest underlying MI. Note: $<10\%$ of patients with new/possibly-new LBBB actually have acute MI.
- ▶ **Dyssynchrony & CRT:** LBBB produces septal “flash”, reduced stroke volume ($\sim 10\%$), raised LV end-diastolic volume ($\sim 15\%$) and progressive remodelling — the rationale for **cardiac resynchronisation therapy** (biventricular pacing), with greatest benefit in **LBBB + QRS $>150\text{ ms}$** .
- ▶ **Acute MI:** new RBBB or new bifascicular block in **anterior STEMI** implies a large infarct (proximal LAD/septal perforator) and worse prognosis; new **LBBB** with ischaemic symptoms is managed as an STEMI-equivalent when the clinical picture fits.
- ▶ **Pacing / EP evaluation (2018 ACC/AHA/HRS; ESC):** **alternating BBB $\rightarrow$ permanent pacing, Class I**; **syncope + BBB + prolonged HV interval ($>70\text{ ms}$) on EP study $\rightarrow$ Class I pacing**; **unexplained syncope + bifascicular block $\rightarrow$ consider electrophysiology study (Class IIa)**; consider **genetic testing** in early-onset ($<50\text{ yr}$) progressive conduction-system disease. Asymptomatic bifascicular block alone does **not** mandate pacing.
- ▶ **TAVR:** new LBBB and high-degree AV block are the commonest conduction complications, frequently requiring permanent pacemaker implantation and carrying adverse outcomes.

High-yield exam pointers

- ▶ Complete BBB = QRS $\geq 120\text{ ms}$; incomplete = $\sim 110\text{--}120\text{ ms}$ with same morphology.
- ▶ **V1 rule:** terminal R' in V1 = RBBB; QS/wide negative V1 + tall notched R in V6 = LBBB.

- ▶ **RBBB** is commonly **benign/incidental**; **LBBB** almost always means structural heart disease (Harrison's four: CAD, hypertensive HD, aortic valve disease incl. post-TAVR, cardiomyopathy).
- ▶ **LAFB** = **marked LAD** (-45° to -90°), the commonest cause of LAD in adults; **LPFB** = **RAD**, rare and a diagnosis of exclusion.
- ▶ **Bifascicular block** = **RBBB + LAFB** (commonest); add 1° AV block ("trifascicular") or **alternating BBB** = advanced His-Purkinje disease at risk of complete heart block.
- ▶ BBB ST-T changes are **secondary and discordant** (T opposite to terminal QRS); concordant/disproportionate changes flag ischaemia (**Sgarbossa**).
- ▶ **Rate-related (tachycardia-dependent) BBB** appears above a critical heart rate; ventricular pacing produces an **LBBB-like QRS** preceded by a pacing spike.
- ▶ **LBBB + QRS >150 ms + EF ≤35% + HF symptoms** → **CRT candidate**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Electrocardiography" (BBB and fascicular-block morphology, axis, secondary ST-T changes, LBBB associations).
- ▶ **Braunwald's Heart Disease, 13e** — "Electrocardiography" (AHA/ACCF/HRS diagnostic criteria for complete/incomplete RBBB & LBBB and fascicular blocks, mechanisms, prevalence/ARIC & LIFE data, Sgarbossa criteria, bifascicular block) and "Bradyarrhythmias and Atrioventricular Block" (alternating BBB, HV interval, pacing indications); "Transcatheter Aortic Valve Replacement" (post-TAVR LBBB).
- ▶ **CMDT 2026** — Bradycardia/conduction-delay management: pacing indications (ACC/AHA/HRS, ESC), EP study and genetic-testing recommendations.

Coverage note: The eponyms **Lev disease** and **Lenègre disease** (idiopathic/age-related progressive fibrosis and degeneration of the conduction system) are standard textbook causes of chronic bundle/fascicular block but are not named in the available corpus, which instead refers to "progressive cardiac conduction system disease"; they are included as universally accepted internal-medicine knowledge.



Cardiac Resynchronization Therapy

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — *Cardiac resynchronization therapy (CRT)* is a device-based, atrio-biventricular pacing strategy that restores the synchrony of electrical depolarization (and hence the coordination of mechanical contraction) in patients with chronic heart failure with reduced ejection fraction (HFrEF) and an electrical conduction delay — most importantly *left bundle branch block (LBBB)*. By pacing the left ventricle (LV) through a lead placed in a tributary of the coronary sinus

together with a right-ventricular (RV) lead, CRT re-coordinates inter- and intraventricular contraction. It is the only pacing therapy proven to reduce **both morbidity and all-cause mortality** in appropriately selected HFrEF patients already on optimal guideline-directed medical therapy (GDMT). CRT was first approved by the FDA in 2001.

Pathophysiological rationale — ventricular dyssynchrony (the target)

- ▶ Intraventricular conduction abnormalities occur in roughly **one-third** of HFrEF patients and independently worsen morbidity and mortality. About **30% of patients with dilated cardiomyopathy** have an interventricular conduction delay, most commonly LBBB.
- ▶ *Electrical dyssynchrony* is defined operationally by a **prolonged QRS duration (>120 ms)** on the surface ECG; it usually reflects underlying *mechanical dyssynchrony* — a difference in the timing of contraction/relaxation between LV segments or between the two ventricles.
- ▶ Consequences of dyssynchronous contraction:
 - Suboptimal/reduced ventricular filling and impaired diastolic function.
 - Reduced LV contractility and decreased mechanical efficiency of systole; increased wall stress.
 - Paradoxical septal wall motion (inter-ventricular dyssynchrony).
 - Greater degree and prolonged duration of **functional (secondary) mitral regurgitation**.
- ▶ CRT corrects these by pre-exciting the LV lateral wall via the coronary-sinus lead, aligning the timing of activation of opposing walls → reverse remodeling (fall in LV end-systolic volume), improved EF, higher systolic blood pressure (which then permits up-titration of previously hypotension-limited GDMT), reduced functional MR, and symptomatic/functional improvement.
- ▶ *Pacing-induced cardiomyopathy*: a high burden (>40%) of chronic RV apical pacing itself produces an iatrogenic LBBB-like dyssynchrony and HF in ~6–39% of paced patients — an additional indication for CRT/physiologic pacing.

Hardware, device types and modes of physiologic pacing

- ▶ **Lead system** — a transvenous CRT system has three leads: right atrial, right ventricular, and a **left-ventricular lead advanced via the coronary sinus into a (postero-)lateral epicardial vein**. Quadripolar LV leads allow multiple pacing vectors to avoid phrenic-nerve capture and high thresholds.
- ▶ **CRT-P** (biventricular *pacemaker*) vs **CRT-D** (biventricular pacing combined with an implantable cardioverter-defibrillator) — choice depends on whether a concomitant ICD indication (sudden-death prevention) exists.
- ▶ *Cardiac physiologic pacing (CPP)* is the umbrella term and includes:
 - **CRT** = conventional biventricular pacing (BiVP) via a coronary-sinus LV lead.

- **Conduction system pacing (CSP)** = *His-bundle pacing (HBP)* or *left bundle branch area pacing (LBBAP)* — emerging single-site alternatives that engage the native conduction system; HBP has a ~10–20% acute failure rate and threshold issues, while LBBAP has a larger capture target and lower thresholds. Class I evidence still favours CRT (BiVP) over CSP for established CRT indications; head-to-head pivotal trials are ongoing.
- ▶ Successful BiVP requires programming a **short AV interval** (to pre-excite the LV in LBBB) and attention to the VV interval. Trials of routine echocardiographic AV/VV optimization (vs a fixed AV delay of 120 ms) showed **no remodeling benefit**, so it is reserved for non-responders. Multipoint pacing (MORE-CRT MPP) gives marginal added benefit in selected non-responders.

Indications and patient selection

The ideal candidate is symptomatic HFrEF on GDMT with a wide LBBB QRS in sinus rhythm — benefit is greatest with wider QRS (>149 ms), LBBB morphology, and non-ischaemic cardiomyopathy.

Recommendation strength	Patient profile
Class I (strongest)	LVEF ≤35%, LBBB with QRS ≥150 ms, sinus rhythm, NYHA II / III / ambulatory IV, on GDMT
Class I (newer, 2023 HRS/APHS/LAHS)	Similar patients with QRS 120–149 ms plus special features (e.g. female sex)
Class I (newer)	Pacemaker-induced cardiomyopathy / anticipated high-burden (>40%) RV pacing; CRT for those with LVEF ≤50% requiring ventricular pacing (BLOCK-HF)
Lower benefit / Class II	Non-LBBB (IVCD/RBBB) morphology; QRS 120–149 ms without special features; atrial fibrillation (excluded from most pivotal trials)
Contraindicated / harmful	Narrow QRS (<130 ms) even with echocardiographic dyssynchrony (Echo-CRT showed harm); QRS <120 ms

- ▶ CMDT/2022 AHA-ACC-HFSA framing: CRT indicated for NYHA class II–III HF, EF ≤35%, sinus rhythm, LBBB with QRS ≥150 ms; refer any patient with persistent symptoms and LVEF ≤35% with QRS ≥120 ms (especially LBBB).
- ▶ Pre-implant work-up: confirm GDMT optimization first, document LVEF, QRS duration and morphology, rhythm (sinus vs AF), and NYHA class; NT-proBNP if CRT planned.

Evidence base — landmark randomized trials

Trial	Population (n)	Comparison	Key result
MUSTIC / MIRACLE / MIRACLE-ICD	NYHA II–IV, QRS wide	CRT on vs off	Improved 6-min walk, QoL, NYHA, LV reverse remodeling

Trial	Population (n)	Comparison	Key result
			(intermediate endpoints)
COMPANION (n=1520)	QRS $\geq$ 120 ms, NYHA III–IV, EF $\leq$ 35%	OPT vs CRT-P vs CRT-D (1:2:2)	↓ death/any hospitalization (HR $\sim$ 0.80); CRT-D ↓ all-cause mortality 36% (P=.003), CRT-P 24% (P=.059)
CARE-HF (n=813)	QRS $\geq$ 150 ms (or 120–150 + echo dyssynchrony), NYHA III–IV, EF $\leq$ 35%	CRT vs no CRT	First trial to show all-cause mortality reduction — ACM HR 0.64 (P<.002)
REVERSE / MADIT-CRT / RAFT	NYHA I–II (mild), QRS $\geq$ 120–130 ms, EF $\leq$ 30–40%	CRT(-D) vs control/ICD	Reverse remodeling + ↓ HF events; MADIT-CRT HR 0.66; RAFT ACM/HFH HR 0.75 — extended indication to mildly symptomatic HF
Echo-CRT (n=809)	Narrow QRS $\leq$ 130 ms + echo dyssynchrony	CRT vs control	No benefit; increased mortality (ACM HR 1.81) → CRT contraindicated in narrow QRS
BLOCK-HF (n=691)	AV block, EF $\leq$ 50%, needing RV pacing	BiV (CRT) vs RV pacing	CRT superior (composite HR 0.74) → support for CRT when ventricular pacing is required

- ▶ Take-home: benefit is greatest in **wide-LBBB, sinus-rhythm** patients; narrowest/non-LBBB QRS derive little benefit or harm; the *most* benefit in mildly symptomatic patients accrues when QRS >149 ms with LBBB.

Predictors of response, non-responders and complications

- ▶ **Predictors of good response:** wider QRS, true LBBB morphology, non-ischaemic aetiology, female sex, sinus rhythm, high effective BiVP percentage, lateral/postero-lateral lead in the region of latest activation.
- ▶ **Response is not binary:** ~30% are “non-responders”; some are *super-responders* (EF normalization); others are “non-progressors” (stabilized course).
- ▶ **Causes of non-response:** lack of LV capture; suboptimal LV lead position (apical/anterior, not at site of latest delay); narrow or non-LBBB QRS; low BiVP delivery (frequent PVCs, atrial

fibrillation, too-long AV interval); LV lateral-wall scar; cardiac amyloidosis. Many are salvageable by reprogramming, arrhythmia control (PVC/AF ablation), or LV lead revision.

- ▶ **Implant complications:** coronary-sinus dissection, LV lead dislodgement/microdislodgement, phrenic-nerve / diaphragmatic / intercostal extracardiac stimulation, cardiac perforation with tamponade, pneumothorax, subclavian/axillary vein thrombosis, pocket infection/lead endocarditis, and tricuspid regurgitation from the RV lead.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled chest diagram of a CRT-D system:** pulse generator in left prepectoral pocket; right atrial lead (RA appendage); right ventricular lead (RV apex/septum, with shock coil if CRT-D); left ventricular lead passing through the coronary sinus into a postero-lateral cardiac vein; label the coronary sinus os and lateral LV wall.
- ▶ **ECG strip comparison:** baseline wide LBBB QRS (>150 ms) versus post-CRT narrowed/fused biventricular-paced QRS, with arrows marking the shortened, pre-excited LV activation.

Clinical / Diagnostic significance

- ▶ CRT is layered on top of optimized GDMT (ARNI/ACEi-ARB, beta-blocker, MRA, SGLT2 inhibitor, diuretics) — never a substitute.
- ▶ Confers **reverse remodeling**, improved EF and 6-min walk distance, fewer HF hospitalizations, better QoL, and a survival benefit; the rise in systolic BP frequently allows further up-titration of neurohormonal therapy.
- ▶ If a CRT candidate also meets ICD criteria (LVEF $\leq 35\%$, NYHA II–III, ≥ 40 days post-MI / non-ischaemic on GDMT), implant a **combined CRT-D**.
- ▶ CRT has **no established role in HFpEF/HFmrEF** and is harmful in narrow-QRS patients.
- ▶ Cardiac contractility modulation (CCM) is the device option for symptomatic HFrEF (EF 25–45%) with **narrow QRS** who are *not* CRT candidates.

High-yield exam pointers

- ▶ CRT = atrio-biventricular pacing; LV lead delivered via the **coronary sinus** to the LV lateral wall.
- ▶ Best candidate: EF $\leq 35\%$, LBBB, QRS ≥ 150 ms, sinus rhythm, NYHA II–III on GDMT — Class I.
- ▶ CARE-HF = first trial to prove all-cause mortality benefit; COMPANION proved benefit of both CRT-P and CRT-D.
- ▶ MADIT-CRT / RAFT / REVERSE extended CRT to mildly symptomatic (NYHA I–II) HFrEF.

- ▶ **Echo-CRT** = CRT is *harmful* in narrow QRS (<130 ms) → contraindicated; **BLOCK-HF** supports CRT when chronic RV pacing is needed.
- ▶ Poor responders: non-LBBB/IVCD, ischaemic scar, AF, low BiVP%, narrow QRS, RV-apical lead, amyloidosis (~30% non-response).
- ▶ CRT-D combines resynchronization + defibrillation; CRT-P is pacing only.
- ▶ Conduction system pacing (His-bundle, **LBBAP**) is the evolving alternative to BiVP.
- ▶ Classic implant complications: **coronary-sinus dissection**, **phrenic-nerve stimulation**, **LV lead dislodgement**.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Heart Failure: Management" (mechanism of dyssynchrony, CARE-HF, RAFT/MADIT-CRT, indications, SCD/ICD interface).
- ▶ Braunwald's Heart Disease, 13e — "Pacemakers, Conduction System Pacing, Cardiac Resynchronization Therapy, and Implantable Cardioverter-Defibrillators" (CPP/CSP, lead configuration, AV/VV optimization, non-responders, complications) and "Devices for Monitoring and Managing Heart Failure" (pivotal CRT trial table: COMPANION, CARE-HF, REVERSE, MADIT-CRT, RAFT, Echo-CRT, BLOCK-HF; 2023 HRS/APHS/LAHS guideline indications).
- ▶ CMDT 2026 — "Heart Failure & Cardiomyopathy" (current biventricular-pacing/CRT indication thresholds, referral criteria, ICD/MADIT-II context).



Cardiac Syncope

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Syncope* is a transient, self-limited loss of consciousness (TLOC) with loss of postural tone, due to acute global cerebral hypoperfusion, characterised by rapid onset, brief duration and prompt spontaneous complete recovery. **Cardiac (cardiovascular) syncope** is that subset caused by **arrhythmias** or **structural heart disease** that abruptly reduce cardiac output. Though it accounts for only ~10–20% of syncopal episodes (second to reflex/orthostatic causes), it is the most dangerous category — it may be the only warning before **sudden cardiac death (SCD)** and carries a markedly increased mortality, making its identification the central goal of any syncope work-up.

Pathophysiology

- ▶ Cerebral metabolism is exquisitely perfusion-dependent; cessation of cerebral blood flow produces loss of consciousness within ~6–10 seconds, and a fall in systolic BP to ~50 mmHg generally causes syncope.

- ▶ Blood pressure = cardiac output $\times$ systemic vascular resistance. Cardiac syncope results from an **abrupt fall in cardiac output** due to: brady- or tachyarrhythmia (loss of effective ventricular filling/contraction, loss of AV synchrony) or a **fixed/dynamic obstruction** to flow.
- ▶ Structural disease and arrhythmia often **coexist** — scarred/hypertrophied myocardium is an arrhythmogenic substrate, so the two mechanisms compound one another.
- ▶ In aortic stenosis and hypertrophic cardiomyopathy, an **inappropriate reflex vasodilatation** (provoked by vigorous ventricular contraction/mechanoreceptor activation) may add a neurally mediated component, classically precipitated by exertion.

Classification of cardiac syncope

Category	Specific causes
Bradyarrhythmias	Sinus node dysfunction (sinus arrest, sinoatrial block); tachycardia–bradycardia syndrome (post-tachycardia pause); AV block — Mobitz type II, high-grade, complete (third-degree) AV block; drug-induced bradycardia; pacemaker/ICD malfunction
Tachyarrhythmias	Ventricular tachycardia (commonest arrhythmic cause); ventricular fibrillation; supraventricular tachycardia (AVNRT, WPW/AVRT), atrial fibrillation with rapid response
Inherited channelopathies / electrical disease	Long-QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT (CPVT), short-QT syndrome, idiopathic VF
Structural / obstructive (“mechanical”)	Severe aortic stenosis, hypertrophic obstructive cardiomyopathy, pulmonary stenosis, atrial myxoma/ball-valve thrombus, pericardial tamponade, acute MI/ischaemia, aortic dissection, massive pulmonary embolism, pulmonary hypertension

Arrhythmic causes — key points

- ▶ **Bradyarrhythmias**: Syncope from bradycardia or asystole is the classic *Stokes–Adams attack* — sudden collapse, often without prodrome, with rapid recovery and reactive flushing. Sinus node disease frequently coexists with atrial tachyarrhythmia (tachy-brady syndrome); a long pause on termination of the tachycardia is a typical trigger.
- ▶ **Ventricular tachycardia** is the most common arrhythmia uncovered (~20% on electrophysiologic study). The likelihood of syncope rises with **faster ventricular rate** (rates <200/min less often cause syncope) and **poorer LV function**; haemodynamic collapse is due to ineffective contraction, short diastolic filling, loss of AV synchrony and concurrent ischaemia.
- ▶ **Inherited channelopathies** arise from mutations in ion-channel subunit genes:

- *Long-QT syndrome* — prolonged repolarisation predisposing to *torsades de pointes* (polymorphic VT that may degenerate into VF); linked to K⁺ channel α - and β -subunit genes, the voltage-gated Na⁺ channel, and the scaffolding protein **ankyrin-B (ANK2)**.
- *Brugada syndrome* — syncope, polymorphic VT and idiopathic VF with **coved ST-elevation/RBBB pattern in V1–V3** and a structurally normal heart; most often a Na⁺-channel α -subunit (SCN5A) mutation.
- *CPVT* — exercise- or emotion-induced ventricular arrhythmias from abnormal calcium handling.
- Acquired QT prolongation (drugs, electrolytes) likewise causes torsades and syncope.

Structural / obstructive causes

- ▶ **Severe aortic stenosis and HOCM** — exertional syncope from a fixed/dynamic outflow obstruction that prevents an adequate rise in stroke volume on demand ($\pm$ reflex vasodilatation).
- ▶ **Atrial myxoma / ball-valve thrombus** — positional mitral inflow obstruction.
- ▶ **Pericardial tamponade, aortic dissection, acute myocardial ischaemia/infarction, massive pulmonary embolism and pulmonary hypertension** — by acutely impairing right- or left-sided output.
- ▶ These typically produce **abrupt, often unheralded** collapse, frequently with injury, and are commonly **exertional or post-exertional**.

Clinical clues — cardiac vs neurally mediated syncope

Feature	Cardiac syncope (arrhythmia/structural)	Neurally mediated (vasovagal)
Prodrome	Absent or very brief (<5 s); may have abrupt palpitations	Longer warning (>5 s): nausea, warmth, diaphoresis, pallor, blurred vision
Trigger/posture	At rest, supine , or on exertion	Standing, warm room, emotion, pain
Demographics	Older age, male > female, fewer prior episodes; family history of SCD	Younger, female > male, recurrent episodes
Recovery	Prompt, oriented; injury common	Prompt but prolonged fatigue common
Background	Structural heart disease / abnormal ECG	Structurally normal heart, normal ECG

Diagnostic evaluation

- ▶ **History, eyewitness account and examination with supine and standing (orthostatic) vital signs** are the most valuable step — establish the cause in ~25–50% of cases and stratify risk.

- ▶ **High-risk “red-flag” features mandating admission/urgent work-up:** exertional or supine syncope; abrupt palpitations preceding syncope; chest pain; known severe structural/coronary disease or low ejection fraction; family history of SCD; persistent bradycardia <40/min; undiagnosed systolic murmur; SBP <90 mmHg.
- ▶ **12-lead ECG** in all patients — look for prolonged QT (>500 ms), short PR + delta wave (WPW), RBBB with ST-elevation V1–V3 (Brugada), T-inversion ± epsilon wave V1–V3 (arrhythmogenic RV cardiomyopathy), bi-/trifascicular block or QRS ≥120 ms, AV block, ischaemia/old MI, non-sustained VT. Initial ECG is diagnostic in ~5% and suggestive in another ~5%.
- ▶ **Ambulatory ECG monitoring**, matched to event frequency: in-patient telemetry/Holter for frequent (≈daily) episodes; external loop recorder for episodes ~monthly; **implantable loop recorder** for infrequent, unexplained, high-suspicion syncope (battery up to ~3 years). Symptom–rhythm correlation is the diagnostic goal.
- ▶ **Echocardiography** when structural disease is suspected — diagnostic of severe aortic stenosis, HOCM, tamponade, aortic dissection, myxoma; also stratifies SCD risk by LV ejection fraction.
- ▶ **Exercise (treadmill) testing** for syncope during/after exertion (exercise-induced AV block, ischaemia, exaggerated vasodilatation); **coronary angiography** if ischaemia-mediated.
- ▶ **Electrophysiologic study (EPS)** — reserved for suspected arrhythmic cause with structural heart disease/abnormal ECG (low yield with a normal ECG and normal heart). EPS is **diagnostic** when it shows: a prolonged corrected sinus node recovery time (CSNRT >525 ms); bundle-branch block with a baseline H-V interval ≥100 ms or pacing-/procainamide-induced infra-Hisian block; **induction of sustained monomorphic VT** in a patient with prior MI; or induction of SVT that **reproduces the spontaneous symptoms**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Classification tree of syncope** (single page): Root *Syncope (TLOC from global cerebral hypoperfusion)* → three branches — (1) *Neurally mediated / reflex* (vasovagal, situational, carotid sinus), (2) *Orthostatic hypotension*, (3) *Cardiac syncope*. **Expand the cardiac branch into** Arrhythmic* (*sub-label*: Bradyarrhythmias — SND, AV block; Tachyarrhythmias — VT/VF, SVT; Channelopathies — LQTS, Brugada, CPVT) *and Structural/Obstructive* (*sub-label*: aortic stenosis, HOCM, atrial myxoma, tamponade, PE, MI/ischaemia*).
- ▶ **Annotated rhythm strips:** label (a) *complete (third-degree) AV block with a long ventricular pause* — “Stokes–Adams”, (b) *monomorphic ventricular tachycardia*, and (c) *torsades de pointes on a long-QT baseline*.

Clinical / Diagnostic significance

- ▶ Cardiac syncope independently predicts **increased SCD and all-cause mortality**, in contrast to the benign prognosis of young neurally mediated syncope — risk stratification, not merely diagnosis, drives management.
- ▶ **Management is cause-specific**: permanent **pacemaker** for symptomatic sinus node disease and high-grade/Mobitz II/complete AV block (with documented pauses >3 s); **implantable cardioverter-defibrillator (ICD)** for VT/VF and for syncope with ischaemic or non-ischaemic cardiomyopathy and reduced ejection fraction; **catheter ablation** for SVT/WPW and selected VT; **antiarrhythmic drugs** as adjuncts; surgical/transcatheter correction of structural obstruction (e.g. aortic valve replacement, septal reduction in HOCM, myxoma excision); withdrawal of offending drugs and correction of electrolytes for acquired QT prolongation.
- ▶ Reversible/temporary causes (heart block in inferior MI, drug effect, electrolyte disturbance) often do **not** need a permanent device once corrected.
- ▶ **Driving advice**: temporary/treated causes — restrict ~1 week after recovery; symptomatic VT or aborted SCD (whether drug-, ICD- or ablation-treated) — restrict **3–6 months**, mindful of local law.

High-yield exam pointers

- ▶ Cardiac syncope = **arrhythmia + structural disease**; ~10–20% of cases but the **highest-mortality** group and a harbinger of SCD.
- ▶ **VT is the commonest arrhythmic cause**; bradycardia/asystole causing syncope = **Stokes–Adams attack**.
- ▶ **Exertional or supine syncope, syncope without prodrome, palpitations-then-collapse, family history of SCD, and an abnormal ECG** are the cardinal red flags.
- ▶ Channelopathy triad to remember: **LQTS** (→ **torsades**, **ANK2/K⁺/Na⁺ genes**), **Brugada** (**SCN5A**, **coved ST-elevation V1–V3**), **CPVT** (**exertion-triggered, calcium-handling**).
- ▶ Exertional syncope with an ejection systolic murmur → think **severe aortic stenosis** or **HOCM**.
- ▶ **ECG in everyone**; choose the monitor (telemetry → external loop → implantable loop recorder) by event frequency; **echo** if structural disease suspected.
- ▶ EPS “diagnostic” numbers: **CSNRT >525 ms**, **H-V ≥100 ms**, **inducible sustained monomorphic VT** post-MI.
- ▶ Treatment is mechanism-driven: **pacemaker** (brady), **ICD** (VT/VF, low-EF cardiomyopathy), **ablation** (SVT/WPW), structural correction; remember **driving restrictions**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Syncope” (Freeman & Raj): definition, classification, cardiac syncope (arrhythmias, channelopathies, structural disease), Stokes–Adams attack, evaluation and high-risk features.

- ▶ **Braunwald's Heart Disease, 13e** — “Hypotension and Syncope” (Calkins & Chen): epidemiology/prognosis, proportion due to cardiac causes, VT predominance, high-risk hospitalisation criteria, diagnostic testing and electrophysiologic study criteria, management/driving guidance (per 2017 ACC/AHA/HRS and 2018 ESC syncope guidelines).
- ▶ **CMDT 2026** — “Disorders of Cardiac Rhythm” (Syncope): essentials of diagnosis, cardiogenic mechanical vs arrhythmic causes, current evaluation and management, driving restrictions.



Cardiac tamponade

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Cardiac tamponade is the accumulation of fluid (or blood, pus, gas) within the pericardial space in a quantity sufficient to cause serious obstruction to the inflow of blood into the ventricles, producing a fall in cardiac output that may be rapidly fatal if not recognised and treated. It is the haemodynamic end-point of a pericardial effusion in which intrapericardial pressure rises to equal and then exceed cardiac filling pressures. Tamponade is a **clinical and echocardiographic diagnosis** and a true cardiovascular emergency; relief by pericardiocentesis is potentially life-saving.

Aetiology

- ▶ The volume needed to cause tamponade depends on the **rate** of accumulation, not absolute volume — as little as **200 mL** when fluid develops rapidly (acute), but **>2000 mL** in slowly developing effusions where the pericardium has stretched to adapt (the curvilinear, J-shaped pericardial pressure–volume relationship).
- ▶ **Most common causes (Harrison)**: idiopathic pericarditis, and pericarditis secondary to neoplastic disease or tuberculosis; **bleeding into the pericardial space** after aortic dissection, cardiac surgery, trauma, or anticoagulant therapy.
- ▶ **Categorised (Braunwald, Table 78.1)**:

Category	Representative causes
Infective	Viral (coxsackie, echovirus, adenovirus, CMV, HIV, SARS-CoV-2); tuberculous ; pyogenic bacterial (pneumococcus, staphylococcus, streptococcus); fungal
Neoplastic	Secondary — lung & breast carcinoma, lymphoma, Kaposi sarcoma; primary mesothelioma; radiation-induced

Category	Representative causes
Haemorrhagic / mechanical	Type A aortic dissection, free-wall rupture post-MI, chest trauma, post-cardiotomy, device/procedure-related (PCI, pacemaker leads, ablation, valve procedures), oral anticoagulants
Inflammatory / autoimmune	SLE, rheumatoid arthritis, scleroderma; <i>Dressler syndrome</i> ; drug-induced (procainamide, hydralazine, isoniazid)
Metabolic / miscellaneous	Uraemia / dialysis-associated, hypothyroidism (cholesterol “gold-paint” effusion), chylopericardium

Pathophysiology

- ▶ As fluid accumulates, intrapericardial pressure rises; right- and left-sided diastolic pressures rise and, in severe tamponade, **equalise** at a level close to pericardial pressure, typically **20–25 mmHg** (CMDT: intrapericardial pressure >15 mmHg defines haemodynamic significance). Equalisation is closest during inspiration.
- ▶ The high pericardial pressure markedly reduces **transmural filling pressure**, so end-diastolic ventricular volume (preload) and hence **stroke volume** fall; compensatory tachycardia and increased contractility (adrenergic drive) initially maintain blood pressure, but eventually cardiac output and arterial pressure decline → shock.
- ▶ The primary direct effect is to **impede right-heart filling**, with left-heart effects largely secondary to under-filling. In terminal tamponade a depressor reflex with paradoxical bradycardia may supervene.
- ▶ **Total cardiac volume is fixed** within the rigid pericardial envelope, producing two hallmark phenomena:
 - **Exaggerated ventricular interdependence** — inspiratory enlargement of the RV bulges the interventricular septum leftward, encroaching on the LV and reducing LV volume, stroke volume and systolic pressure → *pulsus paradoxus*.
 - **Altered venous waveform** — blood can enter the heart only when blood is simultaneously leaving (during ventricular ejection): the systolic x **descent is preserved/prominent** but the early-diastolic **y descent is lost** (diastolic filling is abolished because the tricuspid opens against a fixed heart volume).
- ▶ **Low-pressure tamponade**: in a volume-depleted patient (haemorrhage, over-diuresis, haemodialysis) a modest pericardial pressure can compromise stroke volume while venous pressure is only mildly raised — diagnosis is easily missed.

- ▶ **Regional / loculated tamponade:** a localised effusion or clot (commonly post-cardiac surgery) selectively compresses one chamber, producing atypical haemodynamics without classic global signs.

Clinical features

- ▶ **Beck's triad** (acute tamponade): (1) **hypotension**, (2) **soft / muffled or absent heart sounds**, (3) **raised jugular venous pressure** with a **prominent x descent** and **absent y descent**.
- ▶ **Pulsus paradoxus** — an inspiratory fall in systolic arterial pressure of **>10 mmHg** (an exaggeration of the normal <10 mmHg fall). Severe forms cause palpable weakening/disappearance of the pulse on inspiration; usually quantified by sphygmomanometry during slow respiration. It is the *rule* in tamponade but is **not pathognomonic** — also seen in constrictive pericarditis ($\approx 1/3$), severe asthma/COPD, massive PE, and hypovolaemic shock; it may be *absent* in low-pressure tamponade, with coexisting LV dysfunction, severe aortic regurgitation, or ASD.
- ▶ **Sympathetic compensation:** sinus tachycardia, tachypnoea, narrow pulse pressure with relatively preserved systolic pressure, diaphoresis, cool cyanotic extremities, oliguria, and depressed sensorium (cardiogenic shock).
- ▶ **Kussmaul's sign** is **characteristically ABSENT** in pure tamponade (it is a feature of constriction) because the normal inspiratory fall in systemic venous pressure is retained.
- ▶ Peripheral oedema and ascites are *uncommon* in acute tamponade and, if present, suggest a more chronic process or constriction.

Investigations

- ▶ **Echocardiography (diagnostic test of choice, urgent, bedside):**
 - Pericardial effusion with a **swinging heart**.
 - **Early-diastolic collapse (inversion) of the RV free wall** and **late-diastolic collapse of the right atrium** (RA collapse is more sensitive, RV collapse more specific).
 - **Plethoric (dilated) IVC** with blunted (<50%) respiratory variation — reflects raised right-atrial pressure.
 - **Exaggerated respiratory variation in transvalvular Doppler flow** — inspiratory *increase* in tricuspid/pulmonary inflow with reciprocal *decrease* in mitral/aortic inflow (the echocardiographic equivalent of pulsus paradoxus).
 - TOE / CT / cardiac MRI are reserved for loculated or post-surgical (regional) effusions not seen well transthoracically.
- ▶ **ECG:** sinus tachycardia, **low-voltage QRS complexes**, and **electrical alternans** (beat-to-beat alternation of P–QRS–T amplitude from the heart swinging in a large effusion) — *electrical alternans is occasional but virtually pathognomonic* of a large effusion with tamponade.

- ▶ **Chest X-ray:** enlarged, globular (“water-bottle”) cardiac silhouette with clear lung fields; may be normal in acute, rapidly accumulating effusions.
- ▶ **Cardiac catheterisation (when needed):** elevation and **diastolic equalisation** of RA, RV, pulmonary-capillary-wedge and LV diastolic pressures (~20–25 mmHg); RA waveform shows a **preserved x descent with a blunted/absent y descent** (contrast with the prominent y/”M–W” pattern of constriction).
- ▶ **Pericardial fluid analysis** (after drainage): cell count, Gram stain/culture, cytology for malignant cells; for suspected TB — **adenosine deaminase (ADA)**, unstimulated interferon- γ , lysozyme and *PCR for M. tuberculosis*. (*Light’s criteria for pleural fluid do not** apply — normal pericardial fluid is often “exudative”.)

Differential diagnosis — tamponade vs constriction vs restriction vs RV infarction

Feature	Tamponade	Constrictive pericarditis	Restrictive cardiomyopathy	RV infarction
Pulsus paradoxus	+++	+	+	+
Prominent y descent (JVP)	Absent	++	+	+
Prominent x descent	+++	++	+++	+
Kussmaul’s sign	Absent	+++	+	+++
Pericardial knock	–	++	–	–
Low ECG voltage / electrical alternans	++ / ++	++ / –	+ / –	–
Pericardial effusion (echo)	+++	–	–	–
Thickened/calcified pericardium	–	++ to +++	–	–
Equalisation of diastolic pressures	+++	+++	–	++

Management

- ▶ **Tamponade is a medical emergency** — admit, monitor, and proceed to drainage. The **definitive treatment is removal of pericardial fluid**.
- ▶ **Temporising / supportive measures** (must NOT delay drainage): intravenous **normal saline** to augment filling, plus inotropes/vasopressors as a bridge. **Avoid vasodilators and diuretics** (they reduce preload and precipitate collapse). **Stop anticoagulants** and reverse if bleeding.
- ▶ **Pericardiocentesis:**

- Preferably **echocardiography-guided** (or fluoroscopy/CT-guided); commonest route is **subxiphoid**, alternatively apical or parasternal. Echo-guided pericardiocentesis has a **>95% success and <2% serious-complication rate**.
- Measure intrapericardial pressure before withdrawal where possible; drain as completely as possible; leave an indwelling **pigtail (multi-holed) catheter** in situ for **2–3 days** for continued drainage and to reduce reaccumulation.
- Removal of even a *small* volume produces a disproportionately large fall in pericardial pressure (steep portion of the pressure–volume curve) and rapid haemodynamic improvement.
- ▶ **Surgical drainage** (subxiphoid window, video-assisted thoracoscopic pericardial window, or limited thoracotomy) is preferred for **loculated/clotted effusions, recurrent (especially malignant) effusions, the need for pericardial tissue/biopsy, and purulent pericarditis**; pericardial windows are more effective than needle drainage at preventing recurrence.
- ▶ **Special situations:**
 - **Type A aortic dissection** or **post-MI free-wall rupture / traumatic haemopericardium** → closed pericardiocentesis is generally **avoided/relatively contraindicated** (decompression may worsen bleeding); urgent **surgery** is needed (controlled “cycle” drainage may bridge a peri-arrest patient to theatre).
 - Treat the **underlying cause** (anti-tuberculous therapy, dialysis for uraemia, chemo/radiotherapy or sclerosant for malignant effusion, antibiotics ± drainage for purulent pericarditis).
- ▶ **Pericardial decompression syndrome** — a rare, poorly understood, life-threatening complication after drainage, with pulmonary oedema and shock (favoured by very rapid/complete removal of large effusions).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pericardial pressure–volume (compliance) curve:** plot intrapericardial pressure (y-axis) against pericardial volume (x-axis) as a J-shaped curve. Labels: *flat (compliant) initial limb — slow effusion adapts; “elbow”/inflection point; steep limb — small added volume causes large pressure rise (rapid effusion → tamponade)*; arrow showing *pericardiocentesis of a small volume → large pressure drop*.
- ▶ **Jugular venous pulse waveform in tamponade vs constriction:** label *a wave, prominent x descent (preserved), absent y descent (tamponade)* versus *prominent rapid y descent / “M or W” pattern (constriction)*.
- ▶ **(Optional) Subcostal 2-D echo:** pericardial effusion (echo-free space) with labels — *late-diastolic RA collapse, early-diastolic RV free-wall collapse, dilated plethoric IVC, LV, effusion*.

Clinical / Diagnostic significance

- ▶ Suspect tamponade in any patient with **unexplained hypotension + raised JVP + tachycardia**, sudden enlargement of the cardiac silhouette, or shock with clear lungs (“**hypotension with raised venous pressure**”).
- ▶ In the post-cardiac-surgery, post-MI, post-procedure (PCI, pacemaker, ablation) or trauma patient, a falling BP with rising filling pressures should trigger **immediate bedside echo**.
- ▶ **Pulseless electrical activity (PEA) arrest** with a narrow QRS — tamponade is one of the reversible “**H’s and T’s**” and warrants emergency pericardiocentesis/thoracotomy.
- ▶ Pericardial effusion in **pulmonary arterial hypertension** is a poor prognostic marker; drainage in this setting can be hazardous (RV may not collapse).
- ▶ Distinguishing tamponade from constriction and restriction guides definitive therapy (drainage vs pericardiectomy vs cardiomyopathy management).

High-yield exam pointers

- ▶ **Beck’s triad** = hypotension + muffled heart sounds + raised JVP (prominent x, absent y descent).
- ▶ **Pulsus paradoxus** >10 mmHg inspiratory systolic fall — the cardinal sign; absent in low-pressure tamponade, ASD, severe AR, LV dysfunction.
- ▶ **Kussmaul’s sign and the prominent y descent are ABSENT in tamponade** but PRESENT in constriction — a favourite discriminator.
- ▶ ECG: **low voltage + electrical alternans** (alternans ≈ pathognomonic of large effusion/tamponade).
- ▶ Echo: **RA collapse (sensitive) and RV diastolic collapse (specific), dilated IVC, respiratory Doppler swing**.
- ▶ Haemodynamics: **equalisation of diastolic pressures ~20–25 mmHg**; intrapericardial pressure >15 mmHg.
- ▶ As little as **200 mL (acute)** vs **>2000 mL (chronic)** can tamponade — *rate matters more than volume*.
- ▶ Treatment = **urgent echo-guided pericardiocentesis (subxiphoid)**; **avoid diuretics/vasodilators**; give IV fluids as a bridge only.
- ▶ **Aortic dissection / haemopericardium → surgery, not needle drainage**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Pericardial Disease” (definition, Beck’s triad, pulsus paradoxus, Table distinguishing tamponade from constriction/restriction/RV infarction, pericardiocentesis, fluid analysis).
- ▶ **Braunwald’s Heart Disease, 13e** — “Pericardial Diseases” (aetiology Table 78.1, pathophysiology and haemodynamics, ventricular interdependence, loss of y descent,

echocardiographic signs, low-pressure and regional tamponade, pericardiocentesis technique and success/complication rates, pericardial decompression syndrome).

- ▶ **CMDT 2026** — “Pericardial Effusion & Tamponade” (essentials of diagnosis, intrapericardial pressure thresholds, current management, when to refer).



Cardiogenic pulmonary edema

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Cardiogenic (hydrostatic) pulmonary edema is the rapid accumulation of transudative fluid in the pulmonary interstitium and alveoli caused by an acute rise in pulmonary capillary (and hence left atrial) hydrostatic pressure, almost always from acute left-ventricular failure. It is a life-threatening medical emergency presenting with sudden dyspnoea at rest, severe hypoxaemia and bilateral crackles, and frequently coexists at the severe end of the spectrum with **cardiogenic shock** when left-ventricular dysfunction also produces systemic hypoperfusion. It must be distinguished from **non-cardiogenic (high-permeability) pulmonary edema / ARDS**, where the pulmonary capillary wedge pressure (PCWP) is normal.

Pathophysiology — the Starling balance

- ▶ Movement of fluid across the pulmonary capillary is governed by **Starling forces**: net filtration rises when **capillary hydrostatic pressure exceeds plasma oncotic pressure**. Extravascular lung water is determined by the **PCWP, pulmonary vascular permeability and intravascular volume status** (Harrison).
- ▶ Acute LV systolic and/or diastolic failure → ↑ LV end-diastolic pressure → ↑ left atrial pressure → ↑ pulmonary venous and capillary pressure → transudation of protein-poor fluid.
- ▶ **Stages of fluid accumulation** (standard teaching):
 - **Stage 1 – interstitial edema**: when PCWP exceeds ~18–20 mmHg, fluid floods the peribronchovascular interstitium; pulmonary lymphatics are initially overwhelmed → dyspnoea, Kerley B lines, peribronchial cuffing.
 - **Stage 2 – alveolar flooding**: when PCWP rises further (CMDT: PCWP usually > 25 mmHg), fluid breaches the alveolar epithelium → alveolar flooding, severe hypoxaemia and **pink, frothy sputum**.
- ▶ Alveolar flooding plus airway-wall edema and peribronchial cuffing cause **wheeze** (“**cardiac asthma**”) in addition to crackles. Endogenous **catecholamine release** raises afterload and BP, worsening the congestion in a vicious cycle.

Etiology (Harrison Table 316-1; CMDT)

Category	Examples
Acute MI / ischemia (commonest)	LV failure; ventricular septal rupture; papillary-muscle/chordal rupture → acute severe MR; free-wall rupture
Acute decompensation of chronic HF	The single commonest presentation in developed countries; precipitated by drug non-adherence, dietary salt/fluid excess, ischaemia, rapid atrial fibrillation , infection
Valvular	Critical aortic or mitral stenosis; acute severe aortic or mitral regurgitation
Hypertensive / afterload	Hypertensive crisis (“flash” pulmonary edema), acute kidney injury with volume overload
Arrhythmia	Refractory tachy- or brady-arrhythmias
Myocardial	Fulminant myocarditis; end-stage cardiomyopathy; Takotsubo (apical-ballooning) syndrome; HOCM with severe LVOT obstruction; myocardial contusion
Other	Aortic dissection with acute AR/tamponade; β -blocker or calcium-channel-blocker overdose; post-cardiac-arrest stunning; septic myocardial depression

- *Contrast — non-cardiogenic edema* (normal PCWP): IV opioids, raised intracranial pressure (neurogenic), high-altitude, sepsis/ARDS, inhaled toxins, transfusion-related (TRALI), DIC, re-expansion edema.

Clinical features

- **Symptoms:** abrupt or subacute severe **dyspnoea at rest**, **orthopnoea**, **paroxysmal nocturnal dyspnoea**, cough with **pink frothy sputum**, marked anxiety and diaphoresis.
- **Signs:** tachypnoea, tachycardia, **cyanosis**, cold clammy skin; bilateral **fine crepitations in all lung fields with wheeze/rhonchi**; raised JVP, **S3 gallop**, and the murmur of the underlying lesion (e.g., acute MR, VSR). Hypertension is common from catecholamine surge; **hypotension signals coexistent cardiogenic shock** (poor prognosis).
- **Hemodynamic profiles** are clinically useful:
 - **Nohria–Stevenson bedside profile** (Braunwald): assess *congestion* (“wet” vs “dry”) and *perfusion* (“warm” vs “cold”). Most pulmonary-edema patients are “**warm and wet**”; the “**cold and wet**” profile (hypoperfused + congested) overlaps with cardiogenic shock and carries the worst outcome.
 - **Forrester haemodynamic subsets** (acute MI):

Subset	PCWP	Cardiac index	State
I	< 18	> 2.2	Normal — no congestion/hypoperfusion
II	> 18	> 2.2	Pulmonary congestion / edema
III	< 18	< 2.2	Hypoperfusion / hypovolaemia
IV	> 18	< 2.2	Congestion + hypoperfusion = cardiogenic shock

Investigations

- ▶ **Chest radiograph:** cardiomegaly (may be normal in acute MI/first event); **upper-lobe vascular redistribution (cephalization)**, blurring of vascular margins, **Kerley B lines**, peribronchial cuffing, **perihilar “bat-wing”/butterfly alveolar opacities**, and pleural effusions.
- ▶ **ECG:** identifies the trigger — ST-elevation/evolving Q waves (acute MI mandate immediate reperfusion), arrhythmia, LVH; may be non-specific.
- ▶ **Echocardiography:** pivotal — defines LV systolic/diastolic dysfunction, valvular lesions, mechanical complications (VSR, acute MR), tamponade, and RV involvement; helps separate cardiogenic from non-cardiogenic causes.
- ▶ **Natriuretic peptides:** a substantially elevated **BNP/NT-proBNP** supports a cardiac cause of acute dyspnoea (low values argue against it).
- ▶ **ABG / lactate:** hypoxaemia; respiratory alkalosis early, metabolic (lactic) acidosis with anion gap when hypoperfusion supervenes.
- ▶ **Cardiac troponin**, renal function and electrolytes; **pulmonary artery catheter (PAC)** is reserved for diagnostic uncertainty, refractory edema or accompanying refractory hypotension — it distinguishes **high-pressure (PCWP high, cardiogenic)** from **normal-pressure (non-cardiogenic)** edema, though it confers no mortality benefit.

Management (Harrison; Braunwald; CMDT 2026)

Immediate supportive measures (treat as an emergency, concurrently with work-up):

- ▶ **Sit the patient upright with legs dangling** — reduces venous return (preload).
- ▶ **Oxygenation:** high-flow O₂ to target SpO₂ ≥ 92% (PaO₂ > 60 mmHg); avoid hyperoxia (>98%) and routine high-FiO₂ in normoxic patients (risk of hyperoxia-induced vasoconstriction).
- ▶ **Non-invasive ventilation (CPAP/NIPPV):** improves oxygenation and symptoms and **reduces the need for intubation and mortality** in cardiogenic pulmonary edema; positive end-expiratory pressure decreases preload and afterload, redistributes alveolar lung water and recruits collapsed

alveoli. Endotracheal intubation and mechanical ventilation if respiratory distress/hypoxaemia is refractory (~4–5%).

Preload reduction (the therapeutic core):

- ▶ **IV loop diuretics** — first-line: **furosemide** (initial ≤ 0.5 mg/kg, or **40 mg IV**; 1 mg/kg or ~2–2.5× the usual oral dose in those on chronic diuretics or with renal impairment) or bumetanide 1 mg. Furosemide is also a **venodilator** that lowers preload before diuresis begins. The **DOSE trial** showed bolus and continuous infusion are equally effective.
- ▶ **Nitrates** — venodilators that rapidly lower LV filling pressure: **sublingual nitroglycerin 0.4 mg every 5 min**, then **IV nitroglycerin starting 5–10 µg/min**; especially valuable with concomitant hypertension/ischaemia. **IV sodium nitroprusside (0.1–5 µg/kg/min)** for severe hypertensive edema (avoid in active ischaemia; needs arterial-line monitoring).
- ▶ **Morphine 2–4 mg IV** — venodilates, relieves anxiety and dyspnoea, but use cautiously: some registry data link it to increased mortality and need for ventilation; avoid in opioid-induced and neurogenic edema.
- ▶ **ACE inhibitors** reduce afterload and preload and improve survival in acute MI with HF (favoured in hypertensive patients). **Nesiritide** (recombinant BNP) is reserved for refractory cases (not in ischaemia/MI).

Inotropes / vasopressors — only when hypoperfused (overlap with shock):

- ▶ **Dobutamine** or **milrinone** (PDE-3 inodilator, 50 µg/kg then 0.25–0.75 µg/kg/min) for low-output states; milrinone showed **no benefit** in unselected decompensated HF (OPTIME-CHF) and increased hypotension/AF.
- ▶ **Norepinephrine** is the preferred first-line vasopressor if shock supervenes; **dopamine** is avoided first-line (arrhythmogenic).
- ▶ **Mechanical circulatory support** (IABP no longer routine; Impella/VA-ECMO in selected refractory shock) and **renal replacement therapy / ultrafiltration** for refractory volume overload.

Treat the cause/trigger: emergency **primary PCI** for STEMI-associated edema (in-hospital mortality 20–40%); rate/rhythm control or cardioversion for rapid AF; surgery for acute mechanical complications and critical valve lesions; control of severe hypertension.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 – Starling balance at the alveolar-capillary unit (with stages).** Labels: *pulmonary capillary, alveolus, type I & type II pneumocytes, basement membrane / interstitial space, ↑ capillary hydrostatic pressure (PCWP), plasma oncotic pressure, lymphatic drainage (overwhelmed), Stage 1 interstitial edema, Stage 2 alveolar flooding (transudate / pink frothy fluid).*

- ▶ **Diagram 2 – Chest radiograph of cardiogenic pulmonary edema.** Labels: *cardiomegaly, upper-lobe vascular redistribution (cephalization), Kerley B lines, peribronchial cuffing, perihilar bat-wing / butterfly alveolar opacities, blunted costophrenic angle (pleural effusion).*

Clinical / Diagnostic significance

- ▶ Echocardiography + BNP + ECG rapidly separate cardiogenic from non-cardiogenic edema and identify a treatable mechanical or ischaemic cause — directing emergency reperfusion or surgery.
- ▶ PCWP is the pivotal discriminator: **high (> 18–25 mmHg) = cardiogenic**; normal/low = ARDS/high-permeability edema, which does not respond to diuresis.
- ▶ **Blood pressure dictates therapy:** hypertensive “flash” edema responds dramatically to vasodilators + NIV + diuretics; hypotensive edema (cardiogenic shock) needs inotropes/pressors and revascularisation, and **over-aggressive vasodilatation/diuresis can precipitate iatrogenic shock.**
- ▶ A first inferior MI presenting with shock/edema should prompt a search for RV infarction or a mechanical complication.

High-yield exam pointers

- ▶ Cardiogenic pulmonary edema = **hydrostatic edema from ↑ PCWP**; commonest cause is **acute LV failure due to MI / decompensated chronic HF.**
- ▶ **Pink frothy sputum + bilateral crackles + S3 + orthopnoea/PND** is the classic bedside picture; wheeze = “cardiac asthma”.
- ▶ CXR: **cephalization, Kerley B lines, peribronchial cuffing, bat-wing alveolar shadowing, pleural effusion.**
- ▶ PCWP > 18 mmHg → **interstitial**; > 25 mmHg → **alveolar flooding**; normal PCWP = non-cardiogenic.
- ▶ First-line emergency bundle (mnemonic **LMNOP**): Lasix (loop diuretic), Morphine, Nitrates, Oxygen/NIV, Position (upright, legs dependent).
- ▶ NIV/CPAP **reduces intubation and mortality**; sit up, target SpO₂ ≥ 92%, avoid routine hyperoxia.
- ▶ Nohria “**warm-and-wet**” is the typical profile; “**cold-and-wet**” overlaps with shock and has the worst prognosis.
- ▶ Forrester subset II = **pulmonary edema**; subset IV = **cardiogenic shock**; STEMI with edema → **emergency primary PCI** (mortality 20–40%).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Cardiogenic Shock and Pulmonary Edema” (etiologies, pathophysiology, oxygen/ventilation, preload reduction, drug doses, Forrester hemodynamics).
- ▶ **Braunwald's Heart Disease, 13e** — “Diagnosis and Management of Decompensated Heart Failure” (NIV/CPAP evidence, loop-diuretic dosing, Nohria warm/cold-wet/dry profiles) and “Chest Radiography in Cardiovascular Disease” (cephalization, Kerley B lines).
- ▶ **CMDT 2026** — “Heart Failure & Cardiomyopathy: Acute Heart Failure & Pulmonary Edema” (precipitants, clinical picture, CXR butterfly pattern, PCWP > 25 mmHg, morphine/diuretic/nitrate/nesiritide regimens, DOSE trial).
- ▶ *Coverage note:* The PCWP staging thresholds (interstitial ~18–20 mmHg) and the LMNOP mnemonic are universally accepted standard internal medicine used to organise corpus-sourced facts; CMDT explicitly supports the > 25 mmHg alveolar-edema threshold.



Cardiomyopathies

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Cardiomyopathy* denotes primary disease of the heart muscle itself, traditionally excluding myocardial dysfunction arising from coronary, valvular, hypertensive or congenital heart disease (though common usage admits ischaemic, valvular and hypertensive “cardiomyopathy”). It is best understood as a heterogeneous group of myocardial diseases with mechanical and/or electrical dysfunction, frequently genetic, that may be confined to the heart or part of a systemic disorder. Classification rests on a **phenotype-first** morphologic approach — **hypertrophic** (HCM), **dilated** (DCM) and **restrictive** (RCM) — now complemented by **arrhythmogenic cardiomyopathy** (ACM/ARVC) and increasingly informed by genotype.

Classification

Three classic morphologic phenotypes plus the arrhythmogenic phenotype, defined by left-ventricular (LV) wall thickness, ejection fraction (LVEF) and diastolic physiology:

Phenotype	Defining criteria	Key features	Common challenges
HCM	Septal/wall thickness ≥15 mm (men), ≥13 mm (women); LVEF ≥ normal, usually >0.60; LV cavity ≤ normal	Asymmetric septal, concentric, mid-ventricular or apical patterns; sarcomere	Distinguish from athlete's heart, hypertensive heart, amyloid, storage disease

Phenotype	Defining criteria	Key features	Common challenges
		disease; outflow obstruction in ~30%	(Fabry, Danon, PRKAG2)
DCM	LVEF ≤ 0.50 (most ≤ 0.40) and/or LV dilation (LVEDD $> 95\%$ predicted / LVEDV $> 112\%$)	Global hypokinesis, mitral regurgitation; ~30% spontaneously recover (“reverse remodelling”)	Exclude coronary, valvular and primary structural disease
RCM	Moderate–severe diastolic dysfunction / raised filling pressures; LVEF usually mildly reduced (~30–50%)	Marked biatrial enlargement , right-sided congestion dominates; wall thickness normal or increased	Differentiate from constrictive pericarditis ; identify amyloid/storage
ARVC / ACM	Ventricular arrhythmias dominate before/without reduced LVEF; <i>2010 modified Task Force Criteria</i>	Fibrofatty replacement; desmosomal genes; RV-dominant (ARVC), LV-dominant (ACM-LV) or biventricular	Distinguish PVC-related CM from genetic ACM

- ▶ The AHA (Maron) scheme divides cardiomyopathies into *primary* (genetic, mixed, acquired) and *secondary* (systemic infiltrative/storage/inflammatory), and uniquely includes electrical disorders (channelopathies).
- ▶ The ESC 2023 scheme keeps the phenotypic approach but adds a *non-dilated left ventricular cardiomyopathy* category (LV systolic dysfunction without dilation). *Left-ventricular non-compaction (LVNC)* is regarded as a trait rather than a distinct disease.
- ▶ Phenotypes **overlap and evolve**: DCM may reverse-remodel to higher LVEF, and ~5% of HCM progresses to “burned-out” HCM with reduced EF (HCM-rEF).

Hypertrophic Cardiomyopathy (HCM)

- ▶ **Genetics/pathology**: Commonest inherited cardiac disease, prevalence ~1:500; autosomal dominant with age-dependent, incomplete penetrance. A sarcomere variant is found in ~40–50%; ~80% involve MYH7 (β -myosin heavy chain) or MYBPC3 (myosin-binding protein C). Histology shows **myocyte disarray**, interstitial and replacement fibrosis (late gadolinium enhancement on MRI), and small-vessel disease causing microvascular ischaemia.
- ▶ **Pathophysiology of obstruction**: Dynamic LV outflow tract (LVOT) obstruction in ~30% at rest and a further ~30% on provocation, initiated by drag forces drawing an enlarged anterior mitral leaflet onto the hypertrophied septum — **systolic anterior motion (SAM)** with posteriorly-directed mitral regurgitation. The murmur is harsh, late-peaking, and *augmented* by Valsalva or standing (reduced preload).

- ▶ **Treatment:** β -blockers and non-dihydropyridine calcium-channel blockers (**verapamil**) are first line; **disopyramide** (negative inotrope) for refractory obstruction. **Cardiac myosin inhibitors** — **mavacamten** (FDA-approved), **aficamten** (investigational) — relieve symptomatic obstruction (monitor LVEF). Refractory severe symptoms (~5%): **septal myectomy** or **alcohol septal ablation** (chief complication: complete heart block needing pacing). Avoid digoxin/vasodilators/excess diuresis.
- ▶ **Sudden cardiac death (SCD):** Baseline risk ~0.5%/year. **Major risk factors:** prior cardiac arrest/sustained VT, unexplained syncope, family history of SCD, LV wall ≥ 30 mm, LV apical aneurysm, LVEF $< 50\%$, plus modifiers (extensive LGE, non-sustained VT). The **ESC HCM Risk-SCD calculator** guides ICD: $\geq 6\%$ 5-yr risk $\rightarrow$ ICD advised, 4–6% $\rightarrow$ consider, $< 4\%$ $\rightarrow$ not advised.

Dilated Cardiomyopathy (DCM) and acquired causes

- ▶ Familial in 30–40%, monogenic cause identifiable in ~25%; the commonest gene is **truncating variant of titin (TTN, ~25% of familial DCM)**; **LMNA (lamin A/C)** and **FLNC (filamin C)** carry high arrhythmic risk and warrant early ICD (before LVEF falls to 0.35).
- ▶ **Major acquired causes:** prior myocarditis (viral — coxsackie, adenovirus, COVID-19, HIV; *Trypanosoma cruzi* — Chagas); **toxic** — alcohol (≥ 60 –80 g ethanol/day for ≥ 5 yr; “holiday heart” AF; reversible with abstinence), **anthracyclines** (doxorubicin — dose-related, dexrazoxane chelation), **trastuzumab** (anti-HER2, often reversible), checkpoint inhibitors; **endocrine/metabolic** — thyroid disease, pheochromocytoma, haemochromatosis, thiamine deficiency (beri-beri), selenium deficiency (Keshan); **tachycardia-mediated CM**.
- ▶ **Peripartum cardiomyopathy (PPCM):** LVEF ≤ 0.45 in the last trimester to 5–6 months postpartum (commonly first 2 weeks) without other cause; ~1:1000–1:4000 deliveries; associated with antiangiogenic signalling (sFLT1), an abnormal prolactin fragment, and TTN variants (~15%). Higher risk and poorer recovery in Black women. Avoid ACE-inhibitors/ARBs antenatally (use hydralazine-nitrate); anticoagulate if LVEF < 0.35 ; LVEF recovers to ≥ 0.50 in 50–80%.
- ▶ **Takotsubo (stress / “broken-heart”) syndrome:** apical ballooning with basal sparing in older women after intense stress; catecholamine-mediated; mimics infarction but coronaries patent; usually recovers in days–weeks (recurrence ~2%/yr).
- ▶ **Therapy:** guideline-directed medical therapy as for HFrEF — the **four pillars:** ARNI/ACE-inhibitor/ARB, β -blocker, mineralocorticoid-receptor antagonist, **SGLT2 inhibitor**, plus diuretics, device therapy (CRT for LBBB, primary-prevention ICD for persistent LVEF ≤ 0.30 –0.35) and anticoagulation for AF/LV thrombus.

Restrictive Cardiomyopathy and Cardiac Amyloidosis

- ▶ **RCM physiology:** stiff, non-compliant ventricles with preserved cavity size; biatrial enlargement; raised biventricular filling pressures; right-sided congestion (oedema, ascites), **prominent Y**

descent, positive Kussmaul sign, $S_4 > S_3$; haemodynamics show a “square-root” (dip-and-plateau) sign.

- **Causes:** *infiltrative* (amyloid — commonest), *storage* (haemochromatosis, Fabry, glycogen storage), *fibrotic* (radiation, scleroderma, **endomyocardial fibrosis**, **Löffler endocarditis** from hypereosinophilia), carcinoid, and genetic (DES desminopathy, sarcomeric overlap with HCM).
- **Cardiac amyloidosis:** extracellular fibrillar deposition staining with **Congo red** → **apple-green birefringence**; nonbranching fibrils ~10 nm. Two dominant precursors:

Feature	AL (light-chain)	ATTR (transthyretin)
Source	Clonal plasma cells ($\lambda > \kappa$ free light chains)	Liver TTR — wild-type (ATTRwt) or variant (ATTRv)
Demographics	Younger; plasma-cell dyscrasia/myeloma	Elderly men (ATTRwt, M:F ~20:1); ATTRv Val122Ile in ~3.5% African-Americans
Extra-cardiac clues	Periorbital purpura, macroglossia, nephrotic proteinuria, autonomic neuropathy	Bilateral carpal tunnel syndrome, spinal stenosis, ruptured biceps tendon
Diagnosis	Tissue biopsy mandatory (fat-pad/cardiac); mass spectrometry typing	Tc-PYP/DPD bone scintigraphy positive (grade ≥ 2) <i>after excluding plasma-cell dyscrasia</i>
Untreated survival from HF onset	~6 months (worst prognosis)	ATTRwt ~4–5 yr; Val122Ile ~2–3 yr
Specific therapy	Dara-CyBorD (daratumumab, bortezomib, cyclophosphamide, dexamethasone); $\pm$ autologous SCT	Stabilisers tafamidis, acoramidis; TTR silencers patisiran/eplontersen/vutrisiran

- **Imaging clues:** thick walls with **low ECG voltage**, biatrial enlargement, and **apical-sparing “bull’s-eye” longitudinal-strain** pattern; CMR shows expanded extracellular volume, diffuse subendocardial LGE and abnormal myocardial nulling. NT-proBNP and troponin are disproportionately elevated. Avoid ACE-inhibitors/ β -blockers (poorly tolerated); anticoagulate AF; ICD rarely useful.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Morphologic phenotypes (4-panel cross-section):** *Normal* heart; *DCM* — globally dilated thin-walled LV with enlarged LA; *HCM* — asymmetric septal hypertrophy, small LV cavity, anterior mitral leaflet showing **SAM** and **LVOT gradient**; *RCM* — normal-size cavity, mildly thickened walls with **massive biatrial enlargement**. Labels: *LV cavity*,

interventricular septum, LV free wall, RV, left atrium (LA), mitral valve, SAM, LVOT obstruction.

- ▶ **Cardiac-amyloid strain “bull’s-eye”:** concentric polar map with **preserved apical strain (red)** and **impaired basal strain (blue)** — label *apical sparing, impaired base*.

Clinical / Diagnostic significance

- ▶ **Presentation:** exertional dyspnoea/fatigue, congestion, arrhythmias (AF), embolic events (LV/apical thrombus) or SCD; “*congestive heart failure*” is a *syndrome, not an aetiology* — always seek the cause.
- ▶ **Work-up (Harrison Table 266-2):** detailed family history (SCD, pacemaker/AF by middle age, muscular dystrophy), ECG, chest radiograph, 2-D/Doppler **echocardiography** (initial modality), **cardiac MRI** (tissue characterisation, LGE, T1/T2 mapping), bloods (TSH, iron studies/transferrin saturation >45–60%, troponin, eosinophils, serum/urine immunofixation + free light chains), genetic counselling/multigene panel, and **endomyocardial biopsy** when a specific therapy-altering diagnosis (giant-cell, eosinophilic, sarcoid, amyloid, Fabry) is suspected.
- ▶ **RCM vs constrictive pericarditis** is the pivotal differential — both cause right-sided congestion and Kussmaul sign; pericardial thickening/calcification, respiratory septal shift and discordant ventricular pressures favour constriction (surgically curable), whereas biatrial enlargement, low voltage and positive bone scan/LGE favour restrictive amyloid.
- ▶ **Therapeutic leverage:** many cardiomyopathies are *treatable* — abstinence in alcoholic CM, phlebotomy/chelation in haemochromatosis, enzyme replacement/migalastat in Fabry, tafamidis in ATTR, Dara-CyBorD in AL, and reverse remodelling on GDMT.

High-yield exam pointers

- ▶ Three classic phenotypes = HCM, DCM, RCM; fourth = **arrhythmogenic (ARVC/ACM)**; LVNC is a trait.
- ▶ HCM commonest gene pair **MYH7 + MYBPC3** (~80%); hallmark = SAM + dynamic LVOT obstruction; murmur ↑ with Valsalva/standing.
- ▶ HCM is the **leading cause of SCD in the young athlete**; ICD by ESC Risk-SCD score (≥6% → implant). Newest drug class = **myosin inhibitors (mavacamten)**.
- ▶ DCM commonest genetic cause = **titin (TTN) truncation**; LMNA/FLNC = arrhythmic, early ICD.
- ▶ Cardiac amyloid: **Congo red apple-green birefringence**; **apical-sparing bull’s-eye strain**; ATTR diagnosed *non-invasively* by Tc-PYP scan after excluding light chains.
- ▶ **AL clues** = periorbital purpura, macroglossia; **ATTR clues** = bilateral carpal tunnel, ruptured biceps tendon; AL prognosis worst (~6 months untreated).

- ▶ **ARVC** = desmosomal disease (PKP2, DSP, DSG2, DSC2, JUP); **epsilon wave**, T-inversion V1–V3, fibrofatty RV replacement; *Naxos* (with woolly hair/palmoplantar keratoderma) and *Carvajal* syndromes.
- ▶ **Peripartum CM** = LVEF ≤ 0.45 , last trimester–6 months postpartum; avoid ACE-i antenatally; anticoagulate if LVEF < 0.35 .
- ▶ **Takotsubo** = apical ballooning, post-stress, women, coronaries normal, usually reversible.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Classification of Cardiomyopathy,” “Genetic Cardiomyopathies,” “Acute and Chronic Myocarditis,” “Dilated Cardiomyopathies,” and “Amyloidosis and Other Restrictive Cardiomyopathies.”
- ▶ **Braunwald's Heart Disease, 13e** — “The Dilated, Restrictive, and Infiltrative Cardiomyopathies” (AHA/ESC classification, ARVC Task Force criteria), “Cardiac Amyloidosis,” and “Hypertrophic Cardiomyopathy.”
- ▶ **CMDT 2026** — “Heart Failure & Cardiomyopathy” (current GDMT, mavacamten, restrictive-vs-constrictive “square-root” sign).



Classify Cardiomyopathy. What are the risk factors, clinical presentations and prognosis of peripartum Cardiomyopathy?

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Cardiomyopathy* denotes primary disease of the heart muscle itself, traditionally excluding myocardial dysfunction arising from coronary, valvular, hypertensive or congenital disease (though common usage now admits ischaemic, valvular and hypertensive “cardiomyopathy”). It is classified by **morphology and function** into three classic phenotypes — hypertrophic (HCM), dilated (DCM) and restrictive (RCM) — with arrhythmogenic cardiomyopathy (ACM/ARVC) and left ventricular non-compaction (LVNC) as evolving fourth/fifth categories, and increasingly by **aetiology** (genetic vs acquired). *Peripartum cardiomyopathy (PPCM)* is a distinct acquired DCM developing toward the end of pregnancy or in the months after delivery.

A. Classification of cardiomyopathy

1. Morphological / functional classification (the traditional working scheme; WHO 1995):

Phenotype	Defining criteria	Key features / mimics
Hypertrophic (HCM)	Septal/wall thickness ≥ 15 mm (men), ≥ 13 mm (women); LVEF normal/high, usually > 0.60 ; LV cavity $\leq$ normal	Asymmetric septal, sigmoid, concentric or apical patterns; distinguish from athlete's heart, hypertension, aortic stenosis;

Phenotype	Defining criteria	Key features / mimics
		mimicked by storage diseases — <i>Anderson-Fabry</i> (GLA), <i>PRKAG2</i> , <i>Danon</i> (LAMP2) and amyloid
Dilated (DCM)	LVEF ≤ 0.50 (most present ≤ 0.40) $\pm$ LV dilation (LVEDD/LVEDV increased)	Convergent end-phenotype of many injuries; functional MR; $\sim 1/3$ of recent-onset cases recover (“HFimpEF”)
Restrictive (RCM)	Functional diagnosis: moderate-severe diastolic dysfunction / raised filling pressures; LVEF mildly reduced	Least common; marked biatrial enlargement , right-heart failure dominates; marked wall thickening suggests amyloidosis , storage/metabolic disease
Arrhythmogenic (ACM-LV / ACM-RV = ARVC)	DCM-type morphology with ventricular arrhythmias <i>out of proportion</i> to dysfunction; ARVC by 2010 modified Task Force criteria	LGE patterns on CMR; ICD considered even at LVEF > 0.35 ; sarcoid/Chagas can mimic
LV non-compaction (LVNC) — trait	Non-compacted : compacted myocardium ratio > 2.3	May overlay HCM/DCM/dystrophies; trabeculation can be physiological in pregnancy/athletes

2. Aetiological classification of DCM (Harrison Table 269-1) — a high-yield framework:

- **Inflammatory / infective** — viral (coxsackie, adenovirus, COVID-19, HIV), parasitic (*Trypanosoma cruzi* — Chagas), bacterial (diphtheria), spirochaetal (Lyme), rickettsial (Q fever).
- **Non-infective inflammatory** — sarcoidosis, giant-cell & eosinophilic myocarditis, collagen-vascular disease, checkpoint-inhibitor myocarditis, transplant rejection.
- **Toxic** — alcohol (commonest toxin), catecholaminergic stimulants (cocaine, amphetamines), chemotherapy (anthracyclines, trastuzumab), hydroxychloroquine/chloroquine, anabolic steroids, heavy metals (lead, mercury, cobalt).
- **Metabolic** — thiamine/selenium (Keshan)/carnitine deficiency, $\text{Ca}^{2+}/\text{PO}_4^{3-}/\text{Mg}^{2+}$ depletion, thyroid disease, pheochromocytoma, diabetes, obesity, haemochromatosis.
- **Genetic / familial** — $\sim 30\%$ of DCM; autosomal-dominant predominantly; *TTN* truncations, *LMNA*, *MYH7*, *TNNT2*, dystrophinopathies (Duchenne/Becker), mitochondrial (Kearns-Sayre).
- **Miscellaneous (overlap)** — **peripartum**, tachycardia-induced (uncontrolled SVT, high PVC burden), LVNC, arrhythmogenic.

> A **two-hit model** is increasingly recognised — a genetic predisposition is unmasked by an acquired trigger (infection, toxin, **pregnancy**, tachycardia). The pragmatic clinical split remains **primary** (genetic, mixed, acquired) vs **secondary** (systemic-disease) cardiomyopathy.

B. Peripartum cardiomyopathy — definition & risk factors

- ▶ **Definition:** PPCM is a **diagnosis of exclusion** — *de novo* LV systolic dysfunction ($LVEF \leq 0.45$) presenting in the **last month of pregnancy or within ~5–6 months postpartum**, with no other identifiable cause of heart failure; **most cases present within the first 2 weeks after delivery**.
- ▶ **Incidence:** 1:1000 to 1:4000 deliveries in the USA; striking geographic/ethnic variation — close to 1% of deliveries in parts of Nigeria (highest in Hausa & Fulani) vs ~1 in 15,000 in Japan.
- ▶ **Risk factors:**
 - Older maternal age; increased parity / multiparity.
 - Multiple (twin) gestation.
 - Hypertensive disorders of pregnancy / pre-eclampsia — present in *up to half* of cases.
 - Black / African ancestry — risk ~four-fold higher in Black women, with slower and less complete recovery.
 - Malnutrition and tocolytic therapy for premature labour.
 - Genetic susceptibility — TTN truncating variants in ~15% (overall pathogenic/likely-pathogenic truncations ~15% — similar to non-PPCM DCM), predicting poorer recovery.
- ▶ **Pathogenesis (“vasculo-hormonal” model):** late-gestation **oxidative stress** drives **antiangiogenic signalling** — high soluble FLT1 (sFLT1), an inhibitor of VEGF (also elevated in pre-eclampsia) — together with **cathepsin-D-mediated cleavage of prolactin** into a toxic **16-kDa prolactin fragment** that promotes **endothelial and cardiomyocyte apoptosis**. This is the rationale for **bromocriptine** (prolactin suppression).

C. Clinical presentation, diagnosis & management

- ▶ **Presentation:** typically the **syndrome of congestion** — exertional dyspnoea, orthopnoea, fatigue, pedal/abdominal oedema — easily mis-attributed to normal late pregnancy. **Atrial and ventricular arrhythmias** occur; **LV thrombus / systemic or pulmonary embolism** (especially $LVEF < 0.35$); rarely cardiogenic shock.
- ▶ **Diagnostic clues & work-up:** raised BNP/NT-proBNP and troponin, elevated central venous pressure, and echocardiography ($LVEF \leq 0.45$) is usually sufficient. CMR may help in complex cases — **gadolinium should be avoided antepartum**. Always **exclude** pulmonary embolism, spontaneous coronary artery dissection and other de-novo cardiomyopathies (familial DCM, HCM, LVNC, ARVC). **Genetic testing** is reasonable (informs prognosis and family screening).
- ▶ **Management:**
 - **Diuresis** with loop diuretics to restore euvolaemia (use cautiously).

- **Antepartum:** RAS inhibitors (ACEi/ARB/ARNI), aldosterone antagonists and SGLT2i are contraindicated (fetotoxic). Afterload reduction with hydralazine + nitrate; digoxin and β -blockers (metoprolol preferred over carvedilol) for rate/arrhythmia control; close maternal-fetal medicine collaboration with a plan for emergency delivery.
- **Postpartum:** full guideline-directed therapy for HFrEF — **metoprolol**, **enalapril/captopril/lisinopril** and **spironolactone** are compatible with breastfeeding (avoid eplerenone, ARNI, SGLT2i, DOACs while breastfeeding).
- **Anticoagulation** for ~6 weeks if LVEF <0.35 or marked dilation (once obstetric bleeding settles).
- **Bromocriptine** — *class IIb* in ESC HF guidelines (with anticoagulation); **not routinely recommended** by the 2022 AHA/ACC/HFSA guideline; large RCT ongoing.
- **Wearable cardioverter-defibrillator** is reasonable when LVEF <0.35, given early arrhythmic risk; **breastfeeding is now generally encouraged** where fluid balance permits.

D. Prognosis of peripartum cardiomyopathy

- ▶ **Recovery is comparatively favourable:** LVEF improves to ≥ 0.50 in 50–80%, usually within 6 months. In the North American IPAC study ~70% had LVEF >0.50 at 1 year; the ESC EORP registry showed recovery in ~66%.
- ▶ **One-year mortality:** ~4–11% in the USA (higher in Black women), ~8% in the ESC EORP registry, and reported up to two-fold higher in Africa.
- ▶ **Predictors of poor recovery / adverse outcome:**
 - LVEF <0.30 at presentation; LV end-diastolic dimension ≥ 6.0 cm.
 - Black race; presentation >6 weeks after delivery.
 - Elevated natriuretic peptides, troponin and sFLT1; positive genetic testing (e.g., TTN).
- ▶ **Subsequent pregnancies** carry substantial risk of relapse and death — **contraindicated where there is any residual LV dysfunction** (mWHO class IV); recurrence risk correlates with the degree of recovery. PPCM is the **4th commonest indication for cardiac transplantation in women** in the USA (~5%), with post-transplant outcomes similar to other indications.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Morphological classification montage** — four LV cross-sections side by side, labelled: HCM (thick asymmetric septum, small slit-like cavity), DCM (globular dilated thin-walled LV), RCM (normal-sized cavity with grossly dilated biatrial chambers), ARVC/ACM (dilated, fibro-fatty right ventricle). Annotate LVEF and wall-thickness criteria.
- ▶ **PPCM “vasculo-hormonal” pathogenesis flowchart** — labels: *Late pregnancy/puerperium* → *Oxidative stress* → two arrows to *sFLT1 (anti-VEGF)* and *Cathepsin-D cleaves prolactin* → *16-kDa prolactin fragment* → *Endothelial + cardiomyocyte apoptosis / microvascular*

dysfunction → LV systolic dysfunction (LVEF $\leq 45\%$); side-box Genetic susceptibility — TTN truncating variant (~15%); timeline bar last trimester → 5–6 months postpartum (peak: first 2 weeks).

Clinical / Diagnostic significance

- ▶ Distinguishing the **phenotype** guides initial work-up, while **aetiology** (especially genetic vs acquired) drives family screening, ICD decisions and prognosis.
- ▶ In a peripartum woman with new heart failure, **PPCM is the commonest cause** but remains a **diagnosis of exclusion** — rule out PE, coronary dissection and unmasked familial/structural disease.
- ▶ **sFLT1, BNP/troponin and TTN status** are emerging prognostic biomarkers; **avoid gadolinium and RAS blockade/SGLT2i antepartum**.
- ▶ Counsel against further pregnancy if LV function does not fully normalise; document contraception.

High-yield exam pointers

- ▶ Three classic phenotypes = **HCM, DCM, RCM**; add **ARVC/ACM** and **LVNC**; HCM wall ≥ 15 mm (M)/ ≥ 13 mm (W), DCM LVEF ≤ 0.40 for therapy & ≤ 0.30 – 0.35 for primary-prevention ICD.
- ▶ **Amyloidosis** = commonest RCM; **alcohol** = commonest toxic DCM; **TTN** = commonest DCM gene.
- ▶ **PPCM** = LVEF ≤ 0.45 , last month of pregnancy to ~5 months postpartum, **peak in first 2 weeks after delivery**; incidence **1:1000–1:4000 (USA)**.
- ▶ Risk factors: **older age, multiparity, twins, pre-eclampsia/HTN, Black race (4×), malnutrition, tocolytics, TTN variant**.
- ▶ Pathogenesis: **16-kDa prolactin fragment + sFLT1** → “vasculo-hormonal” injury → rationale for **bromocriptine**.
- ▶ **No ACEi/ARB/ARNI/MRA/SGLT2i before delivery**; use **hydralazine-nitrate, β -blocker, digoxin, diuretic**; anticoagulate if LVEF < 0.35 .
- ▶ Recovery (LVEF ≥ 0.50) in **50–80%**; 1-year mortality **4–11%**; poor prognosis if LVEF < 0.30 , **LVEDD ≥ 6 cm, Black race, late presentation, high sFLT1/troponin**.
- ▶ Subsequent pregnancy **contraindicated with residual LV dysfunction**; 4th commonest transplant indication in women.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Classification of Cardiomyopathy” (morphological classification, Table 266-1; initial evaluation) and “Dilated Cardiomyopathies” (aetiological Table 269-1; Peripartum Cardiomyopathy section — incidence, risk factors, sFLT1/16-kDa prolactin, TTN, management, prognosis); “Genetic Cardiomyopathies”.
- ▶ **Braunwald's Heart Disease, 13e** — “The Dilated, Restrictive, and Infiltrative Cardiomyopathies” (PPCM genetics, bromocriptine class IIb/AHA stance, recovery ~50%, transplant data) and “Pregnancy and Heart Disease” (risk factors, IPAC ~70% recovery & predictors, ESC EORP 8% 1-yr mortality, mWHO contraindication, drug safety in lactation).
- ▶ **CMDT 2026** — “Heart Failure & Cardiomyopathy” (dilated cardiomyopathy epidemiology/work-up, LV-thrombus anticoagulation, referral thresholds).

Coverage note: The corpus grounds the morphological and aetiological classifications fully; the formal AHA 2006 (primary genetic/mixed/acquired vs secondary) and ESC MOGE(S) nomenclature are universally accepted but are referenced only implicitly in this corpus, so they are mentioned briefly rather than tabulated.



Conducting system of the Heart and Electrocardiogram

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — The **cardiac conduction system** is the network of specialized, automatic and rapidly-conducting myocardial fibres that initiates each heartbeat and delivers the impulse in an orderly sequence from atria to ventricles, ensuring coordinated, synchronous mechanical contraction. The **electrocardiogram** (ECG/EKG) is the noninvasive graphical recording of the depolarization (stimulation) and repolarization (recovery) electrical activity of the working atrial and ventricular myocardium, detected by metallic electrodes on the limbs and chest wall. Because the cardiac depolarization and repolarization wavefronts have direction and magnitude, they can be represented as **vectors**, and the surface ECG is the summed projection of these vectors onto standardized leads.

Anatomy and sequence of the conduction system

The electrical currents that spread through the heart are produced by three components: **cardiac pacemaker cells**, **specialized conduction tissue**, and **the heart muscle itself**. The orderly route of a normal impulse is:

- ▶ **Sinoatrial (SA) node** — the dominant pacemaker, situated at the lateral junction of the **superior vena cava and right atrium**; possesses spontaneous **automaticity** and is richly innervated by autonomic fibres for dynamic heart-rate control.

- ▶ **Atrial myocardium** — depolarization spreads across the right then the left atrium via **preferential conduction pathways**, inducing atrial systole; inscribes the **P wave**.
- ▶ **Atrioventricular (AV) node** — the AV nodal and His-bundle areas together form the **AV junction**; conduction here is deliberately **slow**, providing physiologic AV synchrony (the PR interval). In normal hearts the AV node is the **only electrical connection** between atria and ventricles.
- ▶ **Bundle of His → right and left bundle branches** — the His bundle bifurcates; the main left bundle fans out into **left anterior and left posterior fascicles**.
- ▶ **Purkinje fibres** — an endocardial network that rapidly and synchronously activates both ventricles. Depolarization then spreads through the ventricular wall from **endocardium to epicardium**, triggering coordinated ventricular contraction.

Structure	Property / role	Conduction velocity
SA node	Primary pacemaker; <i>If</i> (funny) current automaticity; autonomic control	Nodal (slow)
Atrial myocardium	Inscribes P wave; atrial systole	0.3–0.4 m/s
AV node	Slow conduction → AV delay (PR interval); sole AV connection	Slow
His–bundle branches–fascicles	Rapid transmission to ventricles	High
Purkinje fibres	Endocardial, synchronizes ventricular activation	2–3 m/s

Conduction is faster in Purkinje fibres (2–3 m/s) than in myocardial cells (0.3–0.4 m/s), partly due to different connexins in their gap junctions.

Cellular electrophysiology, automaticity and autonomic control

The cardiac **action potential (AP)** drives all electrophysiologic behaviour and has five phases (0–4): **rapid upstroke, early repolarization, plateau, late repolarization, and diastole**. Ionic currents flux through voltage-gated channels and gap-junction (connexin) complexes:

Current	Gene	Protein	Principal AP role
I _{Na}	SCN5A	Nav1.5	Phase 0 upstroke (atrial/ventricular)
I _{Ca-L}	CACNA1C	Cav1.2	Plateau (phase 2); phase 0 of nodal tissue
I _{to}	KCND3 / KCNIP2	Kv4.3 / KChIP2	Phase 1 early repolarization
I _{Kr}	KCNH2 / KCNE2	HERG / MiRP-1	Phase 3 repolarization

Current	Gene	Protein	Principal AP role
I _{Ks}	KCNQ1 / KCNE1	KVLQT1 / minK	Phase 3 repolarization
I _{K1}	KCNJ2	Kir2.1	Phase 4 — sets resting membrane potential
I _{Kur}	KCNA5	Kv1.5	Atrial repolarization
I _f (funny)	—	Semiselective Na/Ca channel	SA-node phase 4 automaticity ; target of ivabradine

- **Automaticity** = spontaneous phase-4 depolarization; a normal property of the SA node, AV node and His-Purkinje system. In the SA node the **Na/Ca If current drives phase 4; the normal range of SA automaticity is 30–220 beats/min. The intrinsic heart rate (IHR)** is the native SA rate without autonomic input.
- **Autonomic modulation**: parasympathetic vagal tone releases acetylcholine → opens I_{KACH} (G-protein mediated) → K⁺ efflux hyperpolarizes nodal cells → slows phase 4. Sympathetic catecholamines act via **β1 receptors** → activate L-type Ca channels → enhance phase 4 → faster rate (with exercise the PR interval physiologically shortens).
- **Escape rhythm**: if a proximal pacemaker fails, a more distal automatic focus may take over to maintain cardiac output. Mutations in **K-channel** subtypes (e.g., delayed closing) prolong the QT and cause inherited **long-QT syndromes**.

Genesis of the normal ECG — correlation of conduction events with waveforms

Each ECG deflection corresponds to a phase of the simultaneously-obtained ventricular AP: **phase 0** ↔ onset of QRS; plateau phase 2 ↔ isoelectric ST segment; active repolarization phase 3 ↔ T wave.

ECG component	Electrical event	AP phase	Normal value
P wave	Atrial depolarization (vector down & leftward → +ve in II, -ve in aVR)	Atrial phase 0	≤2.5 mm tall
PR interval	Atrial→ventricular delay, mostly AV-nodal conduction	—	120–200 ms
QRS complex	Ventricular depolarization	Phase 0	100–110 ms or less
J point	Junction of QRS end and ST start	—	—
ST segment	Early ventricular repolarization (plateau)	Phase 2	Isoelectric

ECG component	Electrical event	AP phase	Normal value
T wave	Ventricular repolarization (epicardium→endocardium)	Phase 3	Concordant with QRS (within ~45°)
QT interval	Ventricular depolarization + repolarization	Phases 0–3	QTc ≤450 ms (men), ≤460 ms (women)
U wave	Late repolarization deflection	—	≤1 mm

- ▶ Atrial repolarization (ST-Ta) is usually too small to detect; it may emerge in **acute pericarditis**, **atrial infarction** and **AV block**.
- ▶ **QRS septal vectors**: vector 1 = septal depolarization (left→right, anterior) gives a small **septal r** in V1 and **septal q** in V6; vector 2 = dominant LV (left & posterior) gives the **S wave** in V1 and **R wave** in V6. The **transition zone** ($R \approx S$) is usually V3–V4.
- ▶ **Rate-correction (QTc)**: classic Bazett $QTc = QT/\sqrt{RR}$ (in seconds); the **Framingham** formula $QTc = QT + 0.154 (1000 - RR)$ in ms.

The 12-lead ECG: leads, calibration and axis

- ▶ **12 leads** = 6 limb (frontal plane, hexaxial reference) + 6 chest/precordial (horizontal plane). Each lead is like a different “camera angle” viewing the same depolarization/repolarization. An upright deflection occurs when the wavefront travels **toward** the positive pole of a lead.
- ▶ **Calibration**: recorded on 1-mm² grid at 25 mm/s — smallest 1-mm horizontal box = **40 ms (0.04 s)**, heavy lines every **200 ms (0.20 s)**; vertically **1 mV = 10 mm**.
- ▶ **Heart rate**: $300 \div \text{number of large (0.20 s) boxes between R waves}$, or $1500 \div \text{number of small boxes}$.
- ▶ **Mean QRS axis**: normal -30° to $+100^\circ$; more negative than -30° = **left axis deviation**, more positive than $+90$ to $+100^\circ$ = **right axis deviation**.
- ▶ **Supplementary leads**: V3R–V6R (right ventricular infarction), and posterior V7 (**midaxillary**), V8 (**posterior axillary**), V9 (**posterior scapular**) for posterolateral infarction.

Conduction abnormalities and key ECG correlates

- ▶ **Complete bundle branch block**: QRS ≥120 ms; incomplete 110–120 ms. RBBB — terminal vector right & anterior → **rSR'** in V1, **qRS** in V6. LBBB — vector left & posterior → wide **QS** in V1, **monophasic R** in V6; often marks coronary, hypertensive, aortic valve disease, or cardiomyopathy. Both cause **secondary ST-T changes** (T wave opposite to terminal QRS = appropriate discordance).
- ▶ **Fascicular blocks (hemiblocks)**: do not greatly widen QRS but shift the axis — **left anterior fascicular block** (axis more negative than -45° , commonest cause of marked LAD); **left posterior fascicular block** (axis $> +110$ – 120° , rare).

- ▶ **Pre-excitation:** wide QRS via a bypass tract (Wolff-Parkinson-White) — a non-conduction-delay cause of QRS prolongation.
- ▶ **Metabolic/drug effects:** hyperkalemia — peaked/tented T → wide QRS → loss of P → sine-wave → asystole; hypokalemia — prominent U waves, long QT; hypocalcemia prolongs / hypercalcemia shortens QT; hypothermia — Osborn (J) wave; digitalis — ST “scooping,” short QT.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Cardiac conduction system** (schematic, after Fig. 247-1): label SA node, right atrium (RA), left atrium (LA), AV node, AV junction, His bundle, right bundle branch, left bundle branch, ventricular septum, Purkinje fibres, RV, LV, ventricular myocardium, with directional arrows showing impulse sequence.
- ▶ **Diagram 2 — Basic ECG waveforms/intervals** (after Fig. 247-2): label P wave, QRS complex, T wave, U wave, J point, PR interval, QRS interval, ST segment, QT interval (and note the RR interval). Optionally align below it the AP phases 0–4 to show ST ↔ phase 2 and T ↔ phase 3.

Clinical / Diagnostic significance

- ▶ The ECG is **immediately available, noninvasive and inexpensive** — central to diagnosing arrhythmias, conduction disturbances and myocardial ischaemia/infarction, and may reveal life-threatening electrolyte disturbances, drug toxicity and susceptibility to sudden cardiac arrest.
- ▶ The 12-lead resting ECG is the **cornerstone** of arrhythmia evaluation; if active arrhythmia is captured a definitive diagnosis is made. As it samples only ~6 s, transient arrhythmias need **ambulatory monitoring** (Holter, event/patch recorders) or provocation, and **invasive EP study** for mechanism/ablation.
- ▶ ECG localization of ischaemia: **anterior** (V1–V6, I, aVL); **inferior** (II, III, aVF); **right ventricular** (right-sided leads); **posterior** (reciprocal ST depression V1–V3).
- ▶ ECG **voltage criteria** for LVH/RVH have low sensitivity; echocardiography and cardiac MRI give more definitive anatomic/functional data.

High-yield exam pointers

- ▶ Impulse order: SA node → atria → AV node → His → bundle branches → fascicles → Purkinje → ventricular myocardium.
- ▶ AV node = **only normal electrical atria-to-ventricle connection**; its slow conduction creates the PR interval (120–200 ms).
- ▶ P wave = atrial depolarization; QRS = ventricular depolarization; ST-T-U = ventricular repolarization; atrial repolarization is normally hidden in QRS.

- ▶ AP correspondence: **phase 0** → QRS, **phase 2** → ST, **phase 3** → T wave; *IK1 sets resting potential*, *If drives SA automaticity* (ivabradine target).
- ▶ Paper: 1 **small box** = 40 ms, 1 **large** = 200 ms, 1 mV = 10 mm; rate = 300/large boxes.
- ▶ Normal QRS axis -30° to $+100^\circ$; QRS ≥ 120 ms = **complete BBB**; RBBB rSR' in V1, LBBB QS in V1/R in V6.
- ▶ QTc upper limits 450 ms (men), 460 ms (women); Bazett QTc = $QT/\sqrt{RR}$.
- ▶ Hyperkalemia sequence: **tented T** → **wide QRS** → **flat P** → **sine wave** → **asystole**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 247 "Electrocardiography" (Goldberger) and Ch 250 "Principles of Clinical Cardiac Electrophysiology" (Sauer, Koplan, Zei). **Coverage note:** The provided chapters describe conduction anatomy functionally but do not give the nodal blood supply (SA-nodal/AV-nodal arteries), the named internodal/Bachmann interatrial tracts, or the classic resting escape pacemaker hierarchy (SA 60–100, AV junction 40–60, ventricular 30–40 /min) — these are added only where universally-accepted standard internal medicine and are flagged here as outside the supplied text (Harrison gives the dynamic SA range of 30–220 /min and the general "escape rhythm" concept instead).



Constrictive Pericarditis

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Constrictive pericarditis (CP) is the end-stage of a chronic inflammatory process in which a rigid, thickened, fibrotic and often calcified pericardium encases the heart, obliterating the pericardial cavity and limiting diastolic filling of the ventricles. It is the prototype of a *surgically curable* cause of right-heart failure / diastolic heart failure. (Note: the 2019 paper printed the topic as "conservative pericarditis" — a near-universal transcription error for constrictive pericarditis, which is the only recognised clinical entity and is answered here.)

Etiology and Classification

CP results when healing of fibrinous/serofibrinous pericarditis or resorption of a chronic effusion is followed by obliteration of the pericardial cavity by granulation tissue that contracts into a firm, sometimes calcific, scar. Constriction may evolve over weeks–months but typically takes years.

Group	Causes
Idiopathic / viral	Commonest cause in the developed world; risk after viral/idiopathic pericarditis <1%

Group	Causes
Post-surgical	After cardiac surgery of any type (common in transient/reversible CP)
Post-radiation	Mediastinal irradiation (breast cancer, lymphoma) — poor surgical prognosis
Tuberculous	Leading cause in the developing world (India), sub-Saharan Africa; risk after purulent bacterial pericarditis 20–30%, after immune/neoplastic 2–5%
Connective tissue / autoimmune	RA, SLE, scleroderma, sarcoidosis
Others	Chronic renal failure on dialysis (uremic), neoplasm, trauma with organised clot, asbestosis, drug-induced, <i>Mulibrey nanism</i> (familial, AR)

Harrison's clinical-temporal classification of pericarditis places constriction in the **subacute (6 wks–6 months, effusive-constrictive or constrictive)** and **chronic (>6 months, constrictive or adhesive)** categories.

Pathophysiology — the hallmark physiology

- ▶ **Impaired filling:** Ventricular filling is *unimpeded in early diastole* but stops abruptly when the elastic limit of the rigid pericardium is reached ($\approx$ entire stroke volume enters in early diastole). Contrast with tamponade, where filling is impeded *throughout* diastole.
- ▶ **Equalisation of pressures:** Ventricular end-diastolic, mean atrial, pulmonary venous and systemic venous pressures are all elevated and **equal to within ≤ 5 mmHg** of one another (typically ~ 20 – 25 mmHg).
- ▶ **Dissociation of intrathoracic and intracardiac pressures:** The stiff pericardium prevents transmission of the inspiratory fall in intrathoracic pressure to the cardiac chambers. On inspiration, the pressure drop reaches the pulmonary veins but **not** the LA/LV, reducing the pulmonary-vein-to-LA gradient $\rightarrow$ $\downarrow$ left-heart filling.
- ▶ **Enhanced ventricular interdependence:** Because total cardiac volume is fixed by the shell, inspiratory $\downarrow$ LV filling permits $\uparrow$ RV filling with a **leftward septal shift** (“septal bounce”); the reverse occurs in expiration. This is the basis of all the respirophasic Doppler signs.
- ▶ Systolic function is usually preserved (“pure” constriction); advanced disease may extend fibrosis into the myocardium (mixed constriction–restriction / myopericarditis), worsening prognosis.

Clinical Features

- ▶ **Symptoms:** Insidious fatigue, weakness, exertional dyspnoea, orthopnoea; progressive systemic venous congestion — raised abdominal girth, ascites (often *out of proportion to peripheral oedema*), congestive hepatomegaly/jaundice, anasarca, muscle wasting and cachexia in end-stage disease.

- ▶ **Jugular venous pulse:** Markedly elevated, with a **prominent, rapid y descent** and a normal x descent → **M- or W-shaped** waveform; fails to fall (or rises) on inspiration = **Kussmaul's sign**.
- ▶ **Pericardial knock:** Early diastolic sound at LSB/apex, slightly *earlier and higher-pitched* than an S3, from abrupt cessation of ventricular filling.
- ▶ **Pulsus paradoxus:** Present in only about **one-third** of cases (unlike tamponade, where it is the rule).
- ▶ **Other signs:** Distant heart sounds, *Broadbent's sign* (systolic apical retraction), hepatomegaly with pulsatile veins, splenomegaly, pleural effusions, stigmata of cardiac cirrhosis (spider naevi, palmar erythema). Atrial fibrillation is common.
- ▶ A common pitfall is mistaking CP for **hepatic cirrhosis** (ascites + hepatomegaly); inspection of the distended neck veins distinguishes them.

Investigations

- ▶ **ECG:** Non-specific — low-voltage QRS, diffuse T-wave flattening/inversion; **atrial fibrillation in ~one-third**.
- ▶ **Chest X-ray:** Normal or slightly enlarged heart; **pericardial calcification** (best seen in lateral view) — most frequent in tuberculous CP but neither sensitive nor specific; pleural effusions common.
- ▶ **Echocardiography–Doppler (first-line):** Pericardial thickening; **septal “bounce”**; dilated IVC/hepatic veins with blunted respiratory variation; abrupt halt of early LV filling. Doppler: respiratory variation in **mitral E $\geq 25\%$** ($\uparrow$ on early expiration), tricuspid/mitral flows $\sim 180^\circ$ out of phase, hepatic-vein **expiratory diastolic flow reversal**, mitral E deceleration time usually < 160 ms.
- ▶ **Tissue Doppler / strain:** *Annulus reversus* — medial (septal) mitral-annular **$e' > \text{lateral } e'$** ; preserved/increased medial e' (> 8 cm/s) favours constriction over restriction; *strain reversus* (preserved longitudinal, reduced circumferential strain).
- ▶ **CT / CMR:** CT is most accurate for **pericardial thickness** (normal < 2 mm) and calcification; thickening **> 4 mm** supports the diagnosis, but pericardium is of **normal thickness in $\sim 20\text{--}28\%$ of CP** — so normal thickness does *not* exclude it. CMR with T2-STIR/late gadolinium enhancement detects active pericardial inflammation (predicts response to anti-inflammatory therapy / transient CP).
- ▶ **Cardiac catheterisation (confirmatory in equivocal cases):** Elevated and equalised diastolic pressures; “square-root” / **dip-and-plateau** sign; RVEDP $> \frac{1}{3}$ of RV systolic pressure; **discordance** of RV and LV systolic pressures with respiration (RV rises as LV falls) and a **systolic area index > 1.1** ; low pulmonary artery pressure. **BNP is normal/low in CP but elevated in restriction**.

Constriction vs Restriction vs Tamponade

Feature	Constrictive pericarditis	Restrictive cardiomyopathy	Cardiac tamponade
Pulsus paradoxus	~1/3 of cases (+)	Usually absent	Marked (+++)
JVP y descent	Prominent (M/W shape)	Variable	Absent/blunted (x prominent)
Kussmaul's sign	Present (+++)	±	Absent
Pericardial knock	Present	Absent	Absent
S3	Absent	Present	Absent
RV–LV diastolic pressures	Equal (≤ 5 mmHg apart)	LV higher by ≥ 3 –5 mmHg	Equalised
Filling pressure >25 mmHg / severe PHT	Uncommon	Common	—
Respiratory flow variation	Exaggerated, discordant	Normal/concordant	Exaggerated
Pericardium	Thickened $\pm$ calcified	Normal	Effusion present
Septal bounce	Present	Absent	—
Tissue Doppler e' / BNP	e' increased; BNP normal	e' reduced; BNP high	—

Variants

- **Effusive-constrictive pericarditis (ECP):** Tense effusion *plus* visceral pericardial constriction. Constrictive physiology is unmasked **after pericardiocentesis** — defined as failure of RA pressure to fall by $\geq 50\%$ to <10 mmHg once intrapericardial pressure is reduced to ~ 0 . Commonest causes: idiopathic, malignancy, radiation, post-pericardiotomy, TB. Often needs wide excision of *both* visceral and parietal pericardium.
- **Transient / reversible constriction:** Subacute inflammatory CP (esp. early post-cardiac surgery) that resolves over 3–6 months; $\sim 60\%$ avoid surgery with anti-inflammatory therapy (NSAID + colchicine + prednisone $\pm$ IL-1 antagonist), guided by CMR late-gadolinium enhancement and raised hsCRP.

Treatment

- **Surgical pericardiectomy (decortication) is the only definitive cure** and should be as complete as possible (median sternotomy $\pm$ cardiopulmonary bypass; “waffle” procedure for dense epicardial involvement). Perform **early**, before myocardial atrophy/cachexia set in; benefit accrues over weeks–months.
- **Pre-operative coronary angiography** in patients >50 years to exclude CAD.

- ▶ **Operative mortality** 5–15% (up to ~20% in some series), highest with radiation-induced disease, renal/hepatic dysfunction, reduced LVEF, low serum sodium and NYHA class IV.
- ▶ **Medical / bridging therapy:** Salt restriction and aggressive **diuresis** (loop diuretics ± thiazide ± aldosterone antagonist) for volume overload; rate control with digoxin if AF (avoid drugs that slow the compensatory tachycardia). Treat the **specific cause** — e.g. anti-tuberculous chemotherapy for tuberculous CP, with pericardiectomy if constriction persists.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **JVP waveform in CP:** a venous pressure tracing showing a **prominent, steep y descent** with normal x descent giving an **M/W contour**; label *a wave*, *x descent*, *v wave*, *y descent* (*deep*), *Kussmaul's sign* (*inspiratory rise*).
- ▶ **Ventricular pressure tracing:** RV/LV diastolic curves showing the “**square-root**” (**dip-and-plateau**) sign with **equalised, elevated end-diastolic pressures**; label *early diastolic dip*, *diastolic plateau*, *elevated & equal EDP*, *respiratory discordance of RV/LV systolic peaks*.

Clinical / Diagnostic significance

- ▶ CP is one of the few **reversible/curable** causes of refractory right heart failure — always distinguish it from restrictive cardiomyopathy and cirrhosis, because management diverges completely.
- ▶ In India and the developing world, **tuberculosis remains a leading cause**; calcific (“armoured heart”) constriction is classically tuberculous.
- ▶ A multimodality approach (echo-Doppler → CT/CMR → catheterisation) is needed; no single test is definitive, and normal pericardial thickness does not exclude CP.
- ▶ Anti-inflammatory therapy can reverse *transient* inflammatory constriction and spare some patients surgery — identify them with CMR (LGE) and hsCRP.

High-yield exam pointers

- ▶ **Pathognomonic triad:** raised JVP with prominent y descent + Kussmaul's sign + pericardial knock.
- ▶ “**Square-root**” sign (dip-and-plateau) and **equalisation of diastolic pressures** (≤ 5 mmHg) on catheterisation.
- ▶ **Ventricular interdependence / septal bounce** with respirophasic discordance is the unifying mechanism — yields **systolic area index** > 1.1 .
- ▶ Pulsus paradoxus in only $\sim 1/3$ of CP (contrast tamponade) — *low-yield to expect it*.
- ▶ **Annulus reversus** (medial $e' >$ lateral e') and **normal/elevated e' with normal BNP** favour CP over restriction.

- ▶ **Pericardial calcification** = most often TB; thickening >4 mm supportive but absent in 20–28%.
- ▶ **Pericardiectomy** = only cure; **coronary angiography** if >50 y; mortality ~5–15%, worst with prior radiation.
- ▶ **Effusive-constrictive PCarditis**: constriction revealed *after* draining the effusion.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Pericardial Disease" (chronic constrictive pericarditis; effusive-constrictive and tuberculous pericardial disease).
- ▶ Braunwald's Heart Disease, 13e — "Pericardial Diseases" (pathophysiology of ventricular interdependence, echo-Doppler/tissue-Doppler criteria, invasive haemodynamics, pericardiectomy outcomes, effusive-constrictive and transient constriction).
- ▶ CMDT 2026 — "Constrictive Pericarditis" (essentials of diagnosis, current diuretic/surgical management, risk of constriction by aetiology).

Coverage note: The exam printed the topic as "conservative pericarditis," which is not a recognised entity; per the spec note this is a typo for **constrictive pericarditis**, and the answer is grounded accordingly. The corpus covers the topic in depth across all three texts; no fabrication was required.



Cor Pulmonale

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Cor pulmonale* ("pulmonary heart") is **right ventricular (RV) enlargement — hypertrophy and/or dilatation — progressing to right heart failure, caused by pulmonary hypertension that arises from primary disorders of the respiratory system, lung parenchyma, pulmonary vasculature, chest wall or ventilatory control**. By convention it **excludes** RV dysfunction secondary to left heart disease or congenital heart disease. As Braunwald frames it, "cor pulmonale, decompensated right heart failure, is the end-stage result of severe RV–pulmonary arterial (RV–PA) uncoupling." It is the common terminal pathway of advanced chronic lung disease, most often COPD, and carries a poor prognosis once overt RV failure supervenes.

Etiology and classification

- ▶ **Acute cor pulmonale** — sudden RV pressure overload and dilatation, classically from **massive/sub-massive pulmonary embolism**; also severe acute lung injury/ARDS. (Acute RV strain pattern, no time for hypertrophy.)
- ▶ **Chronic cor pulmonale** — slow RV hypertrophy then failure from sustained pulmonary hypertension. The underlying causes map largely onto **WSPH Group 3 (PH due to lung disease/hypoxia)** and **Group 4 (chronic thromboembolic PH)**.

Mechanism / category	Representative causes
Obstructive airway disease	COPD/emphysema (commonest cause), severe chronic asthma, bronchiectasis, cystic fibrosis
Restrictive / parenchymal (ILD)	Idiopathic pulmonary fibrosis, sarcoidosis, pneumoconioses, post-TB fibrosis
Chest-wall / neuromuscular	Kyphoscoliosis, thoracoplasty, obesity-hypoventilation, neuromuscular weakness
Hypoventilation / sleep-disordered breathing	Obstructive sleep apnoea, central hypoventilation syndromes
Chronic hypoxia without lung disease	Prolonged high-altitude residence
Pulmonary vascular disease	Pulmonary arterial hypertension (Group 1), CTEPH/recurrent PE (Group 4), schistosomiasis, sickle-cell disease

- ▶ In COPD, cor pulmonale “typically occurs in individuals who have marked decreases in FEV₁ (<25% of predicted) and chronic hypoxaemia (PaO₂ <55 mmHg)” (Harrison). Severe PH in lung disease is uncommon: ~90% of COPD patients have mPAP >20 mmHg but only ~5% exceed 35 mmHg.

Pathophysiology

- ▶ **Alveolar hypoxia** is the central driver: it triggers **hypoxic pulmonary vasoconstriction** (a reflex diverting blood from poorly-ventilated alveoli), which when chronic and global raises **pulmonary vascular resistance (PVR)**.
- ▶ Sustained hypoxaemia, acidosis and hypercapnia, plus **destruction/obliteration of the pulmonary capillary bed** (emphysema, fibrosis, embolic webs) and vascular remodelling (intimal fibrosis, medial hypertrophy), further increase PVR and pulmonary artery pressure.
- ▶ **Secondary erythrocytosis** (chronic hypoxia) raises blood viscosity, adding to RV load.
- ▶ Pulmonary hypertension is now defined hemodynamically as a **mean PA pressure (mPAP) >20 mmHg** at rest (lowered from the older ≥ 25 mmHg at the 2018 Sixth World Symposium); pre-capillary PH additionally requires **PVR >2 Wood units with PA wedge pressure ≤ 15 mmHg**.
- ▶ Rising **RV afterload** → compensatory **RV hypertrophy** → progressive **RV dilatation** → loss of RV–PA coupling → falling RV output, septal flattening (D-shaped LV), functional **tricuspid regurgitation** and systemic venous congestion = clinical right heart failure.

Clinical features

- ▶ **Symptoms** — exertional dyspnoea and fatigue dominate early; as RV fails, **dependent (pedal) oedema, abdominal bloating/distension** (congestive hepatomegaly, ascites), exertional chest pain, and **pre-syncope/syncope** appear (advanced disease). Symptoms of the underlying lung disease (cough, sputum, wheeze) coexist.

Sign	Underlying basis
Loud / palpable P2, accentuated pulmonic component of S2	Elevated pulmonary artery pressure
Left parasternal heave / RV lift	RV hypertrophy & pressure overload
Right-sided S3 ($\pm$ S4) gallop	RV dysfunction / decreased compliance
Raised JVP with prominent <i>a</i> wave; large <i>v</i> wave if TR	Systemic venous congestion
Pansystolic tricuspid regurgitant murmur (louder on inspiration — <i>Carvallo's sign</i>)	RV/tricuspid annular dilatation
Tender, pulsatile hepatomegaly, ascites, pedal oedema	Right heart failure / congestion
Central cyanosis, clubbing (in ILD/bronchiectasis)	Hypoxaemia / underlying lung disease

- ▶ Harrison: *symmetric* pedal oedema “may suggest cor pulmonale,” whereas asymmetric oedema points to DVT; the syndrome presents “with abdominal bloating or distention and pedal edema.”

Investigations

- ▶ ECG — signs of RV hypertrophy with strain: **peaked (tall) R waves in V1, ST-segment depression in V2–V3 (strain), P pulmonale** (P wave >3 mm / tall peaked in II, III, aVF), **right axis deviation** and RBBB; the acute PE pattern is S1Q3T3 with sinus tachycardia.
- ▶ Chest X-ray — enlarged central/proximal pulmonary arteries with peripheral “pruning,” RV enlargement, and **obliteration of the retrosternal space** on the lateral film; features of the underlying lung disease (hyperinflation in COPD, fibrosis in ILD).
- ▶ Echocardiography (key initial screening test) — estimated PA systolic pressure >35 mmHg / **tricuspid regurgitant jet velocity >2.8 m/s** suggests PH; **RV hypertrophy and dilatation, RA enlargement, interventricular septal flattening in diastole** (pressure overload); agitated-saline “bubble” study to exclude intracardiac shunt.
- ▶ BNP / NT-proBNP — correlate with RV dysfunction and prognosis.
- ▶ PFT + ABG — characterise obstructive vs restrictive disease, document hypoxaemia/hypercapnia; an **isolated low DLCO** is typical of pulmonary vascular involvement.
- ▶ V/Q scan or CT pulmonary angiography — screen for CTEPH; nocturnal oximetry/polysomnography for OSA.
- ▶ Right heart catheterisation — *gold standard* to confirm and classify PH (mPAP >20 mmHg, pre-capillary pattern PVR >2 WU, PAWP ≤ 15 mmHg).

Management

- ▶ Treat the underlying disorder — this is the cornerstone:

- COPD: smoking cessation, inhaled bronchodilators (LABA/LAMA) ± ICS triple therapy, pulmonary rehabilitation; treat exacerbations.
- ILD: disease-specific therapy; OSA/hypoventilation: CPAP/NIV; CTEPH: lifelong anticoagulation + **pulmonary endarterectomy** (curative in suitable cases), or **riociguat**/balloon pulmonary angioplasty if inoperable.
- ▶ **Long-term oxygen therapy (LTOT)** — the single most important measure in chronic hypoxaemic cor pulmonale; reverses hypoxic pulmonary vasoconstriction and **reduces mortality, the benefit being proportional to hours/day used**. Prescribe for **resting PaO₂ ≤55 mmHg or SaO₂ ≤88%, OR PaO₂ 56–59 mmHg / SaO₂ 89% with evidence of cor pulmonale** (dependent oedema, **P pulmonale** on ECG, or **haematocrit >56%**). In acute illness, target SaO₂ 88–92% to avoid CO₂ retention.
- ▶ **Diuretics (± mineralocorticoid-receptor antagonist)** and a **low-salt diet** for congestion/oedema — used cautiously to avoid excessive preload reduction and prerenal azotaemia.
- ▶ **Therapeutic phlebotomy** for symptomatic severe secondary erythrocytosis (Hct >56%).
- ▶ **Caveat on PAH-specific vasodilators** — prostanoids, ERAs, PDE5 inhibitors are *not* routinely beneficial in Group 3 (lung-disease) cor pulmonale and may worsen V/Q matching; inhaled iloprost gave only modest benefit in ILD-PH and a COPD-PH trial was stopped early. They are reserved for Group 1 PAH/selected Group 4 disease at expert centres.
- ▶ **Lung or heart–lung transplantation** in refractory end-stage disease.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology flowchart (label each box):** *Chronic lung disease / alveolar hypoxia → Hypoxic pulmonary vasoconstriction + capillary-bed destruction + vascular remodelling + erythrocytosis → ↑ Pulmonary vascular resistance → Pulmonary hypertension (↑ RV afterload) → RV hypertrophy → RV dilatation → Right ventricular failure (cor pulmonale) → Raised JVP, tender hepatomegaly, ascites, pedal oedema, tricuspid regurgitation.*
- ▶ **ECG of RV hypertrophy / strain (label):** *Tall R wave in V1, deep S wave in V6, right axis deviation, P pulmonale (tall peaked P >2.5–3 mm in II), ST-T “strain” in V1–V3, RBBB pattern.*

Clinical / Diagnostic significance

- ▶ Cor pulmonale is the chief cardiovascular complication of advanced chronic lung disease and a **marker of poor prognosis**; its appearance signals the need to optimise oxygenation and reassess the underlying disorder.
- ▶ Distinguishing cor pulmonale (Group 3/4 PH) from PH due to **left heart disease (Group 2)** and from **pulmonary arterial hypertension (Group 1)** is essential, because management diverges

sharply — LTOT and treating the lung disease for cor pulmonale versus PAH-targeted vasodilators for Group 1.

- ▶ **Symmetric** pedal oedema with raised JVP in a known COPD/ILD patient should prompt evaluation for cor pulmonale rather than being dismissed; an absolutely normal echocardiogram makes significant PH unlikely.

High-yield exam pointers

- ▶ **Definition stresses the cause:** RV failure from a *pulmonary/respiratory* cause — left heart and congenital disease are *excluded*.
- ▶ **COPD is the commonest cause of chronic cor pulmonale; massive PE** is the classic cause of acute cor pulmonale.
- ▶ **Hypoxic pulmonary vasoconstriction** is the central mechanism; chronic hypoxia + capillary loss + remodelling → ↑PVR → PH → RV failure.
- ▶ **PH now = mPAP >20 mmHg** (revised 2018 WSPH); pre-capillary PH adds PVR >2 WU, PAWP ≤15 mmHg; **RHC is the gold standard**.
- ▶ **Cardinal signs:** loud P2, left parasternal heave, raised JVP, tricuspid regurgitant murmur, tender pulsatile hepatomegaly, pedal oedema.
- ▶ **ECG:** P pulmonale (P >3 mm in II/III/aVF), tall R in V1, right axis deviation, RV strain; **echo** shows RV dilatation/hypertrophy and septal flattening.
- ▶ **LTOT reduces mortality** in hypoxaemic cor pulmonale ($\text{PaO}_2 \leq 55 \text{ mmHg}$ / $\text{SaO}_2 \leq 88\%$, or $\leq 59/89\%$ with cor pulmonale signs); benefit is dose-dependent on hours/day.
- ▶ **Do not** give PAH-specific vasodilators routinely in lung-disease cor pulmonale; **treat the underlying disease + oxygen + diuretics**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Pulmonary Hypertension” (definition, hemodynamics, WSPH classification, ECG/CXR/echo/RHC, treatment of PH due to lung disease & CTEPH); “Chronic Obstructive Pulmonary Disease” (cor pulmonale in COPD, $\text{FEV}_1/\text{PaO}_2$ thresholds, oxygen therapy and mortality benefit); “Approach to the Patient with Disease of the Respiratory System” (cor pulmonale symptoms, symmetric oedema); “Interstitial Lung Disease” and “Heart Failure: Pathophysiology and Diagnosis” (cor pulmonale among causes of right heart failure).
- ▶ **Braunwald's Heart Disease, 13e** — “Pulmonary Hypertension” (RV–PA uncoupling definition of cor pulmonale, physical-examination findings of right-sided pressure/volume overload, Group 3 lung-disease PH, TR velocity threshold).
- ▶ **CMDT 2026** — “Pulmonary Disorders” (LTOT prescribing criteria including P pulmonale and haematocrit thresholds; P-pulmonale definition).

Coverage note: The corpus has no chapter titled “Cor Pulmonale”; the entity is covered within the Pulmonary Hypertension, COPD and respiratory-approach chapters. Universally-accepted standard points not separately spelled out in these chapters (e.g., *Carvallo’s sign* for inspiratory accentuation of the TR murmur, the S1Q3T3 pattern of acute PE) are included as established textbook medicine.



Describe conduction system of the heart and add a note on complete heart block

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — The cardiac conduction system is a network of specialised, predominantly non-contractile myocytes that generate and propagate the electrical impulse responsible for the orderly, sequential contraction of the atria and ventricles. It comprises the **sinoatrial (SA) node** (the natural pacemaker), the **atrial preferential/internodal pathways**, the **atrioventricular (AV) node**, the **bundle of His**, the **right and left bundle branches**, and the terminal **Purkinje network**. *Complete (third-degree) heart block* is the most severe AV conduction disturbance, in which no atrial impulse reaches the ventricles, producing complete AV dissociation with a ventricular rate slower than the atrial rate and a constant risk of syncope (Stokes-Adams attacks) and asystolic death.

Anatomy and physiology of the SA node and atrial conduction

- ▶ **SA node** — a cigar-shaped cluster of small fusiform pacemaker cells in the *sulcus terminalis* (*crista terminalis*) on the epicardial surface at the **right atrial–superior vena cava junction**, enveloping the SA nodal artery within a protective extracellular matrix that insulates it from the hyperpolarising atrium.
- ▶ **Blood supply** — SA nodal artery arises from the **right coronary artery (RCA)** in 55–60% and the **left circumflex (LCx)** in 40–45%.
- ▶ **Pacemaker physiology** — nodal cells have no true resting potential; they exhibit spontaneous **phase 4 (diastolic) depolarisation** driven by the *funny current* (I_f) plus T- and L-type calcium currents. Phase 0 upstroke is slow and **calcium-mediated** (fast Na^+ channels absent). Intrinsic discharge rate **60–100 beats/min**, dominant because phase 4 is steepest here.
- ▶ **Autonomic control** — at rest the node is under vagal (parasympathetic) predominance; after complete autonomic blockade the **intrinsic heart rate** $\approx 118.1 - (0.57 \times \text{age})$ beats/min (~ 100 –110/min in young adults).
- ▶ **Atrial spread** — the impulse spreads to the AV node by **preferential intra-atrial pathways** of higher conduction velocity than ordinary atrial muscle. The **Bachmann bundle** carries activation from the right to the left atrium. The classic three *internodal tracts* — **anterior (Bachmann)**,

middle (Wenckebach) and posterior (Thorel) — are traditional eponyms; their existence as discrete insulated tracts remains debated, with preferential conduction now attributed to fibre orientation in atrial myocardium.

Structure and physiology of the AV node and His–Purkinje system

- ▶ **AV node** — a small structure ($\sim 1 \times 3 \times 5$ mm) beneath the right atrial endocardium at the apex of the **triangle of Koch**, bounded by the **coronary sinus ostium** (posteriorly), the **septal tricuspid annulus** (anteriorly) and the **tendon of Todaro** (superiorly).
- ▶ **Zones** — transitional (atrionodal) cells, the compact node, and the penetrating His bundle. Two functional inputs exist in many people: a **slow pathway** (inferior nodal extension) and a **fast pathway** (the substrate for AV nodal re-entry tachycardia).
- ▶ **Slow conduction / “gatekeeper” role** — compact-node cells sit at ~ -60 mV, have slow phase 0 (<10 V/s) mediated by **L-type Ca^{2+} current ($I_{\text{Ca-L}}$)**, sparse gap junctions (predominantly **connexin-40**) and **decremental conduction**. This creates the physiological AV delay (compact node velocity <10 cm/s vs ~ 35 cm/s in atrial muscle), allowing atrial systole to complete ventricular filling and protecting the ventricle from rapid atrial rates. Intrinsic AV-junctional escape rate **20–60/min**.
- ▶ **Blood supply** — AV nodal artery from the **RCA in 80–90%** and **LCx in $\sim 10\%$** (matching coronary dominance); the bundle branches have dual supply from **LAD septal perforators** (LBB, proximal RBB) and the posterior descending artery.
- ▶ **His bundle (penetrating AV bundle)** — pierces the central fibrous body/annulus fibrosus and runs along the ventricular septum; insulated from working myocardium.
- ▶ **Bundle branches** — **right bundle branch (RBB)**, a discrete cord reaching the **moderator band**; **left bundle branch (LBB)**, a broad subendocardial sheet dividing into **anterior and posterior fascicles**.
- ▶ **Purkinje network** — ramifies over both ventricular endocardia; **fastest conduction in the heart** ($1\text{--}3$ m/s), with rapid phase 0, prolonged plateau and modest automaticity (escape $\sim 20\text{--}40/\text{min}$).
- ▶ **Autonomic note** — the AV node is richly innervated by sympathetic and parasympathetic fibres; the His bundle and distal system are not influenced by autonomic tone.

ECG correlation of the conduction sequence

ECG component	Electrical event	Normal value
P wave	SA node firing $\rightarrow$ atrial depolarisation (RA then LA)	<120 ms; upright in II, inverted in aVR
PR interval	Onset of atrial to onset of ventricular depolarisation (mostly AV-nodal delay)	120–200 ms

ECG component	Electrical event	Normal value
PR segment	AV nodal + His conduction delay	isoelectric
QRS complex	His–Purkinje → ventricular depolarisation	≤100–110 ms
ST-T-U	Ventricular repolarisation	—

- ▶ Invasive His-bundle electrogram intervals: AH interval (AV-nodal conduction) normally <130 ms; HV interval (His-Purkinje conduction) normally ≤55 ms. A prolonged HV (>100 ms) carries ~10% annual risk of complete AV block.

Complete (third-degree) heart block — definition and classification

- ▶ **Definition** — complete interruption of AV conduction; atria and ventricles are driven by independent pacemakers (AV dissociation) with the atrial rate exceeding the ventricular (escape) rate. Complete AV block always implies AV dissociation, but not all AV dissociation is complete block.
- ▶ Level of block determines escape characteristics:

Feature	Block in AV node / proximal His	Infra-Hisian (distal) block
Typical setting	Often congenital, inferior MI, drug/vagal, Lyme	Usually acquired, anterior MI, sclerodegenerative
Escape focus	Junctional, near His	Ventricular (Purkinje)
QRS	Narrow	Wide
Escape rate	40–60/min, more stable	<40/min, unreliable
His electrogram	Each ventricular beat preceded by His deflection; P not followed by His	P followed by His; escape not preceded by His
Response to atropine/exercise	Improves	No improvement
Prognosis	Better	Worse, risk of asystole

Aetiology, clinical features and diagnosis of complete heart block

- ▶ **Idiopathic fibrosis/sclerosis** (~50% of acquired block) — *Lev's disease* (proximal bundle-branch fibrosis/calcification, elderly, related to aortic/mitral annular calcification) and *Lenègre's disease* (distal sclerodegeneration in younger patients); accelerated familial forms link to SCN5A mutations (also cause LQT3).
- ▶ **Ischaemic** — AV block complicates 10–25% of acute MI; inferior MI → nodal block, narrow stable escape, usually reversible; anterior MI → distal/infra-nodal block, wide unstable escape, high mortality.

- ▶ **Iatrogenic/drugs** — beta blockers, verapamil/diltiazem, digoxin; valve surgery, TAVR, alcohol septal ablation, catheter ablation.
- ▶ **Infective/infiltrative/autoimmune** — Lyme carditis (*Borrelia burgdorferi*), endocarditis with perivalvular abscess, viral myocarditis, **Chagas' disease**, cardiac sarcoidosis, amyloidosis, SLE/RA/scleroderma.
- ▶ **Congenital** — maternal SLE/anti-Ro antibodies, complex congenital heart disease (TGA, ostium primum ASD, endocardial cushion defects).
- ▶ **Neuromuscular** — myotonic dystrophy, Kearns-Sayre syndrome, Lamin A/C cardiomyopathy.
- ▶ **Clinical features** — fatigue, exertional intolerance, dyspnoea, presyncope and **Stokes-Adams syncope/convulsions**; sudden death from asystole. Signs: **variable-intensity S₁**, **intermittent cannon “a” waves** in the JVP (atrium contracting against a closed AV valve), wide pulse pressure and variable systolic BP.
- ▶ **Investigations** — 12-lead ECG (AV dissociation, atrial rate > ventricular rate, P waves marching through independent QRS); ambulatory/Holter or mobile telemetry for intermittent block; echocardiography for structural disease; **electrophysiology study with His-bundle recording** to localise block; **cardiac MRI / FDG-PET** for sarcoid/amyloid (especially age ≤60); Lyme serology, electrolytes, TSH and drug review for reversible causes.

Management of complete heart block

- ▶ **Acute** — identify and reverse causes (stop AV-blocking drugs, correct electrolytes/ischaemia, treat hypoxia/sleep apnoea). For symptomatic/haemodynamically unstable block: **atropine 0.5 mg IV** (effective only for nodal block), then **isoproterenol, dopamine or epinephrine** infusion; **transcutaneous pacing** (cathode patch over apex anteriorly, anode posteriorly) as a bridge; **transvenous temporary pacing** for reliability when escape is slow or wide-complex.
- ▶ **Definitive** — **permanent pacemaker (PPM)** is the only reliable therapy. Acquired **third-degree (and Mobitz II) AV block** is a **Class I indication regardless of symptoms** when not reversible/physiological. A **dual-chamber (DDD) device** is preferred to preserve AV synchrony.
- ▶ **Physiologic / conduction-system pacing** — in patients with LVEF <50% likely to need ventricular pacing >40% of the time, use **His-bundle or left bundle branch area pacing**, or **cardiac resynchronisation therapy (CRT)**, to avoid pacing-induced heart failure.
- ▶ **In acute MI** — pace for persistent 2nd/3rd-degree block or transient high-grade block with new bundle branch block; transient inferior-MI nodal block usually needs no permanent device.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Conduction system of the heart (coronal heart outline)**. Labels: *SA node (at RA-SVC junction), Bachmann bundle, anterior/middle/posterior internodal tracts, AV node (triangle of Koch — coronary sinus ostium, tendon of Todaro, septal tricuspid annulus),*

bundle of His, right bundle branch → moderator band, left bundle branch with anterior and posterior fascicles, Purkinje fibres.

- ▶ **Diagram 2 — ECG strip of complete heart block.** Labels: *regular P waves (atrial rate), regular but slower QRS (ventricular escape), no fixed PR relationship = AV dissociation, P waves “marching through” QRS, plus a JVP tracing showing intermittent cannon “a” waves.*

Clinical / Diagnostic significance

- ▶ The **physiological AV-nodal delay** times atrial against ventricular contraction (optimising filling) and shields the ventricle during atrial tachyarrhythmias — its decremental property is exploited by AV-nodal blocking drugs for rate control.
- ▶ **Dual blood supply** explains clinical patterns: SA/AV nodes are RCA-dependent, so inferior MI causes (usually reversible) nodal block, whereas anterior (LAD) MI damaging the His-Purkinje system causes dangerous infranodal block.
- ▶ **QRS width + escape rate localise the block** and predict stability — a wide, slow escape mandates urgent pacing.
- ▶ Distinguishing **congenital** (narrow, faster escape, rate rises with exercise) from **acquired** (wide, slow escape, no exercise response) CHB guides prognosis and urgency of pacing.
- ▶ Always exclude **reversible causes** (drugs, ischaemia, hyperkalaemia, hypothyroidism, Lyme, high vagal tone) before committing to a permanent device.

High-yield exam pointers

- ▶ **SA node = pacemaker (60–100/min); AV junction 40–60/min; Purkinje 20–40/min** — hierarchy of subsidiary pacemakers.
- ▶ **Triangle of Koch** = coronary sinus ostium + tendon of Todaro + septal tricuspid annulus → AV node landmark.
- ▶ Normal PR 120–200 ms; AH <130 ms; HV ≤55 ms; QRS ≤110 ms.
- ▶ *Lev’s disease* = proximal/calcific (old); *Lenègre’s disease* = distal sclerodegenerative (young); SCN5A = progressive familial heart block (+LQT3).
- ▶ CHB = AV dissociation with atrial rate > ventricular rate; hallmark sign = cannon “a” waves and variable S₁.
- ▶ Narrow QRS escape = nodal, stable, atropine-responsive; wide QRS escape = infranodal, unstable, atropine-resistant.
- ▶ **Atropine works only for nodal block**; for infranodal/unstable block use isoproterenol + temporary pacing.

- ▶ Acquired third-degree / Mobitz II AV block = Class I indication for permanent pacing irrespective of symptoms.
- ▶ Inferior MI block = nodal, reversible; anterior MI block = infranodal, high mortality, needs pacing.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “The Bradyarrhythmias: Disorders of the Sinoatrial Node” and “The Bradyarrhythmias: Disorders of the Atrioventricular Node” (AV node anatomy, triangle of Koch, AH/HV intervals, aetiology and pacing indications); “Electrocardiography” (P/PR/QRS intervals, conduction sequence).
- ▶ **Braunwald's Heart Disease, 13e** — “Bradyarrhythmias and Atrioventricular Block” (classification of AV block, levels and His-electrogram correlation in complete heart block, AV dissociation, cannon a waves) and “Mechanisms of Cardiac Arrhythmias” / “Electrocardiography” (SA node automaticity, Bachmann bundle, nodal conduction velocities).
- ▶ **CMDT 2026** — “Disorders of Cardiac Rhythm” (current management of AV block, atropine/isoproterenol/pacing, pacemaker nomenclature and indications).
- ▶ *Coverage note:* the named internodal tracts (anterior/Bachmann, middle/Wenckebach, posterior/Thorel) are classic teaching; modern texts (Braunwald) regard discrete insulated internodal tracts as controversial, favouring preferential atrial conduction — presented here with that caveat.



Describe the structure of the Mitral Valve apparatus. Discuss the etiology, clinical features and management of Mitral Stenosis

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — The mitral (left atrioventricular) valve is not a simple flap but a functional “mitral apparatus” comprising six integrated components — the *annulus*, *two leaflets*, *two commissures*, *chordae tendineae*, *papillary muscles* and *the supporting left atrial/ventricular myocardium* — whose coordinated action permits unobstructed diastolic LA-to-LV filling and competent systolic closure. Mitral stenosis (MS) is obstruction to LV inflow at valve level producing a diastolic LA-to-LV pressure gradient — the hemodynamic hallmark. The normal orifice is 4–6 cm²; obstruction becomes significant at <2 cm² and “severe” at <1.5 cm², when an LA pressure of ~25 mmHg is needed to maintain output.

Structure of the mitral valve apparatus

Component	Key anatomical features	Relevance in MS
Annulus	Saddle-/D-shaped fibrous ring at the LA–LV junction; anterior part is in fibrous continuity with the aortic valve, posterior part is muscular; contracts in systole to reduce orifice	Mitral annular calcification with extension onto leaflets is a recognised cause of obstruction
Leaflets (2)	Anterior (aortic/septal) — larger, semicircular, guards ~two-thirds of the orifice area; Posterior (mural) — smaller, quadrangular, with scallops	Rheumatic diffuse leaflet thickening + calcification produces the funnel-shaped , “fish-mouth” valve
Commissures (2)	Anterolateral and posteromedial junctions where the two leaflets meet	Commissural fusion is the cardinal rheumatic lesion; splitting it is the basis of <i>commissurotomy</i>
Chordae tendineae	Fibrous cords from papillary muscle tips to leaflets (marginal/primary, intermediate, basal)	Fusion and shortening of chordae create <i>subvalvular</i> stenosis; surgery must “loosen subvalvular fusion”
Papillary muscles (2)	Anterolateral and posteromedial; arise from LV wall, anchor the chordae and prevent leaflet prolapse	Scarring of the subvalvular apparatus reduces suitability for balloon commissurotomy
LA & LV myocardium	The atrial and ventricular walls form the muscular base of the apparatus	LA dilatation/AF promote appendage thrombus; LV EF is preserved in pure MS

- ▶ The valve functions as a *unit*: leaflet closure depends on annular size, chordal restraint and papillary-muscle/LV-wall integrity acting together.
- ▶ In rheumatic disease the inflammatory injury simultaneously affects **leaflets, commissures and the subvalvular apparatus** — the wider the involvement, the less amenable the valve is to balloon therapy.

Etiology and pathology of Mitral Stenosis

Major causes (Table 274-1)
Rheumatic fever — the leading cause worldwide
Congenital — parachute valve, cor triatriatum
Severe mitral annular calcification with leaflet involvement
SLE, rheumatoid arthritis
Left atrial myxoma

Major causes (Table 274-1)**Infective endocarditis with large vegetations**

- ▶ **Rheumatic fever** is by far the commonest cause; **pure or predominant MS** occurs in ~40% of patients with rheumatic heart disease and a history of rheumatic fever, while lesser MS may accompany MR and aortic disease.
- ▶ Incidence has **fallen in temperate, middle-/high-income countries** but MS **remains a major problem in low-income regions** — sub-Saharan Africa, **India**, Southeast Asia and Oceania.
- ▶ **Pathology**: chronic inflammation → diffuse leaflet thickening with fibrosis and calcific deposits → **commissural fusion, fusion and shortening of chordae tendineae**, rigid cusps and narrowing at the apex of the funnel-shaped (“fish-mouth”) valve. Later changes are aggravated by altered-flow trauma. Calcification immobilises leaflets and narrows the orifice further; thrombus/embolism may arise from the calcific valve or, more often in AF, from the dilated **LA appendage**.

Pathophysiology

- ▶ A reduced orifice obliges flow only across an **abnormally raised LA–LV gradient**; elevated pulmonary venous and PA wedge pressures reduce pulmonary compliance → **exertional dyspnea**.
- ▶ **Tachycardia** (especially rapid AF) shortens diastole disproportionately, raising the transvalvular gradient and LA pressure for any given output — explaining decompensation with fever, exercise, anemia, pregnancy and thyrotoxicosis.
- ▶ **LV diastolic pressure and EF remain normal** in isolated MS.
- ▶ **Pulmonary hypertension** results from (1) passive backward transmission of LA pressure, (2) reactive pulmonary arteriolar constriction (“second stenosis”), (3) interstitial edema of vessel walls, and (4) end-stage obliterative vascular changes → RV enlargement, secondary **TR/PR** and right heart failure.

Clinical features

Symptoms — Latent period of ~2 decades after rheumatic carditis; disability typically in the **fourth decade**.

- ▶ Progressive **exertional dyspnea**, then **orthopnea** and **paroxysmal nocturnal dyspnea**.
- ▶ Onset of **persistent AF** marks a turning point and accelerates symptom progression.
- ▶ **Hemoptysis** from rupture of pulmonary–bronchial venous connections (pulmonary venous hypertension); rarely fatal.
- ▶ **Recurrent pulmonary emboli** (often from RA mural thrombus) — important late morbidity/mortality.
- ▶ **Pulmonary infections** (bronchitis, bronchopneumonia, lobar pneumonia).

- ▶ **Systemic embolization** (incidence 10–20%) — commoner with AF, age >65, and reduced CO; may be the presenting feature even in mild MS.
- ▶ **Ortner's (cardiovocal) syndrome** — hoarseness from compression of the left recurrent laryngeal nerve by an enlarged LA/PA.

Signs

- ▶ **Inspection/palpation: malar flush (“mitral facies”)** with pinched, blue facies in severe MS; prominent jugular **a waves** (in sinus rhythm with severe pulmonary hypertension/TS); a **parasternal lift** (RV enlargement); rarely a diastolic thrill at the apex in left lateral position.
- ▶ **Auscultation (the diagnostic quartet):** **loud (accentuated) S1**; **loud P2** with closely split S2 when PAP is high; **opening snap (OS)** best heard in expiration at or just medial to the apex, following A2 by 0.05–0.12 s; and a **low-pitched, rumbling mid-diastolic murmur** at the apex (left lateral position, accentuated by exercise) with **presystolic accentuation** in sinus rhythm.
- ▶ The **A2–OS interval varies inversely with severity**, and murmur duration correlates with severity when CO is preserved.
- ▶ **Associated murmurs:** functional TR with **Carvallo's sign** (louder on inspiration); **Graham Steell murmur** of pulmonary regurgitation in severe pulmonary hypertension. With very low CO, findings may vanish — “**silent MS.**”

Investigations

- ▶ **ECG: P mitrale** (broad notched P, LA enlargement); tall peaked P in II and upright in V1 with pulmonary hypertension/TS; **right-axis deviation and RV hypertrophy** in severe pulmonary hypertension; AF common.
- ▶ **Echocardiography (investigation of choice):** TTE with color/spectral Doppler gives the **E and A wave** inflow velocities, peak/mean gradients, **mitral valve area**, leaflet calcification/restriction, subvalvular distortion, associated MR, PA systolic pressure (from TR jet) and suitability for balloon valvotomy. The “**echo score**” (leaflet thickening, calcification, mobility, subvalvular thickening) predicts PMBC success — a **lower score = better outcome**. TEE is performed to **exclude LA/appendage thrombus** before PMBC.
- ▶ **Chest X-ray:** straightening of the upper-left cardiac border, prominent main PAs, dilated upper-lobe veins, posterior esophageal displacement by the enlarged LA, and **Kerley B lines** when mean LA pressure exceeds ~20 mmHg.
- ▶ **Cardiac catheterization:** reserved for clinical–echo discrepancy; CT coronary angiography or invasive angiography screens for CAD before intervention.

Management

Medical

- ▶ **Secondary prophylaxis** with penicillin against group A streptococcus; infective-endocarditis prophylaxis only in high-risk patients.
- ▶ **Symptom control:** sodium restriction and low-dose diuretics.
- ▶ **Rate control of AF:** beta blockers, non-dihydropyridine calcium-channel blockers (verapamil/diltiazem), or digitalis glycosides.
- ▶ **Anticoagulation:** vitamin K antagonist (warfarin, INR 2–3) indefinitely for MS with AF, prior thromboembolism or LA thrombus. **DOACs are contraindicated** — a randomized trial showed higher mortality with rivaroxaban than warfarin in rheumatic MS with AF.
- ▶ **Cardioversion** for recent-onset AF after ≥3 weeks of therapeutic anticoagulation (or after heparin + TEE if urgent); rarely sustained in severe MS with large LA or AF >1 year.

Mechanical relief of obstruction (symptomatic NYHA II–IV, severe MS, orifice <~1 cm²/m² BSA or <1.5 cm²):

Procedure	Indication / requirements
Percutaneous mitral balloon commissurotomy (PMBC)	Procedure of choice for pliable, minimally calcified valves; needs little commissural calcium, unscarred subvalvular apparatus, no LA thrombus and MR ≤2+/4+. Inoue balloon via transseptal puncture; event-free survival 80–90% over 3–7 years in patients <45 y. Preferred in pregnancy (TEE-guided, minimal radiation)
Open surgical commissurotomy	When PMBC unsuitable/failed or restenosis; on bypass — split commissures, free subvalvular fusion of papillary muscles/chordae, debulk calcium, remove atrial thrombi; perioperative mortality ~2%
Mitral valve replacement (MVR)	Significant associated MR, severely distorted/calcified valve; chordal attachments preserved to protect LV function; perioperative mortality 2–5%

- ▶ **Success criterion** (any commissurotomy): **≥50% fall in mean gradient and doubling of valve area.**
- ▶ In **asymptomatic** patients, intervene only if recurrent systemic embolization or severe pulmonary hypertension (PA systolic **>50 mmHg at rest or >60 mmHg with exercise**).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Mitral valve apparatus (LV opened, “surgeon’s view”):** label *mitral annulus*, *anterior (aortic) leaflet*, *posterior (mural) leaflet*, *anterolateral commissure*, *posteromedial commissure*, *chordae tendineae*, *anterolateral papillary muscle*, *posteromedial papillary muscle*, *LA*, *LV wall*.

- ▶ **Auscultation timing strip of MS:** label *loud S1, A2, opening snap (OS), mid-diastolic rumble, presystolic accentuation* — with the **A2–OS interval** marked (shorter interval = more severe).

Clinical / Diagnostic significance

- ▶ The diagnostic auscultatory triad — **loud S1 + opening snap + presystolic-accentuated diastolic rumble** — localises the lesion at the bedside; a **short A2–OS interval** flags severe disease.
- ▶ **Echo + echo score** is decisive: it both grades severity and selects patients for **PMBC vs surgery**; mandatory TEE rules out LA thrombus pre-procedure.
- ▶ **AF and the dilated LA appendage** drive thromboembolism — hence lifelong **warfarin** (not DOACs).
- ▶ Distinguish MS from **MR**, the **Austin Flint murmur of AR** (softens with amyl nitrite, no presystolic accentuation), **tricuspid stenosis**, **ASD** and **LA myxoma** (positional murmur, systemic features, IL-6 elevation).

High-yield exam pointers

- ▶ Normal MV area **4–6 cm²**; severe MS **<1.5 cm²**; very severe **<1 cm²**; LA pressure ~25 mmHg sustains output in severe MS.
- ▶ **Rheumatic fever** is the leading cause; pure MS in ~40% of RHD.
- ▶ Lesion quartet: **commissural fusion, leaflet thickening/calcification, chordal fusion-shortening, fish-mouth orifice**.
- ▶ **Ortner's syndrome** = hoarseness from left recurrent laryngeal nerve compression; **Carvallo's sign** = inspiratory accentuation of TR.
- ▶ **P mitrale** on ECG; **Kerley B lines** when mean LA pressure >20 mmHg.
- ▶ **A2–OS interval inversely proportional** to MS severity.
- ▶ **PMBC** = treatment of choice for pliable valves; needs no LA thrombus and MR ≤2+; success = 50% gradient fall + doubling of area.
- ▶ **Avoid DOACs** (rivaroxaban increased mortality vs warfarin); PMBC preferred in pregnancy.

SOURCE & COVERAGE

Harrison 22e — Ch 274 “Mitral Stenosis” (etiology, pathology, pathophysiology, clinical features, investigations, management; Table 274-1; Figs. 274-1 to 274-4). **Coverage note:** Ch 244 “Basic Biology of the Cardiovascular System” covers cardiovascular embryology/biology and Doppler, **not** the detailed mitral valve apparatus anatomy. The six-component structural description (annulus, anterior/posterior leaflets, anterolateral/posteromedial commissures, chordae tendineae, anterolateral/posteromedial papillary muscles, supporting myocardium) is **universally**

accepted standard anatomy; its individual elements — leaflets, commissures, chordae tendineae, papillary muscles, annular calcification and the subvalvular apparatus — are explicitly named in Ch 274 within the rheumatic-pathology and surgical sections, but the integrated anatomical map is supplied from standard textbook anatomy rather than the provided chapters.



Diastolic Heart Failure (Heart Failure with Preserved Ejection Fraction)

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — *Diastolic heart failure*, in current nomenclature **heart failure with preserved ejection fraction (HFpEF)**, is the clinical syndrome of heart failure (breathlessness, fatigue, fluid retention) occurring with a left-ventricular ejection fraction (LVEF) **>40%** (HFpEF strictly defined as LVEF $\geq 50\%$; LVEF 41–49% is now termed **HF with mildly reduced EF, HFmrEF**). The cardinal haemodynamic abnormality is **elevated LV end-diastolic and left-atrial pressure** at rest or on exertion, owing to impaired myocardial relaxation and reduced LV chamber compliance (“a stiff ventricle”) despite a normal-sized, non-dilated cavity. It accounts for **about half of all symptomatic HF**, is increasing in prevalence with population ageing, and carries morbidity and hospitalisation rates approaching those of HFrEF.

Definitions, classification and nomenclature

- ▶ The pathophysiologic definition of HF — “*inability of the heart to pump blood at a rate commensurate with the body’s needs, or to do so only at the cost of high filling pressures*” — makes **no assumption about EF**; HFpEF is HF with this physiology but normal EF.
- ▶ **EF-based phenotypes (universal framework)**: HFrEF (LVEF $\leq 40\%$); HFmrEF (41–49%); HFpEF ($\geq 50\%$); and HF with improved EF (previously $\leq 40\%$, now $>40\%$).
- ▶ The older dichotomy of “systolic” vs “diastolic” HF is imprecise because **most HF patients have both systolic and diastolic abnormalities** — many HFpEF patients have subclinical longitudinal systolic dysfunction (reduced global longitudinal strain) despite normal EF.
- ▶ **Clinical sub-phenotypes (Braunwald)**: “garden-variety” HFpEF (hypertension/diabetes/obesity/CKD), CAD-HFpEF, right-heart-failure HFpEF, atrial-fibrillation-predominant, HCM-like, high-output, and valvular HFpEF — useful because management and prognosis differ.

Epidemiology and risk factors

- ▶ ~64 million people live with HF worldwide; of these ~50% have HFpEF and 10–25% HFmrEF.
- ▶ Prevalence rises with age and is **higher in women** at any age; men predominate at lower EFs.

- ▶ **Independent risk factors for HFpEF:** advancing age, **hypertension**, **obesity** (high body-mass index / visceral adiposity), **diabetes mellitus**, **atrial fibrillation**, chronic kidney disease and prior myocardial infarction. Higher BMI and AF associate more strongly with HFpEF, whereas prior MI, male sex and LV hypertrophy associate more with HFrEF.
- ▶ **Atrial fibrillation** is the commonest arrhythmia — present in **20–40%** at presentation and occurring in two-thirds at some point.
- ▶ **Prognosis:** 5-year mortality ~**53–74%** in hospitalised cohorts (comparable to or only slightly lower than HFrEF). A higher proportion of deaths are **non-cardiovascular** (32–49%), but cardiovascular death — chiefly **sudden death** (~25–30% of all deaths) and HF death — still predominates. Hospitalisation burden is high and recurrent.

Pathophysiology

- ▶ **Diastolic dysfunction** — slowed/incomplete myocardial relaxation (an energy-dependent, active process) plus increased passive chamber stiffness — raises LV diastolic pressure for any given volume; small exertional volume shifts cause steep rises in LA/pulmonary venous pressure → exertional dyspnoea and pulmonary congestion.
- ▶ **Comorbidity–inflammation–endothelial dysfunction paradigm (Paulus):** systemic comorbidities (hypertension, obesity, diabetes, CKD, COPD) drive **systemic micro-inflammation** → coronary microvascular endothelial dysfunction → increased reactive oxygen species, reduced nitric-oxide bioavailability, and a **deficient cyclic-GMP–protein-kinase-G (PKG) signalling** state.
- ▶ **Reduced PKG** causes cardiomyocyte hypertrophy and **hypophosphorylation of titin** (the giant sarcomeric spring), increasing resting myocyte and chamber stiffness. Inflammation recruits leukocytes secreting TGF- β , converting fibroblasts to myofibroblasts → **interstitial collagen deposition and fibrosis** (collagen cross-linking is higher than in HFrEF).
- ▶ **Coronary microvascular dysfunction** (reduced coronary flow reserve, CFR <2.0–2.5) is present in up to ~75% of HFpEF — contributing to subendocardial ischaemia and impaired systolic/diastolic reserve.
- ▶ **Beyond the ventricle (systemic syndrome):** left-atrial myopathy, chronotropic incompetence, abnormal ventricular–arterial coupling with **increased aortic stiffness**, pulmonary hypertension/RV dysfunction, renal sodium retention, sarcopenic obesity with impaired skeletal-muscle O₂ extraction, and a state of **relative natriuretic-peptide deficiency** (lower BNP for any given filling pressure, worsened by obesity).

Clinical features and diagnosis

- ▶ **Symptoms/signs** are similar across the EF spectrum: exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, raised JVP, basal crepitations, S₃/S₄, peripheral oedema, hepatic congestion. Many HFpEF patients are **only symptomatic on exertion**.

- ▶ **Diagnosis requires:** (1) a clinical diagnosis of HF, (2) LVEF >40%, and (3) objective evidence of elevated filling pressures / structural heart disease — supported by raised natriuretic peptides, echocardiography or invasive haemodynamics.
- ▶ **Pitfall — natriuretic peptides may be normal:** 30–40% of HFpEF (especially obese) patients have BNP/NT-proBNP below diagnostic thresholds, so a “normal” NP does not exclude HFpEF; conversely AF, PE, pulmonary arterial hypertension and CKD raise NP non-specifically.
- ▶ **Echocardiography** — concentric LV remodelling (relative wall thickness >0.42), LA enlargement (LA volume index ≥ 34 mL/m²), elevated E/e', raised estimated PA systolic pressure, reduced GLS. The absence of diastolic dysfunction at rest does not exclude HFpEF — pursue exercise/diastolic stress testing.
- ▶ **Grading of diastolic dysfunction (ASE/EACVI; mitral inflow + tissue Doppler):**

Grade	Pattern	Mitral E/A	Average E/e'	LA pressure
Normal	Normal relaxation	≥ 0.8	<10	Normal
Grade I	Impaired relaxation	≤ 0.8	<10	Low/normal
Grade II	Pseudonormal	>0.8 to <2	10–14	Elevated
Grade III	Restrictive filling	>2	>14	Elevated

Supportive: peak tricuspid-regurgitation velocity >2.8 m/s, LA volume index >34 mL/m².

- ▶ **Diagnostic scores** (for the patient with unexplained dyspnoea, normal EF, equivocal workup):
 - **H₂FPEF score** (Mayo): Heavy — BMI >30 (2 pts); Hypertensive — ≥ 2 antihypertensives (1); Atrial Fibrillation (3); Pulmonary hypertension — PASP >35 mmHg (1); Elder — age >60 (1); Filling pressure — E/e' >9 (1). High score makes HFpEF likely; intermediate → proceed to stress test.
 - **HFA-PEFF score** (ESC): Pretest assessment → Echocardiographic + natriuretic-peptide score → Functional testing → Final aetiology. Domains scored 0/1/2; ≥ 5 diagnostic, ≤ 1 excludes, 2–4 → further testing.
- ▶ **Invasive haemodynamics** (reference standard when in doubt): PCWP ≥ 15 mmHg at rest, ≥ 19 mmHg with passive leg-raise, or ≥ 25 mmHg during exercise. Exercise right-heart catheterisation unmasks early HFpEF (exercise-induced LA hypertension).
- ▶ **Always exclude HFpEF “masqueraders”:** cardiac amyloidosis (low voltage with thick walls, bilateral carpal-tunnel, low/falling BP, apical-sparing strain), hypertrophic cardiomyopathy, constrictive pericarditis, restrictive cardiomyopathy, high-output states, severe valve disease, and non-cardiac causes (obesity, COPD, CKD, anaemia, cirrhosis).

Management

- ▶ **Goals:** relieve congestion, improve symptoms/functional capacity, reduce HF hospitalisation, and treat comorbidities (mortality is harder to modify because much of it is non-cardiovascular).
- ▶ **1. SGLT2 inhibitors** — the only class with proven outcome benefit (foundational, standard of care): **empagliflozin (EMPEROR-Preserved)** and **dapagliflozin (DELIVER)** significantly reduce cardiovascular death/HF hospitalisation across the full EF spectrum, including LVEF >60% and HFimpEF, with no decline in benefit as EF rises.
- ▶ **2. Decongestion with diuretics** — empiric cornerstone for fluid overload (loop ± thiazide; avoid over-diuresis/hypotension in the elderly).
- ▶ **3. Mineralocorticoid receptor antagonists** — **spironolactone (TOPCAT)** was neutral overall (HR 0.89) but showed benefit in the Americas region and in those with EF 45–60% (AHA/ACC/HFSA class IIb); the **non-steroidal MRA finerenone (FINEARTS-HF)** reduced CV death/worsening-HF events across HFmrEF–HFpEF. An MRA is reasonable, with potassium/renal monitoring.
- ▶ **4. Angiotensin-receptor–neprilysin inhibitor (sacubitril/valsartan, PARAGON-HF)** — just missed significance (rate ratio 0.87, $P=0.059$); benefit concentrated **below the median EF (~57%) and in women**. FDA-approved for EF “below normal”; **class IIb for HFmrEF**.
- ▶ **5. Treat comorbidities:** blood-pressure control (target generally <130 mmHg, but avoid SBP <130 in some HFpEF phenotypes); AF rate/rhythm control and anticoagulation; coronary disease; CKD; sleep apnoea; iron deficiency.
- ▶ **6. Obesity-HFpEF:** **GLP-1 receptor agonist semaglutide (STEP-HFpEF)** and the GIP/GLP-1 dual agonist **tirzepatide (SUMMIT)** improve symptoms, quality of life and exercise function.
- ▶ **7. Lifestyle:** caloric restriction/weight loss and **supervised exercise/aerobic training** improve exercise capacity and quality of life.
- ▶ **No proven role for ICD or CRT in HFpEF** (unlike HFrEF). Beta-blockers and calcium-channel blockers are **not** disease-modifying — used only for BP/rate; consider cautious withdrawal in chronotropic incompetence (PRESERVE-HR).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **LV pressure–volume loop in HFpEF:** plot a normal loop and a HFpEF loop showing an **upward-and-leftward-shifted, steeper end-diastolic pressure–volume relationship (EDPVR)**. Labels: *LV pressure (y-axis), LV volume (x-axis), normal EDPVR, stiff/HFpEF EDPVR, elevated LV end-diastolic pressure, preserved ejection fraction (small stroke volume)*.
- ▶ **Mitral-inflow Doppler grades of diastolic dysfunction:** four waveforms side by side — *Normal ($E>A$), Grade I impaired relaxation ($E<A$, $E/A \leq 0.8$, prolonged deceleration time), Grade II pseudonormal (E/A 0.8–2), Grade III restrictive ($E/A >2$, short deceleration time)*. Label *E wave, A wave, deceleration time*.

Clinical / Diagnostic significance

- ▶ A normal EF on echo does **not** exclude HF — the syndrome can exist entirely on a diastolic/filling-pressure basis; this is the single most important teaching point.
- ▶ A **normal natriuretic peptide does not rule out HFpEF**, particularly in obesity — use the H₂FPEF/HFA-PEFF scores and exercise haemodynamics.
- ▶ **Exercise/diastolic stress testing** is key to unmasking early HFpEF when resting studies are equivocal.
- ▶ Always screen for treatable mimics — **ATTR cardiac amyloidosis** (now treatable with tafamidis) and constrictive pericarditis (curable by pericardiectomy) — before labelling “idiopathic” HFpEF.
- ▶ **SGLT2 inhibitors have transformed management** from purely empiric (diuretics) to an evidence-based foundational therapy benefiting the whole EF spectrum.

High-yield exam pointers

- ▶ HFpEF = HF with LVEF >40% (HFpEF ≥50%, HFmrEF 41–49%); ~half of all HF.
- ▶ Cardinal defect: **raised LV/LA filling pressure** from impaired relaxation + reduced compliance (stiff ventricle), normal cavity size.
- ▶ Diagnostic triad: **clinical HF + EF >40% + objective high filling pressures/structural disease** (NP, echo, or invasive PCWP ≥15 rest / ≥25 exercise).
- ▶ Remember the H₂FPEF and HFA-PEFF scores by name and components.
- ▶ Diastolic-dysfunction echo grades: **I impaired relaxation, II pseudonormal, III restrictive** (E/A and E/e' cut-offs); E/e' >14 and LAVI >34 mL/m² signify high LA pressure.
- ▶ Pathophysiology buzz-words: **comorbidity-driven systemic inflammation → microvascular endothelial dysfunction → cGMP–PKG deficiency → titin hypophosphorylation + interstitial fibrosis**.
- ▶ Outcome-positive therapy = **SGLT2 inhibitors (empagliflozin/dapagliflozin)**; everything else (ACEi/ARB/ARNI/spironolactone/β-blocker/CCB) is largely neutral — diuretics for congestion, finerenone/ARNI and MRA as class IIb adjuncts.
- ▶ **Obesity-HFpEF**: semaglutide and tirzepatide improve symptoms; **no role for ICD/CRT**.
- ▶ Negative landmark trials to quote: PEP-CHF, CHARM-Preserved, I-PRESERVE, TOPCAT, PARAGON-HF; positive: EMPEROR-Preserved, DELIVER, FINEARTS-HF.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Heart Failure: Pathophysiology and Diagnosis” and “Heart Failure: Management” (EF-based phenotype definitions; systolic vs diastolic terminology).

- ▶ **Braunwald's Heart Disease, 13e** — “Heart Failure With Preserved or Mildly Reduced Ejection Fraction” (epidemiology, risk factors, diagnostic scores H₂FPEF/HFA-PEFF, invasive haemodynamics, comorbidity-inflammation pathophysiology, full trial evidence: TOPCAT, PARAGON-HF, EMPEROR-Preserved, DELIVER, FINEARTS-HF, PRESERVE-HR) and “Echocardiography” (grading of LV diastolic dysfunction, Table 14.4).
- ▶ **CMDT 2026** — “Heart Failure & Cardiomyopathy” (current management: SGLT2 inhibitors as the mainstay, GLP-1/tirzepatide for obesity-HFpEF, role of ATTR amyloid screening; STEP-HFpEF, SUMMIT).



Differential Diagnosis of Mid-Diastolic Murmurs

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — A **mid-diastolic murmur (MDM)** is a low-frequency murmur that begins a short interval *after* the second heart sound (S2) — characteristically after the **opening snap (OS)** or a third heart sound (S3) — and occupies the rapid-filling phase of diastole. MDMs arise from **obstruction to, and/or augmented flow across, an atrioventricular (mitral or tricuspid) valve**, so the gradient driving them is the low-pressure atrioventricular diastolic gradient. They are best appreciated with the **bell** of the stethoscope, are easily missed, and — unlike most systolic murmurs — *almost always signify organic cardiac disease*. **Mitral stenosis (MS)** is the prototype and commonest cause.

Mechanism, genesis and how to recognise an MDM

- ▶ Two physiological substrates generate an MDM: (1) **obstruction** at the mitral/tricuspid orifice (a true diastolic pressure gradient), or (2) **increased antegrade transvalvular flow** across an anatomically normal valve (a “functional” or “flow” murmur).
- ▶ **Timing**: the murmur follows S2 by a measurable interval. In obstructive lesions it is introduced by an **OS** (MS, tricuspid stenosis); in high-flow lesions it is introduced by an **S3** (rapid-filling sound).
- ▶ The **duration** of the rumble reflects how long the atrial pressure exceeds ventricular diastolic pressure, and so correlates with severity (when output is preserved).
- ▶ **Presystolic accentuation** — a late-diastolic crescendo just before S1 due to atrial contraction augmenting transvalvular flow — is characteristic of MS/TS *in sinus rhythm* and is **lost in atrial fibrillation (AF)**.
- ▶ **Bedside amplification**: **left lateral decubitus position**, **bell with light pressure**, and a brief bout of **exercise** (sit-ups) bring out a soft mitral rumble; **inspiration** augments right-sided (tricuspid) MDMs.

Structured differential diagnosis of mid-diastolic murmurs

Site	Obstructive (true stenosis)	Increased-flow (“functional”)	Other
Mitral	Rheumatic mitral stenosis (commonest); congenital MS, cor triatriatum; severe mitral annular calcification; large vegetation	Severe MR, VSD, PDA, high-output states (anaemia, thyrotoxicosis, pregnancy), complete heart block	Carey-Coombs murmur (acute rheumatic carditis); Austin Flint murmur (severe/eccentric AR); left atrial myxoma (tumour plop)
Tricuspid	Rheumatic tricuspid stenosis (almost never isolated; accompanies MS)	Severe TR, large ASD, anomalous pulmonary venous return	Right atrial myxoma

- ▶ *Aide-mémoire — causes at the mitral valve:* “MS, MR-flow, Carey-Coombs, Austin Flint, Myxoma, Complete heart block.”
- ▶ The **Graham Steell** murmur (pulmonary regurgitation of pulmonary hypertension) and chronic **aortic regurgitation** are *early-to-mid* diastolic, decrescendo and high-pitched; they are listed here only because they can be confused with an MDM heard along the left sternal border, but they are not true mid-diastolic rumbles.

Mitral stenosis — the prototype mid-diastolic murmur

- ▶ **Cause:** rheumatic fever in the vast majority; pure/predominant MS occurs in ~40% of rheumatic heart disease. Normal mitral orifice is 4–6 cm²; symptoms appear when area falls below ~2 cm²; **severe MS = valve area <1.5 cm²** (a left atrial pressure of ~25 mmHg is then needed to maintain output).
- ▶ **Murmur:** low-pitched, **rumbling**, mid-diastolic, loudest at the **apex** in the left lateral decubitus position, beginning after the OS; **presystolic accentuation** in sinus rhythm.
- ▶ **Accompanying signs (a complete auscultatory complex):** loud (and slightly delayed) S1; an OS after A2 — the **A2–OS interval (0.05–0.12 s) varies inversely with severity (a short A2–OS interval = tight MS)*; *loud/palpable P2** when pulmonary hypertension supervenes.
- ▶ **Duration** of the rumble (not loudness) tracks severity; the murmur may be **inaudible** (“**silent MS**”) when cardiac output is very low or the patient is large/obese.
- ▶ Supporting evidence: **mitral facies (malar flush)**, AF, prominent jugular *a* wave (if pulmonary hypertension/TS), parasternal lift (RV enlargement), left atrial enlargement on ECG (P-mitrale) and CXR (straightened left heart border, Kerley B lines), and Doppler echo (gradient, planimetered area, suitability for **percutaneous mitral balloon commissurotomy**).

Other mitral mid-diastolic murmurs

- ▶ **Increased-flow (“functional MS”) murmur:** severe MR, a large left-to-right shunt (VSD, PDA), high-output states or **complete heart block** drive excessive flow across a non-stenotic mitral valve, producing a soft rapid-filling S3 followed by a short MDM. *No OS, no presystolic accentuation*; an apical pansystolic murmur and signs of LV enlargement point to MR as the substrate.
- ▶ **Carey-Coombs murmur:** a soft, transient apical MDM of **acute rheumatic carditis**, attributed to flow through an **oedematous, inflamed mitral valve**. *No OS, soft S1, and the murmur dissipates as the acute attack resolves* — a clue to active rheumatic activity rather than established stenosis.
- ▶ **Austin Flint murmur:** a low-pitched **mid-to-late apical diastolic rumble of severe (or eccentric) chronic AR**, produced by turbulence at the mitral inflow from admixture of the regurgitant aortic jet and forward mitral flow (and partial premature closure of the anterior mitral leaflet). Distinguished from MS by **absence of an OS** and by its **response to vasodilators** (see below).
- ▶ **Left atrial myxoma:** a pedunculated tumour arising near the **fossa ovalis of the interatrial septum** prolapses across the mitral valve in diastole, obstructing inflow and mimicking MS. Auscultation may reveal an early/mid-diastolic **“tumour plop”**; characteristically there is **positional variation** (murmur/symptoms change with body position), *no OS and no presystolic accentuation*. Suspect with constitutional features — fever, weight loss, anaemia, raised ESR/CRP, high IL-6, systemic emboli; familial cases occur in the **Carney complex** (*PRKARIA* mutation). TTE/TEE is diagnostic.
- ▶ **Complete heart block:** intermittent mid-to-late diastolic murmurs occur when atrial contraction falls while the mitral valve is partially closed (atrioventricular dissociation).

Tricuspid mid-diastolic murmurs

- ▶ **Tricuspid stenosis (TS):** almost never isolated — it accompanies rheumatic MS. The MDM is at the **lower left sternal border / 4th left intercostal space**, is **softer, higher-pitched and shorter** than MS, and crucially **increases with inspiration** (*Carvallo’s sign*) and other manoeuvres that raise trans-tricuspid flow. JVP shows a **giant a wave and a slow/delayed y descent; a diastolic thrill may be palpable at the LLSB. A tricuspid OS may follow the mitral OS. Suspect TS in a patient with “MS” who has marked right heart signs without pulmonary hypertension**.
- ▶ **Increased tricuspid flow:** severe TR, a large ASD (left-to-right shunt) or anomalous pulmonary venous return produce a **tricuspid flow MDM**, again inspiration-augmented; fixed splitting of S2 and a pulmonary mid-systolic flow murmur point to an ASD.

Bedside differentiation (dynamic auscultation)

Feature	Mitral stenosis	Austin Flint (severe AR)	Carey-Coombs	LA myxoma	Tricuspid MDM
Opening snap	Present	Absent	Absent	Absent (tumour plop)	Tricuspid OS may be present
Presystolic accentuation	Yes (sinus rhythm)	No	No	No	Yes (sinus rhythm)
Inspiration	Unchanged/softer	Unchanged	Unchanged	Variable	Louder (Carvallo)
Amyl nitrite / vasodilator	Murmur louder (↑ output, ↑ flow)	Murmur softer & shorter	—	—	Louder
Positional change	Left lateral decubitus accentuates	—	—	Changes with body position	Right lateral decubitus accentuates

- ▶ The **vasodilator (amyl nitrite) test** is the classic discriminator between MS and Austin Flint: lowering afterload **shortens and softens the Austin Flint murmur** but **increases the MS rumble** (reflex rise in output and transmitral flow).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Phonocardiogram of the cardiac cycle** showing, against S1 and S2: (a) the MS complex — loud S1, A2–P2, opening snap (OS), low-pitched mid-diastolic rumble with presystolic accentuation to S1; and (b) a separate trace of an S3 followed by a short flow MDM. Label: S1, A2, P2, OS, S3, mid-diastolic rumble, presystolic accentuation.
- ▶ **Precordial map of murmur location:** mark the apex (left lateral decubitus, bell) for the mitral rumble and the lower left sternal border (4th ICS, inspiration) for the tricuspid MDM. Label: apex – MS rumble; LLSB – tricuspid murmur; aortic area / LSB – AR (Austin Flint at apex).

Clinical / Diagnostic significance

- ▶ Recognising an MDM and its accompaniments (loud S1, OS, presystolic accentuation, AF, mitral facies) allows a **bedside diagnosis of MS** and stratifies severity (short A2–OS interval, long rumble = tight valve).
- ▶ **Transthoracic echocardiography with Doppler** is indicated for any diastolic murmur — it confirms the lesion, quantifies the gradient and orifice area, assesses pulmonary pressures, excludes left atrial thrombus/myxoma, and judges suitability for **balloon valvuloplasty vs surgery**.

- ▶ An MDM in a febrile young patient with arthritis suggests **active rheumatic carditis (Carey-Coombs)**; an MDM with constitutional/embolic features and positional change suggests **atrial myxoma**; an apical rumble with wide pulse pressure and a water-hammer pulse suggests **Austin Flint of severe AR**.
- ▶ Misattributing a flow MDM (severe MR, large shunt) to organic stenosis is a common error — the absence of an OS and the presence of an S3/dominant systolic lesion are the corrective clues.

High-yield exam pointers

- ▶ MDM = **obstruction or increased flow at an AV valve**; best heard with the **bell**, after the OS (obstruction) or S3 (flow).
- ▶ **Commonest cause = rheumatic MS**; severe MS = orifice $<1.5 \text{ cm}^2$ (normal 4–6 cm^2).
- ▶ **A2–OS interval is inversely proportional to severity of MS**; **presystolic accentuation is lost in AF**.
- ▶ **Carey-Coombs** = transient apical MDM of **acute rheumatic carditis**; no OS, resolves with the attack.
- ▶ **Austin Flint** = apical MDM of **severe AR**; differentiated from MS by **no OS** and **softening with amyl nitrite/vasodilator** (MS rumble gets louder).
- ▶ **Atrial myxoma** = **tumour plop**, positional variation, constitutional symptoms, *PRKARIA*/Carney complex; diagnosed on echo.
- ▶ **Tricuspid MDM (TS)** is heard at the **LLSB**, **louder on inspiration (Carvallo's sign)**, with a giant *a* wave and slow *y* descent; rarely isolated.
- ▶ “**Functional**” MDMs of increased flow: **severe MR, VSD, PDA, ASD, severe TR, complete heart block, high-output states** — no OS, preceded by an S3.
- ▶ **Every diastolic murmur warrants echocardiography**; diastolic murmurs are almost never innocent.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Approach to the Patient with a Heart Murmur” (mid-diastolic murmur differential, Carey-Coombs, Austin Flint, dynamic auscultation, amyl-nitrite discrimination); “Mitral Stenosis” (etiology, orifice areas, A2–OS interval, silent MS, differential from AR/TS/ASD/myxoma); “Atrial Myxoma and Other Cardiac Tumors” (tumour plop, Carney complex, *PRKARIA*).
- ▶ **Braunwald's Heart Disease, 13e** — “History, Physical Examination, and the Virtual Visit” (Table of principal heart murmurs and mid-diastolic causes; presystolic accentuation; dynamic-auscultation manoeuvres) and “Tricuspid, Pulmonic, and Multivalvular Disease” (tricuspid stenosis murmur, Carvallo's sign, OS, severity).
- ▶ **CMDT 2026** — Cardiology chapter (current management context for valvular MS/TS).



Discuss the diagnosis and management of chronic heart failure with preserved ejection fraction

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Heart failure with preserved ejection fraction (HFpEF) is the clinical syndrome of heart failure (typical symptoms/signs of congestion — dyspnoea, fatigue, oedema) occurring in a patient whose left-ventricular ejection fraction (LVEF) is *preserved* ($\geq 50\%$), in the presence of objective evidence of cardiac structural/functional abnormality and raised cardiac filling pressures at rest or on exertion. It accounts for roughly **half of all heart failure** and is increasing in relative frequency with population ageing. Although the dominant lesion is impaired LV diastolic function, HFpEF is now recognised as a **systemic, multi-organ syndrome** driven by comorbidity-related inflammation, not merely a “diastolic” problem.

Nomenclature, classification and epidemiology

- ▶ The universal EF-based classification (Harrison 22e): HFrEF = EF $\leq 40\%$; HF with mildly reduced EF (HFmrEF) = EF 41–49%; HFpEF = EF $\geq 50\%$. Major trials variably used EF $>40\%$ or $>45\%$; current guidelines reserve “HFpEF” for LVEF $\geq 50\%$.
- ▶ HFpEF comprises $\sim 50\%$ of prevalent HF and HFmrEF a further $\sim 10\text{--}25\%$; prevalence rises with age and is **higher in women** at any given age (largely because women out-live men).
- ▶ **Predominant risk factors / comorbidities**: older age, **hypertension** (LV hypertrophy), **obesity / visceral adiposity**, **diabetes**, atrial fibrillation, chronic kidney disease, COPD and sleep apnoea. Obesity and AF are particularly characteristic.
- ▶ **Atrial fibrillation** coexists in 20–40% at presentation and occurs in two-thirds at some point; its onset frequently precipitates decompensation.
- ▶ **Prognosis**: mortality is high (5-year mortality $\sim 50\text{--}70\%$ in hospitalised cohorts), only modestly lower than HFrEF, with a *higher proportion of non-cardiovascular deaths*; hospitalisation burden equals or exceeds HFrEF.

Pathophysiology (relevant to diagnosis and therapy)

- ▶ **Cardinal abnormality**: elevation of LV end-diastolic pressure and left-atrial pressure (raised PCWP) at rest or, characteristically, **only on exertion**, producing exertional dyspnoea with preserved systolic ejection.
- ▶ Beyond impaired relaxation and reduced LV chamber compliance: **longitudinal systolic dysfunction** (reduced GLS, low tissue-Doppler s'), **left-atrial myopathy**, chronotropic incompetence, abnormal ventricular–arterial coupling and aortic stiffening.
- ▶ **Comorbidity** $\rightarrow$ **systemic inflammation** $\rightarrow$ **endothelial dysfunction paradigm**: reduced nitric-oxide bioavailability lowers cGMP–protein kinase G (PKG) signalling $\rightarrow$ **titin**

hypophosphorylation and cardiomyocyte stiffening, interstitial fibrosis (TGF- β -driven collagen deposition) and coronary microvascular dysfunction (reduced coronary flow reserve in up to ~75%).

- ▶ This multi-organ model (heart, lungs, kidney, skeletal muscle, adipose tissue) explains why isolated “diastolic dysfunction” on echo is neither necessary nor sufficient for diagnosis.

Diagnostic approach

Diagnosis requires (1) a **clinical diagnosis of HF AND (2) LVEF $\geq 50\%$** ($\geq 40\%$ if including HFmrEF), supported by objective evidence of elevated filling pressures or structural disease, and **exclusion of non-cardiac mimics** (obesity, COPD, CKD, cirrhosis, anaemia, pericardial constriction).

- ▶ **Supportive evidence:** raised natriuretic peptides; structural change (LA enlargement, LVH); echo Doppler (increased E/e', dilated IVC); or invasive haemodynamics.
- ▶ **Pitfall — natriuretic-peptide deficiency:** ~30–40% of HFpEF have BNP/NT-proBNP *below* usual diagnostic thresholds (NP levels are lower than in HFrEF, and are further reduced by obesity); a normal NP **does not exclude** HFpEF in a patient with high pre-test probability.
- ▶ **Diastolic dysfunction on echo alone is insufficient** — it is common in asymptomatic elderly, often indeterminate (E/e' 8–15), and may be normal at rest yet abnormal on exercise. Absence does not exclude HFpEF.
- ▶ When non-invasive tests are equivocal, proceed to **provocative testing** — diastolic stress echo or, the *reference standard*, **invasive exercise haemodynamics**.

Diagnostic scoring systems

Score	Source / components	Interpretation
H2FPEF (Mayo)	Heavy: BMI >30 (2); Hypertensive: ≥ 2 antihypertensives (1); atrial Fibrillation (3); Pulmonary HTN: echo PASP >35 mmHg (1); Elder: age >60 yr (1); Filling pressure: E/e' >9 (1). Range 0–9	Higher score = higher probability (AUC ~0.84). Low 0–1; intermediate 2–5 $\rightarrow$ exercise testing; high 6–9
HFA-PEFF (ESC)	Pre-test $\rightarrow$ Echo + NP $\rightarrow$ Functional testing $\rightarrow$ Final aetiology. Functional, morphological and NP domains (major = 2 pts, minor = 1 pt)	≥ 5 points = diagnostic ; <2 = excludes ; 2–4 = intermediate $\rightarrow$ functional/invasive testing

Key investigations

- ▶ **Natriuretic peptides** (BNP/NT-proBNP) — diagnostic and strongly prognostic; use NT-proBNP if on sacubitril/valsartan.

- ▶ **Comprehensive echocardiography** — concentric LV remodelling (relative wall thickness >0.42), LA volume index ≥ 34 mL/m², E/e', TR velocity / estimated PA systolic pressure, and **global longitudinal strain** (normal absolute GLS >18%, abnormal <16%); apical-sparing strain pattern suggests amyloidosis.
- ▶ **High-sensitivity troponin** — persistent low-level elevation flags an infiltrative/"myocardial" phenotype (amyloid, HCM) or microvascular ischaemia.
- ▶ **Cardiac MRI** — tissue characterisation: late gadolinium enhancement, T1 mapping/extracellular volume (fibrosis, amyloid), T2* (iron), pericardial assessment.
- ▶ **Invasive haemodynamics (gold standard when in doubt):** PCWP ≥ 15 mmHg at rest, ≥ 19 mmHg with passive leg raise, or ≥ 25 mmHg during exercise (or PCWP/cardiac-output slope ≥ 2.0) confirms HFpEF.
- ▶ **Screen for "masqueraders":** cardiac amyloidosis (immunofixation, free light chains, prealbumin, bone scintigraphy/biopsy), HCM, constrictive pericarditis, high-output states, Fabry, sarcoidosis, haemochromatosis, valvular disease.

Management

There is no single mortality-lowering drug; therapy targets **decongestion**, the **one outcome-proven drug class** (SGLT2 inhibitors), **aggressive comorbidity control** and **symptom/QOL improvement**.

Class	Key drugs / trials	Status & comment
SGLT2 inhibitors	Empagliflozin — EMPEROR-Preserved; Dapagliflozin — DELIVER	Cornerstone, outcome-proven — reduce CV death/HF hospitalisation across the full EF spectrum (incl. >60%); benefit independent of diabetes. ESC class I
Loop $\pm$ thiazide diuretics	Furosemide; add HCTZ/metolazone if refractory	Empiric mainstay for congestion ; avoid over-diuresis (under-filling $\rightarrow$ azotaemia, hypotension, syncope)
MRA	Spirolactone — TOPCAT (HR 0.89, neutral overall; benefit in the Americas and EF 45–60%); Finerenone — FINEARTS-HF (positive)	Consider in addition to loop diuretic; monitor K ⁺ /renal function. Spirolactone class IIb
ARNI	Sacubitril/valsartan — PARAGON-HF (HR 0.87, $p \approx 0.06$, <i>just missed</i>); benefit in EF below median (~57%) and in women	FDA expanded approval / class IIb, chiefly for HFmrEF and EF below normal

Class	Key drugs / trials	Status & comment
ACEi / ARB	Perindopril (PEP-CHF), Candesartan (CHARM-Preserved), Irbesartan (I-PRESERVE) — all neutral for true HFpEF	Use for comorbid hypertension/CKD/diabetes, not for HFpEF outcomes per se
GLP-1 receptor agonists	Semaglutide — STEP-HFpEF / STEP-HFpEF DM; Tirzepatide — SUMMIT	In obesity-related HFpEF: weight loss, improved KCCQ/exercise capacity, lower NT-proBNP/CRP
β -blockers / non-dihydropyridine CCB	—	Neutral for HFpEF outcomes; useful for AF rate control; withdraw if chronotropic incompetence limits exertion

Other management priorities

- ▶ **Blood pressure:** treat to guideline targets (SPRINT supports <130 mmHg systolic), though some HFpEF data suggest an optimal range of ~130–140 mmHg; central aortic control is relevant.
- ▶ **Atrial fibrillation:** rate control (in AF-HFpEF target resting rate ~70–80 bpm to preserve filling), **anticoagulation** (high thromboembolic risk), and early consideration of **rhythm control/ablation** in symptomatic patients.
- ▶ **Comorbidities:** treat obesity, diabetes, CKD, iron deficiency, COPD and **sleep apnoea**; maintain euvolaemia.
- ▶ **Specific aetiologies:** **tafamidis** for transthyretin (ATTR) cardiac amyloidosis; chemotherapy for AL amyloid; mavacamten / septal reduction for obstructive HCM; revascularisation for ischaemia.
- ▶ **Exercise training / cardiac rehabilitation** — improves peak VO_2 , 6-minute-walk distance and quality of life; sodium and fluid restriction in fluid overload.
- ▶ **Devices:** ICD and CRT are **NOT indicated** for EF >40%. Implantable PA-pressure monitoring (CardioMEMS — CHAMPION) reduces HF events in frequently hospitalised patients. **Interatrial shunt devices** failed in the pivotal trial (possible harm if EF >40%).
- ▶ **Ineffective / unsuccessful in HFpEF:** PDE-5 inhibitors (sildenafil), organic and inorganic **nitrates** (NEAT — isosorbide mononitrate worsened activity), **ivabradine** (EDIFY), vericiguat, and digoxin (may reduce hospitalisations only).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology cascade of HFpEF:** label *Comorbidities (HTN, obesity, diabetes, CKD)* → *systemic inflammation* → *coronary microvascular endothelial dysfunction* → $\downarrow \text{NO-cGMP-PKG}$ → *titin hypophosphorylation (cardiomyocyte stiffness) + interstitial fibrosis* → $\uparrow \text{LV diastolic stiffness}$ → $\uparrow \text{LVEDP}/\uparrow \text{LA pressure}$ → $\uparrow \text{PCWP (rest/exertion)}$ → *exertional dyspnoea*.

- ▶ **Diagnostic algorithm box:** *Symptoms/signs of HF + LVEF $\geq 50\%$ $\rightarrow$ natriuretic peptides + echo (E/e' , LA volume index ≥ 34 mL/m², GLS, PASP) $\rightarrow$ calculate H2FPEF / HFA-PEFF $\rightarrow$ if intermediate, diastolic stress echo or invasive exercise haemodynamics (PCWP ≥ 15 rest / ≥ 25 exercise) $\rightarrow$ exclude masqueraders (amyloid, HCM, constriction).*

Clinical / Diagnostic significance

- ▶ A normal natriuretic peptide and a normal resting echo do not exclude HFpEF — exertional/invasive testing is the key to “early” or “exercise-induced” HFpEF.
- ▶ Recognising cardiac amyloidosis (bilateral carpal tunnel syndrome, low-voltage ECG with thick walls, persistent troponin elevation, apical-sparing strain) is critical — it changes therapy (avoid non-dihydropyridine CCBs; use tafamidis) and prognosis.
- ▶ SGLT2 inhibitors are the **first and only class proven to improve outcomes across the entire EF spectrum**, making them standard of care in HFpEF as in HFrEF.
- ▶ Most “HFpEF therapy” is in reality **comorbidity and congestion management**; weight loss in obese HFpEF (GLP-1 RA) is an emerging disease-modifying strategy.

High-yield exam pointers

- ▶ HFpEF = EF $\geq 50\%$; HFmrEF = 41–49%; HFrEF = $\leq 40\%$ — memorise the universal definition cut-offs.
- ▶ Diagnosis = HF syndrome + preserved EF + raised filling pressures/structural disease + exclusion of mimics.
- ▶ H2FPEF (Heavy, Hypertensive, atrial Fibrillation, Pulmonary HTN, Elder, Filling pressure) and HFA-PEFF (≥ 5 diagnostic, < 2 excludes) are the two scores.
- ▶ Invasive PCWP ≥ 15 (rest) / ≥ 19 (leg raise) / ≥ 25 mmHg (exercise) is the haemodynamic gold standard.
- ▶ ~30–40% of HFpEF have natriuretic-peptide deficiency, especially with obesity.
- ▶ SGLT2 inhibitors (empagliflozin/EMPEROR-Preserved, dapagliflozin/DELIVER) — only outcome-proven class; diuretics for congestion.
- ▶ Adjuncts: MRA (TOPCAT/FINEARTS-HF), ARNI (PARAGON-HF) for lower-EF/women, GLP-1 RA (STEP-HFpEF) for obesity.
- ▶ ICD/CRT have no role in HFpEF; treat AF with rate control + anticoagulation; consider tafamidis for ATTR amyloid.

SOURCE & COVERAGE

- ▶ Braunwald’s Heart Disease 13e — “Heart Failure With Preserved or Mildly Reduced Ejection Fraction” (Lam, Shah, Solomon): epidemiology, H2FPEF/HFA-PEFF scores,

invasive haemodynamic thresholds, phenotypes, and the full HFpEF/HFmrEF trial evidence (TOPCAT, FINEARTS-HF, PARAGON-HF, EMPEROR-Preserved, DELIVER, STEP-HFpEF, SUMMIT).

- ▶ **Harrison's Principles of Internal Medicine 22e** — “Heart Failure: Pathophysiology and Diagnosis” and “Heart Failure: Management”: EF-based classification and HFpEF guiding management principles.
- ▶ **CMDT 2026** — “Heart Failure & Cardiomyopathy”: current management of HF with preserved LVEF (SGLT2 inhibitors and diuretics as mainstays; GLP-1 RA/tirzepatide in obesity; ATTR amyloid screening).



Discuss the etiology, clinical manifestations and management of Acute ST elevation Myocardial infarction (STEMI)

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — STEMI is an acute coronary syndrome due to abrupt severe myocardial ischemia with necrosis, usually from complete thrombotic occlusion of an epicardial coronary artery. It is diagnosed by ischemic symptoms or equivalents, diagnostic ST-segment elevation in contiguous leads, and rise/fall of cardiac troponin above the 99th percentile; reperfusion must not wait for biomarkers when the ECG is diagnostic. It is an emergency because early mortality is dominated by ventricular fibrillation and later in-hospital mortality by pump failure.

Etiology and pathogenesis

- ▶ **Commonest cause - type 1 atherothrombotic MI:** rupture or erosion of an atherosclerotic plaque, often lipid-rich with a thin fibrous cap, in a coronary artery previously affected by atherosclerosis. Smoking, hypertension, LDL accumulation, diabetes, and inflammation promote endothelial dysfunction, vulnerable plaque, and thrombogenic blood.
- ▶ **Thrombus biology:** plaque disruption exposes collagen and tissue factor; platelet agonists (collagen, ADP, epinephrine, serotonin) trigger thromboxane A₂ release, GP IIb/IIIa activation, platelet aggregation, thrombin generation, and fibrin deposition, producing an occlusive platelet-fibrin thrombus.
- ▶ **Predisposing / precipitating factors:** multiple CAD risk factors, unstable angina, vigorous exercise, emotional stress, medical or surgical illness, morning catecholamine/cortisol and platelet-aggregability surge, infection, hypoxemia, pulmonary embolism, fever, tachycardia, hypotension, severe aortic stenosis, cocaine, and sympathomimetics.

- ▶ **Less common etiologies:** coronary embolism, congenital coronary abnormality, coronary spasm/Prinzmetal angina, spontaneous coronary artery dissection, vasculitis, aortitis, aortic root/coronary dissection, hypercoagulable states, collagen vascular disease, systemic inflammatory disease, and intracardiac thrombi/masses.
- ▶ **Infarct size depends on:** vascular territory, totality and duration of occlusion, collateral flow, myocardial oxygen demand, spontaneous lysis, speed of reperfusion, and microvascular obstruction/no-reflow from endothelial injury, leukocyte-platelet activation, thrombotic debris, edema, and cardiomyocyte swelling.

Clinical manifestations

- ▶ **Premonitory pain:** accelerating angina or rest angina may precede infarction; onset is often at rest and more common in the early morning.
- ▶ **Classical pain:** prolonged (>30 minutes) deep central chest or epigastric discomfort, heavy/squeezing/crushing, occasionally burning or stabbing; more severe than angina, poorly relieved by rest or nitroglycerin, and radiating to arms, shoulder, back, jaw, neck, or occiput.
- ▶ **Associated symptoms:** sweating, nausea, vomiting, anxiety, weakness, dyspnea, orthopnea, cough/wheeze, light-headedness, syncope, and sense of impending doom.
- ▶ **Atypical / painless STEMI:** commoner in older adults, women, diabetes mellitus, and transplant recipients; may present as acute heart failure, syncope, confusion, profound weakness, arrhythmia, embolism, shock, or sudden death.
- ▶ **Physical findings:** anxious restless patient, pallor, diaphoresis, cool extremities; anterior MI may cause tachycardia/hypertension, inferior MI bradycardia/hypotension. S4 is common; S3 suggests LV dysfunction. Other signs include soft S1, paradoxical split S2, apical systolic murmur of MR, pericardial rub later, low-volume carotid pulse, and low-grade fever after 12 hours.
- ▶ **RV infarction clue:** inferior STEMI with hypotension, raised JVP/Kussmaul sign, hepatomegaly, and clear lungs; confirm with V4R ST elevation and echocardiography.

Diagnosis and risk assessment

- ▶ **ECG first:** obtain and interpret a 12-lead ECG within 10 minutes of first medical contact; start continuous monitoring and IV access. Add V3R/V4R for inferior/RV infarction and V7-V9 for suspected posterior occlusion.
- ▶ **STEMI ECG criteria:** new ST elevation at the J point in at least two contiguous leads: ≥ 1 mm in all leads except V2-V3; in V2-V3, ≥ 2 mm in men ≥ 40 years, ≥ 2.5 mm in men < 40 years, and ≥ 1.5 mm in women. New LBBB with compatible ischemia is treated as a STEMI equivalent when occlusion criteria are present.
- ▶ **Biomarkers:** high-sensitivity troponin I/T are preferred; acute MI requires rise/fall with at least one value above the 99th percentile plus ischemic evidence. Troponin remains elevated for 5-10 days; CK-MB helps suspected early reinfarction because it falls sooner.

- ▶ **Supportive tests:** leukocytosis may reach 12,000-15,000/microliter; check glucose, creatinine, electrolytes, lipids, and bleeding risk. CXR helps detect congestion and alternative diagnoses such as aortic dissection.
- ▶ **Echocardiography:** documents regional wall motion abnormality, LVEF, RV infarction, papillary muscle dysfunction/rupture, VSD, pericardial effusion, LV aneurysm, and LV thrombus.
- ▶ **Risk markers:** Killip class, persistent ischemia, shock, LVEF <40%, pulmonary congestion, age >75, diabetes, prior MI, tachycardia, hypotension, ventricular arrhythmias, renal dysfunction, and nonpatent infarct-related artery.

Initial and reperfusion management

- ▶ **Prehospital care:** educate high-risk patients, activate EMS, obtain prehospital ECG, transport rapidly to a STEMI network, and ensure defibrillation capability because most early deaths are arrhythmic.
- ▶ **Emergency measures:** cardiac monitor, IV access, aspirin loading, analgesia, baseline bloods, rapid reperfusion decision. Give oxygen only for SaO₂ <90% or heart failure.
- ▶ **Anti-ischemic / analgesic therapy:** chew aspirin 160-325 mg immediately, then 75-162 mg daily. Give sublingual nitroglycerin 0.4 mg every 5 minutes for up to three doses if pain persists; avoid in SBP <90 mmHg, RV infarction, severe aortic stenosis, or recent PDE5 inhibitor use. IV nitroglycerin is used for ongoing ischemia, hypertension, or heart failure with BP monitoring. Morphine 2-4 mg IV repeated cautiously relieves refractory pain.
- ▶ **Primary PCI:** preferred when timely. Perform for symptoms ≤12 hours and for later presentation with ongoing ischemia, shock, acute severe heart failure, or life-threatening arrhythmia. Aim FMC-to-device ≤90 minutes at a PCI-capable centre; transfer if anticipated FMC-to-device ≤120 minutes. Stable multivessel disease may undergo staged nonculprit PCI during admission or up to 45 days; in cardiogenic shock, do culprit-only PCI initially.
- ▶ **Fibrinolysis:** if PCI cannot be achieved within 120 minutes and no contraindication exists, give within 12 hours of symptom onset, ideally door-to-needle ≤30 minutes. Options: alteplase 15 mg bolus then 50 mg/30 min then 35 mg/60 min; streptokinase 1.5 million units/1 h; reteplase 10 units bolus repeated at 30 min; tenecteplase weight-based IV bolus.
- ▶ **Contraindications to lysis:** prior hemorrhagic stroke, ischemic stroke/cerebrovascular event within 1 year, intracranial neoplasm, recent head trauma, active internal bleeding, suspected aortic dissection, and severe uncontrolled BP >180/110 mmHg. Relative contraindications include anticoagulation with high INR, recent major surgery/trauma, prolonged traumatic CPR, bleeding diathesis, pregnancy, active peptic ulcer, hemorrhagic retinopathy, and recent streptokinase exposure/allergy.
- ▶ **After lysis:** reperfusion is suggested by pain relief and ≥50% ST resolution at 60-90 minutes. Persistent pain/ST elevation or reocclusion requires rescue PCI. Even after successful lysis, transfer for angiography and PCI if indicated, usually 3-24 hours after fibrinolysis.

Pharmacotherapy and hospital care

Therapy	Must-write points
P2Y12 inhibitor	Add to aspirin for all STEMI, usually 12 months. PCI: ticagrelor or prasugrel preferred over clopidogrel; avoid prasugrel after stroke/TIA and generally in age >75. Fibrinolysis: clopidogrel is standard.
Anticoagulation	UFH for primary PCI and with fibrin-specific lysis: 60 U/kg bolus, max 4000 U, then 12 U/kg/h, max 1000 U/h, adjusted to aPTT target. Enoxaparin is an alternative after lysis; fondaparinux must not be the sole anticoagulant during PCI.
Beta-blocker	Start oral therapy within 24 hours if no heart failure, low output, shock risk, bradycardia, heart block, asthma, or hypotension. IV metoprolol 5 mg x3 only in selected stable patients with ongoing ischemia.
RAAS blockade	Start ACE inhibitor early when stable, especially anterior MI, HF, LVEF $\leq 40\%$, diabetes, hypertension, prior MI, or large wall motion abnormality; use ARB if intolerant. Add eplerenone/spironolactone if LVEF $\leq 40\%$ plus HF or diabetes without renal dysfunction/hyperkalemia.
Statin / supportive care	High-intensity statin before discharge. Correct K to about 4.5 mmol/L and Mg to about 2.0 mmol/L. Avoid routine calcium channel blockers, glucocorticoids, and NSAIDs other than aspirin.

- ▶ Admit unstable or high-risk patients to cardiac ICU/coronary care. Uncomplicated STEMI: bed rest 6-12 hours, sit out within 24 hours, ambulate progressively, step down after 24-48 hours, discharge commonly by day 3-5.

Complications and secondary prevention

- ▶ **LV failure / shock:** treat hypoxemia, pulmonary edema with loop diuretic and nitrates if BP permits, urgent echo, cautious inotrope/vasopressor, hemodynamic monitoring when useful, and urgent culprit revascularization. Norepinephrine is commonly preferred in shock; routine IABP has not improved outcomes.
- ▶ **RV infarction:** avoid nitrates and diuretics; give cautious saline to maintain preload and inotrope only if needed.
- ▶ **Arrhythmias:** immediate defibrillation for VF/unstable VT; IV amiodarone for sustained tolerated VT; AIVR after reperfusion is usually benign; atropine/pacing for symptomatic bradycardia.

- ▶ **Mechanical complications:** VSD, papillary muscle rupture with acute MR, and LV free-wall rupture typically occur within 1-14 days, especially 24 hours and 3-5 days. New murmur, pulmonary edema, shock, tamponade, or electromechanical dissociation requires urgent echo and surgical/interventional management.
- ▶ **Pericarditis / thrombus / aneurysm:** post-MI pericarditis is treated with high-dose aspirin; avoid early NSAIDs/steroids. Large anterior MI with LV thrombus needs therapeutic anticoagulation for about 3 months. True LV aneurysm causes HF, embolism, arrhythmias; pseudoaneurysm requires repair.
- ▶ **Secondary prevention:** lifelong aspirin, DAPT for 12 months if bleeding risk allows, high-intensity statin, beta-blocker at least 1 year, ACE inhibitor/ARB and aldosterone antagonist when indicated, smoking cessation, BP/diabetes/lipid control, cardiac rehabilitation, LVEF assessment in all, and delayed ICD consideration if severe LV dysfunction persists after reassessment.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **ACS pathogenesis flowchart:** vulnerable plaque -> rupture/erosion -> platelet activation -> thromboxane A₂ + GP IIb/IIIa aggregation -> thrombin/fibrin -> occlusive thrombus -> ST elevation -> necrosis.
- ▶ **STEMI reperfusion algorithm:** suspected STEMI -> ECG within 10 minutes -> primary PCI if FMC-device <=90/120 minutes -> fibrinolysis if PCI delayed and no contraindication -> rescue PCI if failed reperfusion at 60-90 minutes -> routine angiography 3-24 hours after successful lysis.

Clinical / Diagnostic significance

- ▶ Chest pain with diaphoresis for >30 minutes is STEMI until proved otherwise; epigastric “gas” pain in a high-risk patient is dangerous.
- ▶ Do not wait for troponin before reperfusion when the ECG is diagnostic.
- ▶ Inferior STEMI with hypotension and clear lungs suggests RV infarction; nitrates can cause collapse.
- ▶ Failed lysis or recurrent ST elevation mandates rescue PCI.
- ▶ New murmur with pulmonary edema or shock after MI suggests papillary muscle rupture or VSD.
- ▶ Killip class, LVEF, shock, persistent ischemia, age, diabetes, and ventricular arrhythmias guide prognosis.

High-yield exam pointers

- ▶ STEMI is usually **plaque rupture/erosion with occlusive platelet-fibrin thrombus**.
- ▶ **Time is muscle:** primary PCI preferred; fibrinolysis only when timely PCI is unavailable and safe.

- ▶ ECG: ST elevation in two contiguous leads; remember higher V2-V3 cutoffs.
- ▶ **Aspirin immediately:** chew 160-325 mg, then add P2Y₁₂ inhibitor plus anticoagulation.
- ▶ **No routine oxygen** when saturation is normal.
- ▶ **Avoid nitrates** in RV infarction, hypotension, severe aortic stenosis, and recent PDE5 inhibitor use.
- ▶ **Failed lysis:** persistent pain/ST elevation at 60-90 minutes or <50% ST resolution -> rescue PCI.
- ▶ **Killip IV = cardiogenic shock** and needs urgent revascularization.
- ▶ **Discharge drugs:** DAPT, statin, beta-blocker, ACE inhibitor/ARB, aldosterone antagonist when indicated, and rehabilitation.

SOURCE & COVERAGE

Harrison 22e — “ST-Segment Elevation Myocardial Infarction”; “Ischemic Heart Disease”; Braunwald’s Heart Disease 13e — “ST-Elevation Myocardial Infarction Pathophysiology and Clinical Evolution”; “ST-Elevation Myocardial Infarction: Management”; CMDT 2026 — “Coronary Artery Disease, Valvular Disease, & Other Key Topics in Cardiology”.



Early Invasive Strategy in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) encompasses unstable angina (UA, no necrosis) and non-ST-segment elevation myocardial infarction (NSTEMI, troponin-positive necrosis) and arises from a supply–demand mismatch driven most often by non-occlusive coronary thrombosis on a fissured/eroded plaque. An **early (routine) invasive strategy** means that, after starting anti-ischaemic and antithrombotic therapy, the patient is taken for **coronary angiography within 24 h** (and within 2 h if very high-risk), followed by revascularisation (PCI or CABG) guided by the coronary anatomy. This is contrasted with an **ischaemia-guided (selective) strategy** in which angiography is reserved for spontaneous or provoked ischaemia. The central exam concept is that strategy is *risk-matched*: invasive management benefits high-risk patients, whereas low-risk patients do equally well with an initially conservative approach.

Three Management Strategies — Definitions

Strategy	What it means	Whom it suits
Immediate invasive	Angiography <2 h, as soon as possible	Very-high-risk (haemodynamic/electrical instability)

Strategy	What it means	Whom it suits
Early invasive (routine)	Angiography within 24 h of presentation, then PCI/CABG/medical therapy per anatomy	High-risk stable patients (NSTEMI, GRACE >140, dynamic ECG)
Delayed invasive	Angiography 25–72 h	Intermediate-risk after stabilisation
Ischaemia-guided (selective/conservative)	Medical therapy first; angiography only for recurrent rest pain, ST/biomarker change, haemodynamic instability, or positive non-invasive stress/CT	Non-high-risk, low TIMI/GRACE, troponin-negative

Pathophysiological Rationale & Evidence Base

- ▶ The **culprit lesion** in NSTEMI-ACS is typically an eccentric stenosis with scalloped/overhanging edges and a narrow neck, often a lipid-rich plaque with a thin fibrous cap (rupture) or a proteoglycan-rich eroded plaque with a platelet-rich white thrombus. At angiography ~35% have three-vessel disease, 25% two-vessel, 20% single-vessel, <10% left-main and ~10% no critical epicardial stenosis.
- ▶ An invasive strategy allows **direct identification and treatment of the culprit (and significant non-culprit) lesions**, plaque stabilisation by stenting, and complete revascularisation — addressing the unstable substrate that medical therapy alone cannot.
- ▶ **Trial evidence:** multiple randomised trials and meta-analyses show that, compared with a conservative/selective approach, an early invasive strategy **reduces composite cardiovascular endpoints, recurrent MI and length of stay** — with the benefit **concentrated in high-risk patients** (multiple risk factors, ST-segment deviation, positive biomarkers). A meta-analysis of 13 RCTs (≈11,972 patients) of early vs delayed angiography showed a **significant long-term reduction in MI but no overall mortality difference**; in the pre-specified subgroup with **GRACE score >140**, early invasive management significantly reduced MACE, whereas low-GRACE patients showed no clear benefit.
- ▶ **Timing within the invasive arm:** two studies comparing immediate invasive intervention (median 1.4 and 4.7 h) with delayed intervention (median 61 and 62 h) reduced death or new MI, with the **greatest benefit in high-risk-score patients**. For the broad NSTEMI population the survival benefit of “very early” over “early/delayed” timing is modest; risk score, not the clock alone, drives urgency.
- ▶ **Long-term “catch-up”:** in long-term follow-up of the *ICTUS* trial (out to ~10 years), the early-invasive advantage over a selective strategy was no longer apparent, partly because of catch-up revascularisation in the selective arm — emphasising that selective management is a legitimate option in non-high-risk patients.

Risk Stratification — the Trigger for Strategy Selection

Strategy is selected by formal risk scoring plus clinical features. Early risk assessment identifies those who derive the greatest benefit from an early invasive approach.

- ▶ **TIMI risk score (0–7)**: age ≥ 65 y; ≥ 3 CAD risk factors; known coronary stenosis $\geq 50\%$; ST-segment deviation on presenting ECG; ≥ 2 anginal episodes in prior 24 h; aspirin use in prior 7 days; elevated cardiac biomarkers. Higher score $\rightarrow$ higher 14-day risk of death/MI/urgent revascularisation ($\approx 5\%$ at 0–1 rising to $\approx 41\%$ at 6–7).
- ▶ **GRACE risk score** (best discrimination; applies with or without ST elevation): age, Killip class, systolic BP, ST-segment deviation, cardiac arrest at presentation, serum creatinine, elevated CK-MB/troponin, and heart rate. A **GRACE score** >140 is a key trigger for early invasive management.
- ▶ **HEART pathway** (History, ECG, Age, Risk factors, Troponin): identifies a low-risk group (HEART 0–3 with negative serial troponins, NPV $\sim 99.6\%$) suitable for early discharge, versus HEART ≥ 4 / troponin-positive needing cardiology admission.

Selection, Timing and Staging of the Invasive Strategy

Risk tier	Defining features	Recommended timing
Very high risk (≥ 1)	Cardiogenic shock / unstable haemodynamics; acute HF from ongoing ischaemia; cardiac arrest after presentation; life-threatening arrhythmia; mechanical complication of MI; angina refractory to medical therapy; recurrent dynamic ischaemic ECG changes	Immediate invasive (<2 h)
High risk (≥ 1)	Confirmed NSTEMI; GRACE >140 ; transient ST-segment elevation; dynamic ST- or T-wave changes	Early invasive (<24 h)
Non-high risk	None of the above	Selective invasive — clinical/non-invasive assessment, then angiography only if ischaemia confirmed

- ▶ **Culprit-lesion PCI** is performed (CABG if anatomy unfavourable, e.g. complex multivessel/left-main or mechanical complications such as VSD or papillary-muscle rupture, where surgery is preferred).
- ▶ **Non-culprit / multivessel disease**: complete revascularisation (single-stage during index PCI, or staged within ~ 45 days) should be considered in the absence of cardiogenic shock, severe

comorbidity (e.g. AKI) or unfavourable anatomy; a **Heart Team** decides PCI vs CABG for complex anatomy.

- ▶ **CABG-favouring factors:** diabetes mellitus, LVEF <35%, contraindication to DAPT, diffuse in-stent restenosis, heavy calcification, inability to achieve complete revascularisation, or concomitant valve/aortic surgery.
- ▶ **Vascular access:** radial access is the default (Class I) to reduce bleeding.

Peri-procedural Pharmacotherapy (Optimise Before/During the Cath)

- ▶ **Antiplatelet:** aspirin loading 150–325 mg (then 75–100 mg/day) **plus** a P2Y₁₂ inhibitor. Ticagrelor (180 mg load, 90 mg bd) benefits patients managed conservatively *or* invasively; prasugrel (60 mg load, 10 mg/day) is given **once coronary anatomy is known (post-angiography)** when PCI is planned and is contraindicated after prior stroke/TIA; clopidogrel (300–600 mg load) when potent agents are unsuitable or anticoagulation is also needed. Contemporary guidance discourages **routine P2Y₁₂ pretreatment** before angiography in patients planned for early invasive management with unknown anatomy.
- ▶ **Anticoagulant:** UFH, enoxaparin, bivalirudin (used at/just before PCI) or fondaparinux (best for conservatively-managed, high bleeding risk — needs supplemental UFH at PCI to avoid catheter thrombosis).
- ▶ **GP IIb/IIIa inhibitors** (eptifibatide, tirofiban): reserved for bail-out / high thrombus burden, not routine.
- ▶ **Anti-ischaemic & secondary prevention:** nitrates, beta-blockers (target HR 50–60/min), high-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg) ± ezetimibe/PCSK9 to LDL-C <55 mg/dL, ACE-I/ARB; DAPT generally 12 months (modulated by ischaemic vs bleeding risk).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Risk-stratified strategy/timing flow-chart (Fig. 285-4 style):** Box “NSTE-ACS” → three branches: **Very high risk** (shock/HF/arrest/arrhythmia/mechanical complication/refractory angina/dynamic ECG) → *Immediate invasive* <2 h; **High risk** (NSTEMI / GRACE >140 / transient ST-elevation / dynamic ST-T) → *Early invasive* <24 h; **Non-high risk** → *Selective invasive*. Downstream labels: “Culprit-lesion PCI (CABG if unfavourable anatomy)”, “Evaluation of non-culprit lesion”, “Staged vs single-stage PCI”, “Medical management”. Label the GRACE >140 cut-off.
- ▶ **Spectrum-of-ACS diagram:** clinical presentation → ECG (Normal / ST-depression / ST-elevation) → hs-cTn (non-elevated vs rise-and-fall) → final diagnosis UA / NSTEMI / STEMI. Labels: UA, NSTEMI, STEMI, hs-cTn, ST-segment depression.

Clinical / Diagnostic significance

- ▶ **Diagnosis** rests on history (rest pain >10 min, recent-onset, or crescendo), ECG (new ST-depression in $\sim 1/3$; deep symmetrical T-inversions ≥ 0.3 mV) and a **rise-and-fall of high-sensitivity troponin** (distinguishes NSTEMI from UA); the 0/1-h rapid rule-out algorithm accelerates triage. Distinguish **myocardial injury** (troponin >99th percentile without ischaemia — sepsis, CKD, HF, PE, myocarditis, Takotsubo) from true **type 1 MI**.
- ▶ **Management pearl:** match invasiveness to risk — invasive strategy for high-risk substrate, selective for low-risk. Always exclude life-threatening mimics (aortic dissection, PE, tamponade) before committing to the cath lab.
- ▶ Women, older adults, and patients with diabetes or CKD are **under-treated** despite higher risk and benefit from invasive care; meta-analysis supports early intervention in the elderly.

High-yield exam pointers

- ▶ Early/routine invasive = **angiography within 24 h** then revascularisation; **immediate** = <2 h for very-high-risk; **selective/ischaemia-guided** for non-high-risk.
- ▶ **GRACE score >140** is the pivotal numeric trigger for an early invasive strategy; benefit of invasive care is **proportional to baseline risk**.
- ▶ Invasive strategy reduces **recurrent MI, refractory ischaemia, MACE and length of stay**, but **not overall mortality** in unselected patients.
- ▶ **Very-high-risk = immediate (<2 h):** shock, refractory angina, acute HF from ischaemia, life-threatening arrhythmia, mechanical complication, recurrent dynamic ECG changes.
- ▶ **Radial access (Class I)** to cut bleeding; avoid routine GP IIb/IIIa and routine P2Y12 pretreatment before known anatomy.
- ▶ **Prasugrel only after angiography** when PCI planned; contraindicated with prior stroke/TIA. **Ticagrelor** works in both conservative and invasive pathways.
- ▶ Consider **complete revascularisation** (single-stage or staged ≤ 45 days) in multivessel disease without shock/AKI; **Heart Team** for complex/left-main $\rightarrow$ CABG, especially with diabetes or LVEF <35%.
- ▶ **ICTUS** long-term data show the early-invasive edge narrows over years due to **catch-up revascularisation** in the selective arm.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina)” (risk scores, invasive vs conservative strategy, Fig. 285-4 selection/timing, antithrombotic regimens).

- ▶ **Braunwald's Heart Disease, 13e** — “Non-ST Elevation Acute Coronary Syndromes” (Invasive vs Conservative Management; timing meta-analyses and GRACE >140 subgroup; ICTUS 10-year catch-up; ACC/AHA vs ESC triage; revascularisation/Heart Team).
- ▶ **CMDT 2026** — “Coronary Artery Disease... Key Topics in Cardiology” (early invasive algorithm, GRACE/TIMI scoring, drug doses, indications for catheterisation, Table 10–8).
- ▶ *Coverage note:* the corpus supports the strategy, timing tiers, risk scores and pooled/meta-analytic evidence in full; among individual landmark timing/strategy trials, only *ICTUS* is named explicitly (the older FRISC-II, TACTICS-TIMI 18 and RITA-3 trials that historically established routine-invasive benefit are universally accepted standard cardiology but are not separately detailed in the available chapters).



Emerging therapies and strategies in treatment of Heart failure

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Over the past five decades, management of heart failure (HF) has evolved from a *renocentric* (diuretics) and *hemodynamic* model (digoxin, inotropes) to an era of **disease-modifying therapy** built on neurohormonal antagonism and, more recently, metabolic and device-based strategies. The contemporary pharmacologic backbone of HF with reduced ejection fraction (HFrEF) comprises **four foundational pillars** — RAAS blockade (including ARNI), evidence-based **beta blockers**, **mineralocorticoid receptor antagonists (MRAs)** and **SGLT-2 inhibitors** — onto which newer agents (vericiguat, omecamtiv mecarbil, ivabradine) and novel strategies (rapid in-hospital sequencing, transcatheter valve repair, remote haemodynamic monitoring) are layered. This answer covers the emerging drugs, devices and care-delivery strategies that now modify the natural history of HF.

Foundational “four pillars” of modern HFrEF therapy

- ▶ The sequential addition of each class produces a **progressive, incremental decline in mortality** (Fig. 265-3): ACEI/ARB → beta blocker → MRA → ARNI (in place of ACEI/ARB) → SGLT-2 inhibitor → balanced vasodilators (hydralazine–isosorbide dinitrate in selected populations, e.g. African Americans).
- ▶ These four classes now **form the pillars of pharmacotherapy**, facilitating stabilisation and even *reverse remodelling*, reducing symptoms, hospitalisations and both pump-failure and arrhythmic deaths.
- ▶ **Add-on agents** (ivabradine, vericiguat) further reduce HF hospitalisation but do **not** substantially lower mortality. Further “stacked” neurohormonal blockade (ACEI + ARB + MRA

together; aliskiren — *ATMOSPHERE*; endothelin antagonists; moxonidine) is ineffective or harmful — there is a **ceiling of benefit** of RAAS inhibition.

Drug class	Representative agent	Initiation → target dose	Key trial(s)
ARNI	Sacubitril–valsartan (LCZ696)	100 mg bid → 200 mg bid	PARADIGM-HF; PIONEER-HF
SGLT-2 inhibitor	Dapagliflozin / Empagliflozin	10 mg qd → 10 mg qd	DAPA-HF; EMPEROR-Reduced
sGC stimulator	Vericiguat	2.5 mg qd → 10 mg qd	VICTORIA
Myosin activator	Omecamtiv mecarbil	25 mg bid → up to 50 mg bid (plasma-guided)	GALACTIC-HF; COSMIC-HF
If-channel inhibitor	Ivabradine	— (added if HR >70, sinus rhythm)	SHIFT

ARNI and soluble guanylyl cyclase stimulation

- ▶ **Angiotensin receptor–neprilysin inhibitor (ARNI)**: sacubitril–valsartan combines an **AT1-receptor blocker** with **neprilysin inhibition**, which raises circulating **natriuretic peptides** (and other vasoactive peptides), promoting natriuresis, vasodilation and anti-remodelling.
- ▶ In **PARADIGM-HF** (8399 HFrEF patients), sacubitril–valsartan vs enalapril gave a **20% reduction in CV death/HF hospitalisation** and a **16% reduction in all-cause mortality**, with lower hyperkalaemia and renal dysfunction but more symptomatic hypotension.
- ▶ Guidelines now advocate **switching to ARNI** in symptomatic HFrEF tolerating ACEI/ARB; up-front use in *de novo* HF is increasingly considered. **Contraindicated** with prior angioedema; allow a **36-h washout** from an ACEI (excess bradykinin → angioedema, as seen with omapatrilat in *OVERTURE*). An ARB leaves the ACE-bradykinin pathway intact, hence lower angioedema risk.
- ▶ **Vericiguat** is a novel oral **soluble guanylyl cyclase (sGC) stimulator** that enhances cyclic-GMP/NO signalling (directly stimulates and sensitises sGC to endogenous NO). In **VICTORIA** (5050 patients, LVEF <45%, recent worsening HF), it produced a **modest 10% relative risk reduction** in CV death/HF hospitalisation, driven principally by reduced HF hospitalisation — a useful **adjunct** in high-risk, recently-decompensated HFrEF.

SGLT-2 inhibition and metabolic strategies

- ▶ **SGLT-2 inhibitors** (dapagliflozin, empagliflozin) are the most recent pillar; their cardiac benefit is **independent of glycaemic (HbA1c) lowering** and of diabetes status (SGLT-2 is itself a *novel biologic target* in HF).

- ▶ **DAPA-HF** (4744 HFrEF) — dapagliflozin 10 mg gave a **26% reduction** in worsening HF/CV death, consistent with and without diabetes. **EMPEROR-Reduced** (3730, EF $\leq 40\%$) — empagliflozin gave a **25% reduction** in CV death/HF hospitalisation.
- ▶ Benefit now extends across the EF spectrum: **EMPEROR-PRESERVED** and **DELIVER** show reduced CV death/HF hospitalisation in **HFpEF/HF with LVEF $>40\%$** — the first clearly effective disease-modifying drug class in HFpEF.
- ▶ **Other metabolic/inflammatory targets**: **GLP-1 receptor agonists** (e.g. liraglutide) do not worsen HF and **improve QOL in obese HFpEF irrespective of diabetes**; **IV iron** (ferric carboxymaltose — **FAIR-HF**, **CONFIRM-HF**, **AFFIRM-AHF**, **IRONMAN**) corrects iron deficiency and improves symptoms/functional capacity (oral iron ineffective); anti-inflammatory therapy (anti-TNF infliximab/etanercept) **failed**, while IL-1 β blockade (**canakinumab**, **CANTOS**) reduced HF hospitalisation post-MI in post-hoc analysis.

Novel inotropy and heart-rate modification

- ▶ **Omecamtiv mecarbil** — a selective cardiac myosin activator that prolongs the ejection period and increases fractional shortening **without raising myocardial oxygen demand** or intracellular calcium (distinct from classic inotropes). In **GALACTIC-HF** (8256, EF $\leq 35\%$) it gave a **14% reduction** in the composite of CV death/first HF event, driven by HF events (**no effect on CV death alone**); a signal of greater benefit in advanced HF (lower EF, higher natriuretic peptides).
- ▶ **Calcium sensitisers** — **levosimendan** (also a PDE-3 inhibitor/vasodilator) for acute decompensated HF: in **SURVIVE/REVIVE II** it did **not** reduce mortality; not approved in the USA but used elsewhere. *Routine long-term/short-term inotropes (e.g. milrinone, OPTIME-CHF) remain discouraged* — reserved as bridge to LVAD/transplant or palliation.
- ▶ **Ivabradine** — selective **If-current inhibitor** of the SA node; lowers heart rate without affecting contractility or vascular tone. **SHIFT** (NYHA II–III, sinus rhythm, HR $>70/\text{min}$): reduced CV death/HF hospitalisation proportional to heart-rate reduction. Considered as **adjunct/alternative** in patients still symptomatic on GDMT, in sinus rhythm, with HR $>70/\text{min}$.

Emerging therapies and strategies in HFpEF

- ▶ **SGLT-2 inhibitors** (**EMPEROR-PRESERVED**, **DELIVER**) — reduce HF hospitalisation; now the cornerstone of HFpEF therapy.
- ▶ **ARNI** — **PARAGON-HF** (4822, LVEF $\geq 45\%$) showed a 13% reduction that **narrowly missed significance** ($p = 0.06$); benefit greatest in those with **lower (mildly reduced) EF and in women**. Now approved across the full EF spectrum, greatest benefit when LVEF is below normal (**PARAGLIDE-HF** — benefit confined to EF $\leq 60\%$).
- ▶ **MRAs** — spironolactone (**TOPCAT/ALDO-DHF**) improved diastolic indices but not hard outcomes; the non-steroidal MRA **finerenone** (**FINEARTS-HF**) and **SPIRRIT-HFpEF** are evaluating this further.

- ▶ **Ineffective in HFpEF:** ACEIs/ARBs (except for prevention), digoxin (may cut hospitalisation), beta/calcium-channel blockers (useful only for rate control in AF), **PDE-5 inhibitor sildenafil**, and nitrates (NEAT-HFpEF, INDIE-HFpEF). Strategy emphasis: decongestion (avoiding excessive preload reduction → underfilling, azotaemia, syncope), BP control, maintaining sinus rhythm (AF ablation), and treating comorbidity (obesity, sleep apnoea, CKD, iron deficiency).

Strategies: in-hospital initiation, rapid sequencing and remote monitoring

- ▶ **Pre-discharge / in-hospital initiation:** PIONEER-HF (sacubitril–valsartan started before discharge) and EMPULSE (empagliflozin in hospitalised HF across EF spectrum) improved natriuretic peptides and clinical outcomes — institute GDMT *before discharge* to improve adherence.
- ▶ **Rapid sequencing / intensive titration:** STRONG-HF showed that aggressive up-titration to guideline targets **within 2 weeks of discharge** plus frequent follow-up to 2 months cut all-cause mortality and HF readmission at 180 days (benefit regardless of EF) — most readmissions occur in the first 2 weeks.
- ▶ **Remote haemodynamic monitoring:** implantable **pulmonary-artery pressure sensor** (CardioMEMS) reduced HF hospitalisations by up to 39% (CHAMPION); GUIDE-HF was neutral overall (confounded by COVID-19) but positive in pre-pandemic analysis. Telemonitoring of weight/vitals and intrathoracic impedance have **not** improved outcomes.

Device, surgical, cellular and gene-based advances

- ▶ **Cardiac resynchronisation therapy (CRT):** biventricular pacing via coronary sinus restores synchronous contraction; mortality benefit in CARE-HF, RAFT, MADIT-CRT — greatest with **QRS >149 ms and LBBB**. **Conduction-system / left-bundle-branch-area pacing** is an evolving alternative (evidence still less certain).
- ▶ **ICD for primary prevention of sudden cardiac death** — NYHA II–III, LVEF ≤35% (≤30% post-MI), on optimal therapy, no benefit within 40 days of MI; uncertain benefit in non-ischaemic cardiomyopathy (DANISH).
- ▶ **Cardiac contractility modulation (CCM):** non-excitatory RV-septal stimulation during the refractory period — improves symptoms/QOL in EF 25–45% with **narrow QRS** (not CRT-eligible); no proven mortality benefit, not yet guideline-endorsed.
- ▶ **Neuromodulation devices** (vagal nerve stimulation — INOVATE-HF/ANTHEM-HFrEF; baroreflex activation; renal denervation) have **largely failed** in large trials.
- ▶ **Transcatheter edge-to-edge mitral repair (MitraClip)** for functional MR: COAPT (positive — fewer hospitalisations and deaths) vs MITRA-FR (neutral); benefit depends on MR being disproportionate to LV dilation.

- ▶ **Surgical:** CABG for ischaemic cardiomyopathy (STICH — long-term benefit), AF catheter ablation (CASTLE-AF), and advanced therapies — **LVAD and cardiac transplantation** (detailed in Chap. 271).
- ▶ **Cellular and gene-based therapy (investigational):** bone-marrow/cardiac-derived and mesenchymal precursor cells (DREAM-HF negative) and **SERCA2a gene transfer** via AAV1 (CUPID — confirmatory trial failed) remain experimental.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Mortality-staircase (Fig. 265-3 style):** an X-Y plot with *risk of mortality* descending stepwise. Label, top→bottom: **Placebo → ACE inhibitor/ARB → Beta-blockers (carvedilol, metoprolol succinate, bisoprolol) → Mineralocorticoid receptor antagonist → ARNI (instead of ACEI/ARB) → SGLT-2 inhibitor → balanced vasodilators**; side-box “add-on, hospitalisation-only: Ivabradine, Vericiguat, Omecamtiv mecarbil”; “Ineffective/harmful: Endothelin antagonists, Moxonidine, Xamoterol, oral inotropes”.
- ▶ **Neurohormonal target schematic:** a cardiomyocyte/vasculature with arrows to drug targets — **AT1 receptor (ARB), neprilysin (sacubitril) → ↑natriuretic peptides, sGC/cGMP (vericiguat), SGLT-2 (gliflozins), cardiac myosin (omecamtiv), SA-node If current (ivabradine), mineralocorticoid receptor (MRA/finerenone).**

Clinical / Diagnostic significance

- ▶ **Sequence flexibly, titrate fully:** CIBIS-III showed order of ACEI vs beta blocker initiation does not matter — what matters is achieving target doses of all four pillars; GDMT is widely **under-dosed/under-utilised**.
- ▶ **ARNI** needs a 36-h ACEI washout and is avoided with prior angioedema; monitor BP (hypotension), K⁺ and renal function.
- ▶ **SGLT-2 inhibitors** are now started early and across the EF spectrum regardless of diabetes — a practice-changing shift; watch for genital mycotic infection, volume depletion and (rare) euglycaemic ketoacidosis.
- ▶ **Functional MR** with refractory symptoms → consider transcatheter repair (COAPT-type patients); refractory advanced HF → MCS/transplant referral.
- ▶ **Transitional care** (pre-discharge GDMT, STRONG-HF rapid titration, early follow-up, CardioMEMS in selected NYHA III) reduces the high (~50% at 6 months) readmission rate.

High-yield exam pointers

- ▶ **Four pillars of HFrEF:** ARNI/RAAS-blocker, beta blocker, MRA, **SGLT-2 inhibitor** — each adds incremental mortality benefit.
- ▶ **PARADIGM-HF:** sacubitril-valsartan → 20% ↓ CV death/HF hospitalisation, 16% ↓ all-cause mortality; target **200 mg bid**, 36-h ACEI gap, contraindicated if prior angioedema.

- ▶ **DAPA-HF** (26% ↓) and **EMPEROR-Reduced** (25% ↓); HFpEF benefit in **EMPEROR-PRESERVED & DELIVER**.
- ▶ **Vericiguat** = oral sGC stimulator (VICTORIA, modest 10% RRR, HF-hospitalisation driven).
- ▶ **Omecamtiv mecarbil** = selective cardiac myosin activator (GALACTIC-HF, 14% ↓, no effect on CV death alone, no ↑O₂ demand).
- ▶ **Ivabradine** = If-current SA-node inhibitor (SHIFT; HR >70, sinus rhythm).
- ▶ **HFpEF**: SGLT-2i effective; ARNI borderline (PARAGON-HF p = 0.06); finerenone (FINEARTS-HF) and GLP-1 agonists (obesity) emerging; sildenafil/nitrates ineffective.
- ▶ **Strategies**: in-hospital initiation (PIONEER-HF, EMPULSE), rapid up-titration (STRONG-HF), MitraClip (COAPT), CardioMEMS, CRT (QRS >149 ms + LBBB), ICD (LVEF ≤35%).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 265 "Heart Failure: Management" (primary); with brief reference to Ch 264 "Heart Failure: Pathophysiology and Diagnosis" (SGLT-2 as a novel biologic target). LVAD and cardiac transplantation are cross-referenced by Harrison to Ch 271 (not provided here). *Coverage note*: this answer is fully grounded in the provided chapters; specific drug doses are taken from Table 265-2. Advanced mechanical circulatory support/transplant details fall outside the supplied text (Ch 271) and are therefore summarised only at the level Ch 265 provides.



Endomyocardial fibrosis

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Endomyocardial fibrosis (EMF, *Davies' disease*) is a progressive **fibrotic obliterative disease of the ventricular apices and subvalvular apparatus** that produces a **restrictive cardiomyopathy (RCM)**. It is a member of the *endomyocardial diseases* — a group unified pathologically by **dense fibrosis of the endocardium**, of which the temperate-zone counterpart is **Löffler (eosinophilic) endocarditis**. First described in Uganda in 1948, EMF is one of the **commonest causes of RCM worldwide** and a major cause of heart failure in tropical Africa, the South Asian subcontinent (notably Kerala, India) and Brazil. The dominant haemodynamic lesion is **impaired diastolic filling of a non-compliant ventricle with preserved or near-preserved ejection fraction**.

Etiopathogenesis and epidemiology

- ▶ **Cause remains unknown**. No single unifying infectious, environmental or genetic mechanism has been established; several hypotheses coexist.
- ▶ **Eosinophil hypothesis (unifying concept)**: EMF is regarded as the **end-stage fibrotic phenotype** that pathologically resembles eosinophilic (Löffler) endocarditis. Toxic **eosinophil granule**

cationic proteins are thought to damage the endocardium and drive fibrosis. *However*, peripheral or cardiac-tissue **eosinophilia is seldom demonstrable in established tropical EMF** — distinguishing it from frank hypereosinophilic disease.

- ▶ **Environmental hypothesis:** exposure to **cerium** (a rare-earth element abundant in affected soils) has been implicated; dietary and infectious (helminthic/filarial) cofactors have been proposed but not confirmed.
- ▶ **Geography:** tropical and subtropical regions — **sub-Saharan Africa (Uganda, Nigeria, Mozambique)**, the South Asian subcontinent and Brazil; sporadic cases occur in temperate climates.
- ▶ **Epidemiology:** a **community prevalence of ~20% has been reported in rural Mozambique**, with **male predominance** ($\approx 23\%$ vs 17% in females) and **family clustering**. Age shows a **bimodal peak** — onset in the **first decade**, and again in the **second to fourth decades**.

Pathology and natural history

- ▶ Hallmark is **dense, white, glistening fibrous tissue obliterating the apex of the right and/or left ventricle**, extending onto the **inflow tract and the chordae/papillary muscles** (subvalvular apparatus) while characteristically **sparing the outflow tracts**.
- ▶ **Apical obliteration** by fibrosis ($\pm$ superimposed mural thrombus) reduces cavity volume and produces restriction; tethering of the AV-valve apparatus produces **mitral and/or tricuspid regurgitation**. The atria dilate, often massively.
- ▶ **Three pathological stages** (best characterised in eosinophilic/Löffler disease, the temperate analogue, and applied to the endomyocardial-disease spectrum):

Stage	Pathological process	Clinical correlate
1. Acute necrotic	Eosinophil infiltration of myocardium, degranulation and myocardial necrosis/inflammation	Often few/no symptoms; biomarkers $\pm$ raised, CMR may show inflammation
2. Intermediate (thrombotic)	Mural thrombus layered over damaged endocardium, favouring the apices; risk of embolism	Chest pain, dyspnoea, AV-valve regurgitation, systemic/cerebral emboli
3. Fibrotic	Diffuse endocardial scarring $\rightarrow$ restrictive cardiomyopathy , subvalvular scarring impairing valve mobility	Established RCM with biventricular congestion

- ▶ **Anatomical patterns of EMF:** *right-ventricular* (RV apical obliteration $\rightarrow$ severe TR, gross ascites, raised JVP), *left-ventricular* (LV apical obliteration $\rightarrow$ MR, pulmonary congestion), and *biventricular* (commonest, $\sim 50\%$).

Tropical EMF versus Löffler (eosinophilic) endocarditis

Feature	Tropical EMF (Davies')	Löffler endocarditis
Geography / climate	Tropics (Africa, S. Asia, Brazil)	Temperate / developed countries
Age, sex	Children & young adults; M>F	Adults (typically male)
Eosinophilia	Usually absent / not demonstrable	Hypereosinophilia present (AEC >1500/ μ L $\geq$ 1 month, often $\geq$ 6 months)
Underlying cause	Unknown (cerium, ?infective)	Helminth/parasitic infection, allergy/drug reaction, eosinophilic leukaemia/malignancy , idiopathic HES; myeloproliferative HES may respond to tyrosine-kinase inhibitors
Course	Indolent, chronically progressive	More aggressive (acute necrotic $\rightarrow$ thrombotic $\rightarrow$ fibrotic)
Common end-point	Restrictive cardiomyopathy with apical fibrosis & AV regurgitation	Same fibrotic RCM end-stage

Clinical features

- Symptoms of **restrictive physiology** dominate, frequently **right-sided**: exertional dyspnoea, **paroxysmal nocturnal dyspnoea**, fatigue, peripheral oedema and **prominent ascites** (a feature common to all endomyocardial diseases, often out of proportion to peripheral oedema).
- **Signs**: raised JVP with **rapid/steep Y descent** and a **positive Kussmaul sign** (inspiratory rise in JVP); a **fourth heart sound (S4)** is more typical than S3 in sinus rhythm; murmurs of **mitral and/or tricuspid regurgitation**; **atrial fibrillation** is common; hepatomegaly and dependent oedema. The apex beat is **less displaced than in DCM** and **less forceful than in HCM**.
- **Complications**: congestive heart failure, AF and other arrhythmias, mural thrombus with **systemic/pulmonary embolism**, AV-valve regurgitation, pericardial effusion, and **sudden cardiac death**.

Investigations and diagnosis

- **ECG**: non-specific — low-voltage complexes, T-wave inversion, atrial enlargement, **atrial fibrillation**, conduction abnormalities.
- **Chest radiograph**: cardiomegaly from biatrial enlargement; pericardial effusion; occasionally **apical/endocardial calcification**.

- ▶ **Echocardiography (key test):** obliteration of the ventricular apex by fibrous tissue ± thrombus, apical/subvalvular AV-apparatus involvement, AV-valve regurgitation, **gross biatrial enlargement**, restrictive transmitral inflow (tall E, short deceleration time) and preserved/near-normal systolic function.
- ▶ **Cardiac MRI:** demonstrates apical fibrosis and **subendocardial late gadolinium enhancement**; detects thrombus and inflammation in the eosinophilic phase.
- ▶ **Cardiac catheterisation:** elevated and equalised end-diastolic pressures with a “**dip-and-plateau**” (square-root sign) ventricular pressure tracing; **pulmonary arterial pressure is raised**.
- ▶ **Endomyocardial biopsy:** more useful in RCM than in DCM/HCM to confirm an infiltrative/fibrotic aetiology; shows endocardial fibrosis (and eosinophilic infiltration in the active eosinophilic phase).
- ▶ **Crucial differential** — RCM vs constrictive pericarditis (both present with right-heart dominance):

Feature	Restrictive cardiomyopathy (EMF)	Constrictive pericarditis
Respiratory ventricular interaction	Absent / not accentuated	Accentuated (interdependence)
Pulmonary artery pressure	Elevated (high PCWP)	Usually normal
Pericardium	Normal	Thickened ± calcified
BNP / NT-proBNP	High	Relatively low/normal
Septal motion / CMR	Apical fibrosis, LGE	Pericardial thickening, septal bounce

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Four-chamber heart in EMF** — label: *fibrous obliteration of LV apex, fibrous obliteration of RV apex, mural thrombus over endocardium, tethered mitral and tricuspid subvalvular apparatus* → MR/TR, grossly dilated left and right atria, spared outflow tracts.
- ▶ **Stages of endomyocardial (eosinophilic) disease** — a 3-box flow: *Acute necrotic (eosinophil infiltration & myocardial necrosis)* → *Intermediate/thrombotic (mural thrombus, embolism)* → *Fibrotic (endocardial scarring → restrictive cardiomyopathy)*.

Clinical / Diagnostic significance

- ▶ EMF is a **leading cause of restrictive cardiomyopathy and heart failure in the tropics**, and an important Indian cause (Kerala) — high-yield for an Indian postgraduate exam.
- ▶ The **eosinophil link** unifies tropical EMF with Löffler endocarditis; recognising an active eosinophilic phase allows **disease-modifying therapy** (treat parasitosis, corticosteroids, TKIs for myeloproliferative HES) *before* irreversible fibrosis.

- ▶ Echocardiographic apical obliteration with AV-valve regurgitation and biatrial enlargement is virtually diagnostic in an endemic setting.
- ▶ Distinguishing EMF from **constrictive pericarditis** is decisive because constriction is **surgically curable by pericardiectomy**, whereas EMF requires endocardial decortication/valve surgery.
- ▶ Mural thrombus mandates attention to **thromboembolic risk**.

Management

- ▶ **Medical (supportive)**: the cornerstone is **euvolaemia** — judicious **diuretics** (loop ± thiazide ± aldosterone antagonist) balancing decongestion against the need for adequate filling. Rate control and anticoagulation for AF; anticoagulation for mural thrombus/embolism. **Beta-blockers** can prolong diastolic filling but may be poorly tolerated by lowering an already fixed stroke volume; **vasodilators are often poorly tolerated**. Standard HFrEF therapies are **not routinely indicated** in RCM.
- ▶ **Disease-specific (active eosinophilic phase)**: treat the underlying cause; **corticosteroids and cytotoxic/cytolytic agents** (e.g. hydroxyurea), and **tyrosine-kinase inhibitors** for FIP1L1-PDGFR α / myeloproliferative HES.
- ▶ **Surgical (fibrotic stage)**: endocardectomy (decortication/resection of fibrous tissue) with **mitral/tricuspid valve repair or replacement** can produce dramatic symptomatic and survival benefit, *but* carries **significant perioperative morbidity and mortality**.
- ▶ **Prognosis**: advanced fibrotic EMF with heart failure carries a poor prognosis; outcome depends on ventricular involvement, AV-valve regurgitation and operability.

High-yield exam pointers

- ▶ EMF = **fibrous obliteration of ventricular apices + subvalvular apparatus** → **restrictive cardiomyopathy**; eponym *Davies' disease*; first described in **Uganda, 1948**.
- ▶ One of the **commonest causes of RCM worldwide**; tropical Africa, India (Kerala), Brazil; **male predominance, bimodal age, family clustering**; ~20% prevalence reported in rural Mozambique.
- ▶ **Three histological stages**: acute necrotic → thrombotic → **fibrotic**.
- ▶ **Löffler endocarditis** = **temperate analogue with hypereosinophilia** (AEC >1500/ μ L); EMF usually has **no demonstrable eosinophilia**.
- ▶ **Clues**: ascites out of proportion, raised JVP with steep Y descent + **Kussmaul sign**, S4 > S3, MR/TR murmurs, AF.
- ▶ **Echo**: **apical obliteration + biatrial enlargement + AV regurgitation**; **CMR**: **subendocardial LGE**; **cath**: **square-root (dip-and-plateau) sign**.
- ▶ **Distinguish from constrictive pericarditis**: RCM has **no respiratory ventricular interaction**, **raised PA pressure, high BNP**.

- Treatment: **diuretic-based supportive care**; steroids/cytotoxics/TKI in the eosinophilic phase; **endocardectomy + valve surgery** in the fibrotic stage.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — “*Amyloidosis and Other Restrictive Cardiomyopathies*” (restrictive physiology, Table of causes of RCM listing tropical endomyocardial fibrosis and Löffler's endocarditis) and “*Myocarditis*” (eosinophilic myocarditis → Loeffler endocarditis, hypereosinophilic syndrome).
- **Braunwald's Heart Disease, 13e** — “*The Dilated, Restrictive, and Infiltrative Cardiomyopathies*” (Endomyocardial disease; Löffler eosinophilic endocarditis with the acute/intermediate/fibrotic stages; Endomyocardial fibrosis — Uganda 1948, Mozambique prevalence, cerium, clinical and surgical management). *This dedicated cardiology text supplied the depth on staging, epidemiology and pathology.*
- **CMDT 2026** — “*Heart Failure & Cardiomyopathy*” (restrictive cardiomyopathy essentials; RCM vs constrictive pericarditis — ventricular interaction and PA pressure; diuretic/beta-blocker management principles).

Coverage note: The corpus covers the restrictive-cardiomyopathy framework, the eosinophilic (Löffler) spectrum and the core EMF epidemiology/pathology/management well, but **tropical-EMF-specific minutiae are relatively thin** — points such as the *Davies* eponym, the predominantly Kerala focus in India, calcific endocardial change and the dip-and-plateau/square-root sign are stated as universally accepted standard internal medicine, consistent with (but not all verbatim in) the corpus.



Hypertrophic Cardiomyopathy

Asked in: Paper II Jul 2020 · Paper II May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder defined by **left ventricular hypertrophy (LVH) that develops in the absence of any abnormal loading condition** (hypertension, aortic stenosis) or systemic infiltrative/storage disease that could account for the wall thickening. It is the **commonest monogenic cardiovascular disease (prevalence ≈1:500)**, classically caused by autosomal-dominant pathogenic variants in genes encoding the **cardiac sarcomere**, and is histologically marked by myocyte hypertrophy, **myocyte disarray** and fibrosis. The preferred current term is *hypertrophic cardiomyopathy with or without obstruction* (replacing “HOCM”); it is a leading cause of **sudden cardiac death (SCD) in the young** and an important cause of heart failure.

Etiology and genetic basis

- ▶ **Sarcomeric HCM:** a pathogenic sarcomere-gene variant is found in ~40–50% of all patients — over 60% of those with familial disease or childhood presentation, but ~30–40% of apparently sporadic cases. Inheritance is **autosomal dominant** with **age-dependent, incomplete penetrance** (~60%) and variable expressivity.
- ▶ **>1500 variants in ≥9 genes;** ~80% involve **MYBPC3** or **MYH7** (thick-filament proteins).
- ▶ **Mechanism:** most act as a **dominant-negative** (“poison peptide”); **MYBPC3** is the exception (~90% are truncating variants causing **haploinsufficiency**). At the myofilament level variants produce **increased force generation, increased Ca²⁺ sensitivity, impaired relaxation and abnormal energetics** (increased ATP consumption).
- ▶ **Nonsarcomeric HCM:** polygenic, with **hypertension (esp. diastolic BP) and obesity** as the strongest environmental modifiers (Mendelian-randomisation data).

Sarcomere gene	Protein	Approx. share of genetic HCM
MYBPC3	Myosin-binding protein C	~45%
MYH7	β-myosin heavy chain	~35%
TNNT2	Cardiac troponin T	~5%
TNNI3	Cardiac troponin I	~3%
TPM1 / MYL2 / MYL3 / ACTC1 / TNNC1	Tropomyosin, light chains, actin, troponin C	<3% each

- ▶ **Genocopies / “pseudohypertrophy”** (mimic HCM, must be excluded — often a *short PR / pre-excitation* clue): **Fabry disease** (*GLA*, X-linked; angiokeratoma, renal failure, neuropathy), **Danon disease** (*LAMP2*, X-linked), **PRKAG2 cardiomyopathy** (pre-excitation/AV block), **Friedreich ataxia** (*FXN*), **Noonan/RASopathy** (*PTPN11*), **cardiac amyloidosis** (*TTR* — carpal tunnel, biceps-tendon rupture), and mitochondrial disease.

Pathology and pathophysiology

- ▶ **Macroscopy:** non-uniform wall thickening; **asymmetric septal hypertrophy with reversed septal curvature** is classic and most predictive of a sarcomere variant. Other patterns: **concentric, mid-ventricular, and apical** (apical HCM is less often familial, sarcomere variant in only ~15%, more common in Japanese/Asian descent).
- ▶ **Microscopy:** characteristic **myocyte disarray** (swirling/branching instead of parallel fibres), **interstitial and replacement fibrosis**, and **small thick-walled intramural arterioles** → microvascular ischaemia and angina with normal epicardial coronaries. Endomyocardial biopsy is **not** used to diagnose HCM (changes are patchy/deep) but can exclude infiltrative disease.
- ▶ **LVOT obstruction (dynamic):** present at rest in ~30% and provoked by exercise in a further ~30%. The hypertrophied septum + an enlarged, anteriorly-displaced anterior mitral leaflet

generate **drag forces** → **systolic anterior motion (SAM)** of the mitral valve contacting the septum → late-peaking outflow obstruction and a **posteriorly-directed jet of mitral regurgitation**.

- ▶ **Load dependence:** obstruction worsens with ↓**preload** (dehydration, Valsalva, standing, diuretics), ↓**afterload** (vasodilators) and ↑**contractility** (exercise, digoxin, inotropes); it improves with squatting, handgrip and volume.
- ▶ **Diastolic dysfunction** (stiff, hypertrophied ventricle with impaired relaxation) is near-universal; systolic function is usually preserved/supranormal — an EF <50% is **abnormal** in HCM and signifies systolic decline.

Clinical features and physical signs

- ▶ **Symptoms:** exertional **dyspnoea** (commonest), **angina**, and **post-exertional syncope/pre-syncope** (volume loss + tachycardia worsen obstruction); palpitations; may be asymptomatic and detected on family screening or murmur. SCD may be the first presentation.
- ▶ **Pulse:** sharp, rapidly rising **bisferiens (spike-and-dome) carotid pulse** (contrast with the slow-rising *pulsus parvus et tardus* of aortic stenosis).
- ▶ **Apex:** **triple apical impulse**, prominent **a-wave** in JVP, **loud S4**.
- ▶ **Murmur:** harsh, **late-peaking systolic ejection murmur** at the left sternal border ± apical pansystolic murmur of MR. **Dynamic auscultation is the key bedside test:** murmur **increases** with Valsalva strain and standing from squatting (↓preload); **decreases** with squatting and sustained handgrip (↑afterload/preload) — the opposite of valvular AS.
- ▶ **Brockenbrough–Braunwald–Morrow sign:** a paradoxical **fall in aortic pulse pressure in the post-extrasystolic beat** (augmented contractility increases obstruction) — a classic confirmatory sign of dynamic LVOT obstruction.

Diagnosis and investigations

- ▶ **Echocardiography (diagnostic, first-line):** maximal LV wall thickness ≥15 mm in adults (or ≥13 mm with a family history or proven pathogenic variant; z-score ≥2.5 in children) with a non-dilated, hypercontractile, **small LV cavity**, SAM, dynamic LVOT gradient, and diastolic dysfunction. **Obstruction = peak instantaneous gradient ≥30 mmHg; ≥50 mmHg** (rest or provoked) is the threshold for limiting symptoms/intervention. Use **provocation** (Valsalva, squat-to-stand, exercise echo) if resting gradient <30 mmHg but symptomatic.
- ▶ **ECG** (abnormal but non-specific; insensitive): LVH, deep **inferolateral/septal Q waves**, ST-T changes; **giant T-wave inversions** suggest apical HCM. May be normal in ~25%.
- ▶ **Cardiac MRI:** quantifies hypertrophy in areas missed by echo, and **late gadolinium enhancement (LGE)** identifies fibrosis (arrhythmic substrate and emerging SCD risk marker).
- ▶ **Genetic testing:** multigene panel in the proband chiefly to **enable cascade (predictive) testing of relatives** and to distinguish genocopies; phenotype, not genotype, guides therapy.

- ▶ **Athlete's heart vs HCM:** physiological hypertrophy shows mild LV dilation, normal diastolic function, supranormal VO_2max ($>50 \text{ mL/kg/min}$), no LGE, and regression with detraining — features absent in HCM.

Management

Three pillars: symptom control, SCD-risk/arrhythmia management, and family screening + lifestyle counselling. No therapy yet proven to alter mortality; treat the symptomatic patient.

Setting	Approach
Obstructive, symptomatic	First-line β -blocker OR non-dihydropyridine CCB (verapamil/diltiazem); optimise volume; stop vasodilators. Add disopyramide (negative inotrope, give with AV-nodal blocker) or a cardiac myosin inhibitor (mavacamten) for persistent symptoms
Refractory + gradient $\geq 50 \text{ mmHg}$	Septal reduction therapy — surgical septal myectomy (gold standard; experienced-centre 30-day mortality $<1\%$, 90–95% success) or alcohol septal ablation (for non-surgical candidates / suitable septal-perforator anatomy)
Nonobstructive, symptomatic	β -blocker / verapamil, cautious diuretics for congestion; trials of myosin inhibitors and SGLT2 inhibitors ongoing; transplant for refractory/end-stage disease
Avoid	Arterial vasodilators (ACE-I/ARB, nitrates, dihydropyridine CCB, PDE5 inhibitors) and digoxin ($\uparrow$ contractility worsens obstruction)

- ▶ **Cardiac myosin inhibitors (disease-specific):** mavacamten allosterically inhibits myosin ATPase, favouring the super-relaxed “off” state $\rightarrow$ fewer cross-bridges $\rightarrow$ $\downarrow$ contractility and $\downarrow$ LVOT gradient. **FDA-approved April 2022** for symptomatic obstructive HCM; trials EXPLORER-HCM and VALOR-HCM showed improved exercise capacity, symptoms and reduced need for SRT. Chief risk: **reversible fall in LVEF** $\rightarrow$ mandatory echo monitoring/REMS. **Aficamten** (SEQUOIA-HCM) is the second-in-class agent.
- ▶ **Atrial fibrillation:** common, poorly tolerated (loss of atrial kick worsens filling/obstruction). Rate-control with β -blocker/verapamil, restore sinus rhythm; **disopyramide/amiodarone** preferred antiarrhythmics; ablation for refractory cases. **Anticoagulate regardless of $\text{CHA}_2\text{DS}_2\text{-VASc}$ score**, DOAC preferred over warfarin.
- ▶ **Septal-reduction complication:** **complete heart block needing permanent pacing** (commoner after ablation). Pacing alone is **not** effective primary therapy.
- ▶ **Lifestyle:** recent data show low arrhythmic risk with recreational/competitive sport; blanket restriction is no longer mandated — **shared decision-making**.

Risk stratification for sudden cardiac death

- ▶ Baseline SCD risk ~0.5–1% per year; SCD is not reduced by drugs/septal reduction, so prevention rests on the ICD.
- ▶ **Secondary prevention (Class I ICD):** prior cardiac arrest / sustained VT/VF.
- ▶ **Primary prevention major risk factors** (each weighed for shared decision-making): **family history of SCD, unexplained (non-vagal) syncope, massive LVH ≥ 30 mm, LV apical aneurysm, LV systolic dysfunction (EF $< 50\%$), and non-sustained VT on monitoring.** Extensive LGE on CMR is a modifying marker.
- ▶ The ESC HCM Risk-SCD calculator estimates 5-year risk from age, max wall thickness, LA diameter, LVOT gradient, FH of SCD, NSVT and syncope: $\geq 6\%$ → **ICD advised**; 4–6% → **consider**; $< 4\%$ → **not advised**.
- ▶ **Prognosis:** generally better than older referral series suggested; ~1 in 20 (5–8%) progress to systolic dysfunction / “burnt-out” end-stage HCM (EF $< 50\%$) needing HFrEF therapy or transplant.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Parasternal long-axis echo of obstructive HCM** — label: *hypertrophied interventricular septum, asymmetric LVH, small LV cavity, systolic anterior motion (SAM) of anterior mitral leaflet contacting septum, narrowed LVOT, posteriorly-directed mitral regurgitation jet, enlarged left atrium, aorta.*
- ▶ **Cardiac sarcomere schematic** — label: *thick filament (β -myosin heavy chain MYH7, myosin-binding protein C MYBPC3, myosin light chains), thin filament (actin ACTC1, tropomyosin TPM1, troponin T/I/C complex), Z-disc* — marking the genes mutated in HCM.

Clinical / Diagnostic significance

- ▶ HCM is the **leading cause of sudden death in young athletes**; pre-participation evaluation and family cascade screening (ECG + echo, beginning in adolescence and continued lifelong) are critical.
- ▶ **Dynamic auscultation** distinguishing HCM from aortic stenosis is a high-yield clinical and viva skill.
- ▶ Always **exclude genocopies** (Fabry, amyloid, Danon, PRKAG2) — several are specifically treatable (enzyme replacement / migalastat for Fabry; tafamidis/acoramidis for ATTR amyloid).
- ▶ **Mavacamten** is a landmark first disease-specific therapy reshaping management of symptomatic obstructive HCM.

High-yield exam pointers

- ▶ Commonest **monogenic** CVS disease; **AD inheritance**, prevalence 1:500; MYBPC3/MYH7 ≈80% of sarcomeric cases.
- ▶ Diagnostic wall thickness ≥15 mm (≥13 mm with FH/variant); **obstruction = gradient ≥30 mmHg**, intervene at ≥50 mmHg.
- ▶ **SAM of mitral valve** → LVOT obstruction + **posteriorly-directed MR**; **myocyte disarray** is the histological hallmark.
- ▶ Murmur ↑ **with Valsalva/standing**, ↓ **with squatting/handgrip**; **Brockenbrough sign**; **bisferiens pulse**.
- ▶ **Avoid digoxin, nitrates and vasodilators**; first-line = **β-blocker / verapamil**; add **disopyramide** or **mavacamten**.
- ▶ Refractory obstruction → **septal myectomy** (gold standard) or **alcohol septal ablation**; main complication = **complete heart block**.
- ▶ SCD prevention = **ICD**; major risks = **FH SCD, syncope, LVH ≥30 mm, apical aneurysm, EF <50%, NSVT**; use the **ESC HCM Risk-SCD score**.
- ▶ **AF**: anticoagulate **irrespective of CHA₂DS₂-VASc**; ~5–8% evolve to end-stage (“burnt-out”) HCM.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Genetic Cardiomyopathies” (HCM section: epidemiology, genetics, pathophysiology, treatment algorithm, SCD risk table) and “Classification of Cardiomyopathy.”
- ▶ **Braunwald’s Heart Disease, 13e** — “Hypertrophic Cardiomyopathy” (Ho & Day): diagnosis/morphology, sarcomere genetics and genocopy table, SAM/LVOT pathophysiology, EXPLORER/VALOR/SEQUOIA trials, septal reduction, SCD risk algorithm.
- ▶ **CMDT 2026** — “Heart Failure & Cardiomyopathy” (HCM): physical signs, investigations, current drug/ICD management and 2020 AHA/ACC guideline risk factors.



Left ventricular remodeling

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — **Left ventricular (LV) remodeling** is the process by which the ventricle undergoes progressive changes in **shape, size, mass, wall thickness and geometry** in response to an **index injury** or chronic haemodynamic overload, occurring at the molecular, cellular and chamber levels. It is the structural substrate of heart failure with reduced ejection fraction (**HFrEF**): an index event (e.g., acute myocardial infarction, or chronic pressure/volume overload) is followed by **months**

to years of structural and functional cardiovascular remodeling, during which compensatory mechanisms ultimately become maladaptive and drive disease progression. Initially adaptive, remodeling sets up a **self-perpetuating vicious cycle** of rising wall stress and falling pump function that culminates in clinical heart failure.

Pathophysiology — the remodeling cascade

- ▶ HFrEF is a **progressive disease** that begins with an *index event* — **sudden** (acute MI), **gradual** (chronic pressure or volume overload, e.g., valvular disease), **inherited** (genetic cardiomyopathy), or **congenital** in origin. Despite an early fall in cardiac performance, patients stay asymptomatic for prolonged periods because of **compensatory mechanisms** that later promote progression.
- ▶ The central driver is **increased myocardial wall stress**. By the **Law of Laplace**, wall stress $\propto$ (intracavitary pressure $\times$ chamber radius) $\div$ (2 $\times$ wall thickness) — so chamber dilatation and pressure loading both raise wall stress, while wall thickening lowers it. (*Laplace formula is standard cardiac physiology — see Coverage note.*)
- ▶ **Remodeling stimuli** (Fig. 264-6) acting on the myocardium are: increased **wall stress**, inflammatory **cytokines**, **neurohormonal** signals, and **oxidative stress**.
- ▶ The myocardium responds with **adaptive and maladaptive** changes — myocyte hypertrophy, altered interstitial matrix, fetal-gene re-expression, altered calcium-handling proteins, and myocyte death — producing **ventricular enlargement** and **systolic and/or diastolic dysfunction**.
- ▶ Myocytes unable to adapt to remodeling stimuli are triggered to undergo **apoptosis** (**programmed cell death**). Continued pump impairment plus systemic vasoconstriction and loss of neurohormonal adaptation produce **afterload mismatch**; these events **feed back on remodeling stimuli**, completing a **vicious cycle** that drives clinical HF.

Patterns of remodeling — concentric vs eccentric hypertrophy

- ▶ Different geometric patterns occur in response to **excess cardiac workload**, governed by the type of overload.

Feature	Concentric hypertrophy	Eccentric hypertrophy
Loading stimulus	Pressure overload	Volume overload
Typical causes	Hypertension, aortic stenosis	Aortic regurgitation, mitral regurgitation
Geometry	Increased mass out of proportion to chamber volume	Increased cavity size/volume, wall thinning
Effect on wall stress	Reduces wall stress (adaptive, initially)	Raised wall stress with progressive dilatation

Feature	Concentric hypertrophy	Eccentric hypertrophy
Sarcomere change (standard)	Sarcomeres added in parallel → thicker wall	Sarcomeres added in series → elongated myocytes

- ▶ In **both** forms, increased ventricular mass is accompanied by tissue- and protein-level changes: **myocyte hypertrophy and interstitial fibrosis**; altered **calcium-handling and cytoskeletal protein abundance/function**; and **re-expression of fetal genes**.

Mechanisms of ventricular remodeling (Table 264-3)

- ▶ Remodeling is organised at three levels — **myocyte biology, myocardial composition, and ventricular geometry**:

Level	Mechanisms
Changes in myocyte biology	Abnormal excitation–contraction coupling and crossbridge interaction; fetal gene expression (e.g., β -myosin heavy chain); β -adrenergic receptor desensitisation ; myocyte hypertrophy; impaired cytoskeletal proteins
Changes in myocardial composition	Myocyte necrosis, apoptosis and autophagy; interstitial and perivascular fibrosis ; matrix degradation
Changes in ventricular geometry	Ventricular dilation and wall thinning; increased sphericity and displacement of papillary muscles; atrioventricular valve regurgitation

- ▶ **Neurohormonal activation** is pivotal: activation of the **sympathetic nervous system (SNS)** and the **renin–angiotensin–aldosterone system (RAAS)** initially supports heart rate, BP, contractility and Na^+ /water retention, but unchecked promotes **myocyte hypertrophy, cell death and myocardial fibrosis** — remodeling the heart, vessels and kidneys.
- ▶ **Endothelin** (a potent vasoconstrictor with growth-promoting effects) drives **myocyte hypertrophy and interstitial fibrosis**; **inflammatory cytokines** ($\text{TNF-}\alpha$, $\text{IL-1}\beta$) and **reactive oxygen species** (superoxide, peroxynitrite) also contribute to remodeling.
- ▶ **Counter-regulatory vasodilatory hormones** oppose remodeling — the **natriuretic peptides** (ANP, BNP) cause vasodilation, natriuresis and RAAS inhibition; they are degraded by **neprilysin** (the rationale for **angiotensin receptor–neprilysin inhibition, ARNI**).
- ▶ **Electrical dyssynchrony** (QRS prolongation/LBBB in up to one-third of HF patients) worsens remodeling; **secondary (functional) mitral regurgitation** arises from the **spherical ventricle**, papillary-muscle displacement and **mitral annular dilation**, feeding the vicious cycle.

Post-myocardial-infarction remodeling

- ▶ After STEMI the LV undergoes a series of changes in **shape, size and thickness in both infarcted and non-infarcted segments** — this is **ventricular remodeling**, and it generally **precedes clinically evident heart failure** by months to years.
- ▶ **Acute phase — infarct expansion**: soon after STEMI the LV begins to **dilate** due to **slippage of muscle bundles, disruption of myocardial cells and tissue loss** within the necrotic zone, causing **disproportionate thinning and elongation of the infarct zone**.
- ▶ **Later phase**: **lengthening of the non-infarcted segments** occurs, producing global chamber enlargement.
- ▶ **Determinants of severity**: overall chamber enlargement relates to **infarct size and location** — **anterior wall and apical infarcts** cause greater dilatation, more marked haemodynamic impairment, more frequent HF and a **poorer prognosis**.
- ▶ **Infarct healing** (Fig. 286-3): reparative monocytes and monocyte-derived fibroblasts synthesise **interstitial collagen** that reinforces the myocardial skeleton, **mitigating expansive remodeling** of the infarct and reducing the risk of chronic HF.
- ▶ **LV aneurysm**: defined as **dyskinesis or local expansile paradoxical wall motion**; a **true aneurysm** is composed of **scar tissue** and **neither predisposes to nor is associated with cardiac rupture**. Apical aneurysms are commonest; complications (HF, arterial embolism, ventricular arrhythmias) appear weeks–months later; a **double/diffuse/displaced apical impulse** is the key sign and 2-D echocardiography detects the aneurysm and any **mural thrombus**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — “Remodeling stimuli in heart failure”** (vicious cycle, after Fig. 264-6).
Boxes/arrows with EXACT labels: **Increased wall stress** → stimuli (**Wall stress, Cytokines, Neurohormonal, Oxidative stress**) → myocardial responses (**Myocyte hypertrophy, Altered interstitial matrix, Fetal gene expression, Altered calcium-handling proteins, Myocyte death**) → **Ventricular enlargement** → **Systolic or diastolic dysfunction** → feedback arrow returning to **Increased wall stress** (vicious cycle).
- ▶ **Diagram 2 — Concentric vs eccentric remodeling**. Three LV cross-sections labelled **Normal LV, Concentric hypertrophy (pressure overload — thick wall, small cavity), Eccentric hypertrophy (volume overload — dilated cavity, thin wall)**; annotate Laplace: **wall stress = $(P \times r)/(2h)$** .

Clinical / Diagnostic significance

- ▶ **Reverse remodeling is the therapeutic goal**. Antagonism of the RAAS and SNS with RAS inhibitors (ACEi/ARB), mineralocorticoid-receptor antagonists, and beta-blockers attenuates or reverses ventricular and vascular remodeling and reduces morbidity and mortality; ARNI

(sacubitril/valsartan) and SGLT-2 inhibitors (effects on cardiac/vascular remodeling) extend this benefit in HFrEF.

- ▶ **Post-MI:** ACE inhibitors reduce mortality after STEMI via reduction in ventricular remodeling, with maximum benefit in high-risk patients (anterior infarction, prior infarction, globally depressed LV function); prescribe ACEi/ARB ± beta-blocker when EF <40%. Add an MRA (spironolactone/eplerenone) if EF ≤40% with symptomatic HF or diabetes (no significant renal dysfunction/hyperkalaemia). Note: sacubitril/valsartan was NOT superior to an ACE inhibitor in preventing incident HF early post-MI.
- ▶ **Cardiac resynchronisation therapy** (biventricular/LBBB pacing) for symptomatic HFrEF with LBBB reverses ventricular remodeling, improves contractile function and reduces mitral regurgitation.
- ▶ **Imaging:** chronic HF with remodeling is accompanied by cardiac enlargement with a downward and leftward-displaced apical impulse; echocardiography and serial cardiac MRI (quantifies LV mass, volumes and function) are used to assess remodeling in response to therapy.
- ▶ Reverse remodeling may also follow weight loss in obese HF patients.

High-yield exam pointers

- ▶ Remodeling = change in shape, size, mass, wall thickness, geometry; structural basis of HFrEF; the index event → months–years of remodeling concept is key.
- ▶ **Pressure overload** → concentric (parallel sarcomeres, reduces wall stress); **volume overload** → eccentric (series sarcomeres, dilatation).
- ▶ Three levels of remodeling (Table 264-3): myocyte biology, myocardial composition, ventricular geometry.
- ▶ Fetal gene re-expression classically = β-myosin heavy chain; β-adrenergic receptor desensitisation occurs.
- ▶ Maladaptive geometry → increased sphericity, papillary-muscle displacement → functional mitral regurgitation.
- ▶ Post-STEMI: infarct expansion (muscle slippage, thinning/elongation) → later non-infarct segment lengthening; anterior/apical infarcts remodel worst.
- ▶ **Drugs that reverse remodeling:** ACEi/ARB, ARNI, MRA, beta-blockers, SGLT-2 inhibitors, CRT.
- ▶ **True LV aneurysm** = scar tissue, does NOT cause rupture (contrast with pseudoaneurysm/free-wall rupture).
- ▶ Endothelin blockade does NOT slow LV-failure HF but helps PAH/right HF.

SOURCE & COVERAGE

Harrison 22e — Ch 264 “Heart Failure: Pathophysiology and Diagnosis” (Fig. 264-6, Table 264-3, neurohormonal mechanisms, reverse remodeling, imaging) + Ch 286 “ST-Segment Elevation Myocardial Infarction” (post-MI ventricular remodeling/dysfunction, infarct expansion, RAAS inhibition, LV aneurysm, Fig. 286-3). **Coverage note:** The provided chapters fully cover remodeling triggers, patterns, mechanisms, post-MI remodeling and reverse-remodeling therapy. Two adjuncts are *standard physiology/medicine not stated verbatim in the supplied text* — the explicit **Laplace formula** (wall stress = $P \cdot r / 2h$) and the **parallel- vs series-sarcomere** correlate of concentric vs eccentric hypertrophy — included as universally accepted cardiac physiology to complete the answer.



Management of Supraventricular Tachycardia

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Supraventricular tachycardia (SVT) is a tachyarrhythmia arising from atrial tissue or from circuits using the AV node/accessory pathway, i.e. above or involving the His bundle. In exam practice, “SVT” usually refers to **regular paroxysmal narrow-complex tachycardia**, chiefly **AV nodal re-entrant tachycardia (AVNRT)** and **atrioventricular re-entrant tachycardia (AVRT)**, but focal atrial tachycardia and atrial flutter must be recognized. Management is algorithmic: assess stability, record the rhythm, terminate the episode safely, prevent recurrence, and offer curative ablation when appropriate.

Classification and mechanisms

- ▶ **AVNRT:** commonest paroxysmal SVT; re-entry within dual AV nodal physiology. Typical slow-fast AVNRT has a regular narrow QRS tachycardia with hidden/retrograde P waves, pseudo-r' in V1, or pseudo-S waves in inferior leads.
- ▶ **Orthodromic AVRT:** antegrade conduction through AV node and retrograde conduction through an accessory pathway; narrow QRS unless baseline bundle branch block/aberrancy. It is the usual tachycardia in Wolff-Parkinson-White (WPW) syndrome.
- ▶ **Antidromic AVRT:** antegrade conduction down the accessory pathway and retrograde conduction through AV node/another pathway; produces a regular broad-complex tachycardia and may mimic VT.
- ▶ **Focal atrial tachycardia:** automatic, triggered, or micro-re-entrant atrial focus; P-wave morphology differs from sinus rhythm and AV block may occur without terminating the atrial rhythm.
- ▶ **Atrial flutter / macro-re-entrant atrial tachycardia:** atrial rate often around 250-350/min; ventricular response depends on AV conduction, commonly 2:1 with a rate near 150/min.

- ▶ **Multifocal atrial tachycardia:** irregular atrial tachycardia with at least three P-wave morphologies, often in COPD, hypoxia, pulmonary disease, sepsis, or electrolyte disturbance; do not manage as AVNRT.

Immediate assessment and diagnosis

- ▶ First decide **unstable versus stable**. Instability includes hypotension/shock, acute pulmonary edema, ischemic chest pain, altered sensorium, severe dyspnea, or syncope attributable to tachycardia.
- ▶ Obtain a **12-lead ECG during tachycardia** before treatment if this does not delay emergency care; also record a post-conversion ECG to look for pre-excitation, ischemia, QT interval, and baseline conduction disease.
- ▶ Define the rhythm by **QRS width** and **regularity**:

ECG pattern	Likely diagnosis	Immediate implication
Regular narrow-complex	AVNRT, orthodromic AVRT, atrial tachycardia, flutter with fixed block	Vagal maneuvers and adenosine are useful
Irregular narrow-complex	AF, atrial flutter with variable block, MAT	Avoid reflex "SVT bolus" treatment; identify atrial rhythm
Regular broad-complex	VT, SVT with aberrancy, antidromic AVRT	Treat as VT if uncertain
Irregular broad-complex	AF with pre-excitation, polymorphic VT	Avoid AV nodal blockers; urgent specialist/emergency treatment

- ▶ Look for reversible precipitants: fever, pain, anemia, hypovolemia, hypoxia, pulmonary embolism, myocardial ischemia, thyrotoxicosis, alcohol/stimulants, sympathomimetics, digoxin toxicity, hypokalemia, and hypomagnesemia.
- ▶ Basic work-up after stabilization: electrolytes including Mg/Ca, renal function, glucose, thyroid testing when indicated, troponin only if ischemia is suspected, echocardiography for structural heart disease, ambulatory monitoring for undocumented episodes, and EP study for recurrent/uncertain SVT.

Acute management of regular narrow-complex SVT

- ▶ **Stable patient:** monitor ECG and blood pressure, establish IV access, give oxygen only if hypoxemic, prepare defibrillator, and explain that transient AV block or flushing may occur with adenosine.
- ▶ **Vagal maneuvers** are first-line: modified Valsalva is preferred where feasible; carotid sinus massage may be used with continuous monitoring after excluding carotid bruit, recent stroke/TIA, and significant carotid disease. Do not use ocular pressure.
- ▶ **Adenosine** is the drug of choice for AV node-dependent PSVT:

Step	Dose and method	Key point
First bolus	6 mg rapid IV push followed immediately by saline flush	Use a large proximal vein; record rhythm strip
If no conversion	12 mg rapid IV push	May repeat 12 mg once if needed
Modified dosing	Consider lower initial dose, e.g. 3 mg, with central line, heart transplant, or dipyridamole	Methylxanthines antagonize effect

- ▶ Adenosine terminates most **AVNRT/orthodromic AVRT** and may only transiently slow atrial tachycardia/flutter, thereby revealing flutter waves or atrial P waves.
- ▶ If adenosine is ineffective/contraindicated and the rhythm is definitely narrow-complex without pre-excitation, use **IV diltiazem or verapamil** or an **IV beta-blocker** with BP monitoring.
- ▶ Avoid combining IV beta-blockers with verapamil/diltiazem because of hypotension, bradycardia, or AV block risk. Avoid nondihydropyridine calcium channel blockers in significant LV systolic dysfunction or decompensated heart failure.
- ▶ If drug therapy fails or the patient deteriorates at any step, proceed to **synchronized DC cardioversion**.

Management of unstable SVT and broad-complex presentations

- ▶ **Unstable SVT**: perform immediate **synchronized electrical cardioversion**; give sedation/analgesia if time permits, but do not delay cardioversion for shock, ischemia, pulmonary edema, or altered sensorium.
- ▶ For regular narrow-complex SVT, start with **50-100 J biphasic synchronized shock** and escalate if required. Reassess airway, BP, rhythm, and precipitating cause after conversion.
- ▶ **Regular wide-complex tachycardia** should be treated as VT unless SVT with aberrancy is certain. Adenosine may be diagnostic/therapeutic only in a regular monomorphic rhythm with no evidence of pre-excited AF or polymorphic VT.
- ▶ **Pre-excited AF** is an emergency clue: irregular wide QRS, very rapid ventricular rates, beat-to-beat QRS variation, and WPW features. Avoid adenosine, digoxin, beta-blockers, verapamil, and diltiazem because AV nodal block may accelerate accessory pathway conduction.
- ▶ For stable pre-excited AF or antidromic AVRT, specialist-directed rhythm control with **procainamide or ibutilide** may be used; if unstable, use synchronized cardioversion.
- ▶ Treat electrolyte abnormalities aggressively: correct hypokalemia and hypomagnesemia, stop pro-arrhythmic drugs, and manage ischemia, hypoxia, sepsis, or stimulant/drug toxicity.

Drug choices: indications and cautions

- ▶ **Adenosine:** very short acting; adverse effects are flushing, chest tightness, dyspnea, sense of doom, transient AV block, and rarely bronchospasm or AF. Use caution in asthma/COPD with active bronchospasm.
- ▶ **Verapamil/diltiazem:** useful for AV node-dependent SVT and rate control in atrial tachyarrhythmias without pre-excitation; avoid in hypotension, HFrEF/decompensated HF, wide-complex undiagnosed tachycardia, and pre-excited AF.
- ▶ **Beta-blockers:** useful acutely and chronically for AVNRT/AVRT suppression and adrenergic atrial tachycardia; avoid or use cautiously in severe bronchospasm, acute decompensated HF, marked bradycardia, and advanced AV block.
- ▶ **Class IC drugs** such as flecainide/propafenone may prevent recurrent SVT or AVRT in patients without structural or ischemic heart disease; they require specialist selection and usually AV nodal protection when atrial flutter risk exists.
- ▶ **Amiodarone, sotalol, dofetilide** are not routine first-line drugs for uncomplicated AVNRT; reserve for selected patients with structural heart disease, refractory arrhythmia, or when ablation is not possible, considering QT, renal, pulmonary, thyroid, hepatic, and drug-interaction risks.
- ▶ **Digoxin** has limited contemporary use for PSVT prevention and must be avoided in pre-excited AF; toxicity can itself cause atrial tachycardia with block.

Long-term and definitive management

- ▶ Explain benign prognosis in structurally normal hearts, teach **self-administered vagal maneuvers**, identify triggers, and advise documentation of future episodes by ECG/wearable strip when feasible.
- ▶ **Catheter ablation** is the definitive treatment for recurrent symptomatic AVNRT, AVRT/accessory pathway-mediated tachycardia, recurrent focal atrial tachycardia, incessant SVT, tachycardia-induced cardiomyopathy, high-risk occupation, or patient preference to avoid lifelong drugs.
- ▶ For AVNRT, slow-pathway modification is standard; success is high and recurrence is low, with a small but important risk of AV block requiring pacing.
- ▶ For AVRT/WPW, ablate the accessory pathway, especially with syncope, documented AVRT, pre-excited AF, high-risk pathway properties, multiple pathways, or competitive athletics/high-risk work.
- ▶ If ablation is deferred: use oral beta-blocker, verapamil, or diltiazem for recurrent AVNRT/orthodromic AVRT without pre-excitation during AF; consider class IC drugs only in carefully selected patients without structural heart disease.

- ▶ **Pregnancy:** vagal maneuvers and adenosine are preferred acutely; synchronized cardioversion is safe when unstable. Use beta-blockers or verapamil selectively for prevention; consider low/zero-fluoroscopy ablation only for refractory, poorly tolerated SVT.
- ▶ **MAT** management is treatment of the underlying illness: oxygenation, bronchodilator optimization without excess beta-agonist exposure, correction of K/Mg, treatment of infection or pulmonary disease; cardioversion and adenosine usually do not cure MAT.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Acute SVT algorithm flowchart:** stable/unstable split; unstable -> synchronized cardioversion; stable regular narrow QRS -> vagal maneuver -> adenosine 6 mg -> 12 mg -> calcium channel blocker/beta-blocker -> cardioversion/EP referral; side box: “avoid AV nodal blockers in pre-excited AF.”
- ▶ **Re-entry mechanism sketch:** AVNRT slow and fast AV nodal pathways with retrograde P wave; orthodromic AVRT circuit showing AV node antegrade limb and accessory pathway retrograde limb; label atrium, AV node, His-Purkinje system, ventricle, accessory pathway.

Clinical / Diagnostic significance

- ▶ A narrow regular tachycardia that terminates abruptly with adenosine strongly suggests **AV node-dependent re-entry**; transient slowing without termination suggests atrial tachycardia or flutter.
- ▶ P-wave position is diagnostically useful: short RP tachycardia suggests typical AVNRT/orthodromic AVRT; long RP tachycardia suggests atrial tachycardia, atypical AVNRT, or permanent junctional reciprocating tachycardia.
- ▶ Always obtain a sinus-rhythm ECG after conversion: delta wave and short PR identify WPW; QT prolongation, bundle branch block, ischemic changes, or Brugada pattern alter management.
- ▶ Recurrent incessant SVT may cause **tachycardia-induced cardiomyopathy**, which can improve after rhythm control or ablation.
- ▶ In older patients, SVT may present as falls, presyncope, angina, heart failure, or hypotension rather than palpitations.
- ▶ Troponin elevation can occur after prolonged tachycardia without plaque rupture; interpret in clinical context rather than labelling all cases acute coronary syndrome.

High-yield exam pointers

- ▶ Write the first line of management as **ABC, monitor, IV access, 12-lead ECG, assess hemodynamic stability**.
- ▶ **Unstable SVT = synchronized cardioversion**, not a prolonged drug trial.
- ▶ **Stable regular narrow SVT = vagal maneuver -> adenosine -> AV nodal blocker/cardioversion**.

- ▶ Adenosine dose: 6 mg rapid IV bolus, then 12 mg, then 12 mg with immediate flush and rhythm strip.
- ▶ Do not give AV nodal blockers in pre-excited AF: avoid adenosine, digoxin, beta-blocker, verapamil, and diltiazem.
- ▶ Treat broad-complex tachycardia as VT until proved otherwise.
- ▶ Definitive therapy for recurrent symptomatic AVNRT/AVRT is radiofrequency catheter ablation.
- ▶ Look for reversible triggers: hypoxia, ischemia, thyrotoxicosis, stimulants, alcohol, sepsis, hypokalemia, and hypomagnesemia.
- ▶ Draw the acute algorithm and the AVNRT/AVRT re-entry circuit; these diagrams score quickly in a 10-mark answer.

SOURCE & COVERAGE

Harrison 22e — “Approach to Supraventricular Arrhythmias”; “Paroxysmal Supraventricular Tachycardias”; Braunwald’s Heart Disease 13e — “Supraventricular Tachycardias”; CMDT 2026.



Narrow QRS Tachycardia

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — A narrow QRS (narrow-complex) tachycardia is a heart rate >100 beats/min with a QRS duration <120 ms, reflecting normal ventricular activation over the His–Purkinje system. Because the impulse originates from, or is dependent on conduction through, the atrium or AV node, these are essentially supraventricular tachycardias (SVTs), and the QRS morphology is usually identical to that in sinus rhythm. Their importance lies in correct mechanistic identification at the bedside from a 12-lead ECG, as prognosis and treatment vary widely by mechanism.

Mechanistic Classification of Supraventricular Tachycardia (Table 253-1)

Group	Arrhythmia	Defining feature
Physiologic	Sinus tachycardia	Normal sinus mechanism driven by exertion, stress, stimulants, illness
Atrial origin	Inappropriate sinus tachycardia	Sinus-node-area tachycardia with no precipitant (dysfunctional autonomic regulation)
	Focal atrial tachycardia (AT)	Regular, defined P wave; foci at valve annuli, pulmonary veins, coronary sinus, SVC

Group	Arrhythmia	Defining feature
	Atrial flutter / macroreentrant AT	Macroreentry; sawtooth flutter waves, atrial rate typically >200/min
	Atrial fibrillation (AF)	Chaotic atrial activity, variable ventricular rate; commonest sustained arrhythmia in older adults
	Multifocal atrial tachycardia (MAT)	Multiple discrete P-wave morphologies; pulmonary disease exacerbations
AV node	AV nodal reentry tachycardia (AVNRT)	Paroxysmal regular; P at end of QRS or invisible; commonest PSVT in healthy young adults, women
Accessory pathway	Orthodromic AVRT	Paroxysmal regular; preexcitation (WPW) or concealed pathway
	Preexcited (antidromic AVRT, preexcited AF/flutter)	Wide QRS — exception to the narrow-QRS rule

- ▶ A useful three-way split by mechanism: **AV-nodal-dependent reentry** (AVNRT, AVRT), **macroreentry within atrium** (atrial flutter), and **focal AT** (automaticity or microreentry).
- ▶ Other supraventricular rhythms: premature atrial contractions (PACs), sinus arrhythmia, accelerated junctional rhythm, ectopic atrial rhythm.

Bedside Differential by ECG Pattern (Fig 253-1)

Obtain a full 12-lead ECG with a long rhythm strip and decide first whether the rhythm is **regular** or **irregular**.

ECG appearance	Likely diagnoses
Regular, 1:1 AV response	AVNRT, orthodromic AVRT, atrial tachycardia, rarely atrial flutter
Regular, AV block (more A's than V's)	Atrial flutter, atrial tachycardia, rarely AVNRT with 2:1 block below the His
Regular, VA block (more V's than A's)	Junctional tachycardia
Irregular	Atrial fibrillation, multifocal atrial tachycardia

Characteristic Features of Individual Narrow-QRS Tachycardias

- ▶ AVNRT — the most common PSVT (~60% of cases referred for ablation); manifests in the 2nd–4th decades, more often in women, usually with structurally normal hearts. Reentry uses dual AV nodal pathways within the **triangle of Koch** — a **slow pathway** (right inferior nodal extension)

and a **fast pathway**. Near-simultaneous atrial and ventricular activation places the P wave **at the end of the QRS**, producing a *pseudo-r'* in V1 and *pseudo-S waves* in II, III, aVF. Simultaneous atrial contraction against a closed tricuspid valve gives **cannon A waves** (“frog sign,” fluttering in the neck) and post-tachycardia diuresis via natriuretic peptide release.

- ▶ **Orthodromic AVRT** — the commonest tachycardia caused by an accessory pathway (AP); the wavefront travels **antegrade down the AV node/His–Purkinje system and retrograde up the AP**, so the QRS is **narrow** (or has fixed BBB). The P wave **always follows the QRS** (R-P shorter than P-R), inscribed in the ST segment. AV or VA block terminates it. The AP may be manifest (WPW: short PR <0.12 s, delta wave, wide QRS in sinus rhythm) or **concealed** (retrograde-only, normal sinus ECG).
- ▶ **Focal atrial tachycardia** — regular, with **discrete P waves separated by an isoelectric baseline**, distinct from sinus P; tachycardia can continue despite AV block (AV node not in the circuit).
- ▶ **Atrial flutter** — macroreentry giving **sawtooth flutter waves** (atrial rate typically >200/min, classically ~300/min); commonly conducts 2:1, yielding a regular ventricular rate near 150/min.
- ▶ **Atrial fibrillation** — **irregularly irregular**, no discrete P waves; the commonest sustained arrhythmia in older adults.
- ▶ **Multifocal atrial tachycardia** — irregular with **multiple (≥ 3) discrete P-wave morphologies**, seen in acute pulmonary insufficiency exacerbations.
- ▶ **Junctional (ectopic) tachycardia (JET)** — automaticity within the AV node; **narrow QRS often with VA block / AV dissociation**; rare in adults, more often incessant in children after congenital heart surgery. *Accelerated junctional rhythm* is a junctional automatic rhythm of 50–100/min.

Diagnostic and Therapeutic Effect of AV Nodal Blockade (Fig 253-2)

Vagal maneuvers, carotid sinus massage (CSM), or **adenosine** both **treat and diagnose** by transiently blocking the AV node while the ECG runs continuously.

Response to AV nodal blockade	Inference
No effect	Fascicular VT, or inadequate dose/effect
Tachycardia slows then resumes	Sinus tachycardia, junctional tachycardia
Tachycardia terminates	AVNRT, AVRT, adenosine-sensitive focal AT
Atrial activity continues with transient AV block	Atrial flutter, atrial tachycardia

- ▶ **Vagal maneuvers**: Valsalva (bearing down), modified Valsalva with leg-raise, diver’s reflex (cold-water face immersion), and CSM. CSM should be used cautiously or avoided if carotid bruits, prior stroke, or atherosclerosis risk (embolization).
- ▶ **Adenosine 6 mg, then 12 mg IV rapid push** causes transient AV block; it terminates AV-nodal-dependent SVT and unmasks AT/flutter. Note some focal ATs are adenosine-sensitive, so termination does not exclude AT.

Acute and Long-Term Management

- ▶ **Unstable** (hypotension with altered consciousness or respiratory distress): immediate **QRS-synchronous DC cardioversion** — rarely needed, as adenosine usually works promptly.
- ▶ **Stable PSVT (AVNRT / orthodromic AVRT)**: vagal maneuvers/CSM → IV adenosine → AV nodal blocking drugs (**beta blockers, verapamil or diltiazem**). Chronic options for recurrent episodes include these agents or **flecainide**; a single oral dose at onset (“pill-in-the-pocket”) can abort episodes.
- ▶ **Curative catheter ablation**: slow-pathway ablation for AVNRT is curative in >95%, with <1% risk of AV block needing a pacemaker; AP ablation efficacy ~95%, serious complications <3%, mortality <1 in 1000.
- ▶ **Focal AT**: correct precipitants; rate control with beta/calcium channel blockers; antiarrhythmics (flecainide, propafenone, sotalol, amiodarone) or ablation (>80% success) if recurrent/incessant (risk of tachycardia-induced cardiomyopathy).
- ▶ **Preexcited AF (CRITICAL)**: AV nodal blockers — adenosine, verapamil, diltiazem, beta blockers, IV amiodarone — are **CONTRAINDICATED**, as they can accelerate AP conduction and precipitate VF. Treat with DC cardioversion or IV procainamide / ibutilide. Shortest preexcited R-R <250 ms during AF signals high sudden-death risk.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic flow-chart (Fig 253-1)**: Top box “Narrow-complex tachycardia → 12-lead ECG + long rhythm strip”; branch into **Regular** vs **Irregular**. Under Regular: **1:1 AV response** (AVNRT, ORT/AVRT, AT, rarely atrial flutter); **AV block, more A’s than V’s** (atrial flutter, atrial tachycardia, rarely AVNRT with 2:1 block); **VA block, more V’s than A’s** (junctional tachycardia). Under Irregular: **atrial fibrillation, multifocal atrial tachycardia**.
- ▶ **AVNRT circuit in the triangle of Koch**: label compact AV node (fast pathway), inferior nodal extension (slow pathway), His bundle, tricuspid valve, coronary sinus (CS), and arrows showing slow-pathway antegrade / fast-pathway retrograde reentry, with retrograde P wave at end of QRS (pseudo-r’ in V1).

Clinical / Diagnostic significance

- ▶ Symptoms: palpitations, chest pain, dyspnea, reduced exertional capacity, occasionally syncope; rarely cardiac arrest in WPW or hypertrophic cardiomyopathy.
- ▶ **Ventricular preexcitation on the resting ECG** points to AVRT via an accessory pathway; the diagnosis of SVT requires capturing an ECG during symptoms — increasingly via wearables/smartphone single-lead ECG.

- ▶ Accessory pathways occur in **1 in 1500–2000** people and associate with **Ebstein’s anomaly**, hypertrophic cardiomyopathy (**PRKAG2**), **Danon’s disease**, and **Fabry’s disease**. *Mahaim (atriofascicular) fibers* cause an LBBB-pattern wide-complex tachycardia.
- ▶ Most paroxysmal SVT occurs in structurally normal hearts; AF is the entity most often linked to structural/systemic heart disease, so initial evaluation should screen for it.

High-yield exam pointers

- ▶ **Narrow QRS** = QRS <120 ms = supraventricular origin; morphology usually identical to sinus rhythm.
- ▶ First branch point on the ECG is **regular vs irregular** — irregular narrow QRS = AF or MAT.
- ▶ AVNRT is the commonest PSVT; P at end of QRS → **pseudo-r’ in V1, pseudo-S in II/III/aVF; cannon A waves / frog sign**.
- ▶ **Orthodromic AVRT**: narrow QRS, P always follows QRS, R-P < P-R.
- ▶ **Adenosine 6 then 12 mg** — both diagnostic and therapeutic; terminates AVNRT/AVRT, unmasks flutter/AT.
- ▶ **Atrial flutter**: sawtooth waves, 2:1 conduction → ventricular rate ~150/min.
- ▶ **Preexcited AF**: **never give AV-nodal blockers** — use procainamide/ibutilide or DC shock.
- ▶ **Slow-pathway ablation cures AVNRT in >95%**, AV block needing pacemaker <1%.
- ▶ Unstable narrow-QRS tachycardia → **synchronized DC cardioversion**.

SOURCE & COVERAGE

Harrison 22e — Ch 253 “Approach to Supraventricular Arrhythmias” and Ch 256 “Paroxysmal Supraventricular Tachycardias” (with focal-AT management from the adjoining Ch 255 figure carried in the Ch 256 text file). **Coverage note:** The provided Ch 256 text ends mid-”Treatment of PSVT,” so the full acute drug algorithm beyond adenosine is truncated; specific IV doses of verapamil/diltiazem/beta blockers are not stated in the supplied text and are given here only as drug classes. The “~300/min” flutter rate and “≥3 P-wave morphologies” for MAT are universally accepted textbook standards added to the source’s “rate >200/min” and “multiple discrete P waves.”



Neurally mediated syncope

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — Syncope is a transient, self-limited loss of consciousness (TLOC) due to acute *global* impairment of cerebral blood flow, with rapid onset, brief duration and spontaneous, complete recovery. **Neurally mediated syncope** (synonyms: *reflex, vasovagal, neurocardiogenic*

syncope) is the final common pathway of a complex central-and-peripheral reflex arc in which a transient change in autonomic efferent activity — increased parasympathetic (vagal) outflow plus sympathoinhibition — produces **bradycardia, vasodilatation and/or loss of vasoconstrictor tone**, leading to a fall in systemic blood pressure and cerebral hypoperfusion. It requires an *intact* autonomic nervous system (unlike syncope of autonomic failure) and is the single commonest cause of syncope in population-based studies.

Epidemiology and clinical importance

- ▶ Syncope accounts for **~3% of all emergency-department visits and ~1% of hospital admissions**; lifetime cumulative incidence is up to **40%** (CMDT: ~30% of adults faint at least once).
- ▶ **Bimodal age distribution** — first peak in the young (10–30 yr, median ~15 yr), where neurally mediated syncope dominates; a second sharp rise after age 70 (where orthostatic and cardiac causes climb). Incidence is higher in women; first-degree family history is common in young fainters.
- ▶ Prognosis of neurally mediated (and unexplained non-cardiac) syncope in the young is **excellent** — **life expectancy unaffected**; this contrasts sharply with cardiac syncope, which carries increased risk of sudden cardiac death.

Classification — placing neurally mediated syncope among the causes

Category	Mechanism	Key examples
A. Neurally mediated (reflex)	Transient reflex vasodilatation ± bradycardia; intact ANS	Vasovagal (common faint); situational; carotid sinus syndrome
B. Orthostatic hypotension	<i>Chronic</i> sympathetic vasoconstrictor (autonomic) failure	Synucleinopathies (PD, DLB, MSA/Shy-Drager, pure autonomic failure); diabetic/amyloid neuropathy; drug-induced; volume depletion
C. Cardiac	↓ Cardiac output from arrhythmia or structural disease	SND, AV block, VT/SVT, channelopathies; AS, HOCM, atrial myxoma, tamponade, PE

Sub-classification of neurally mediated syncope — by *afferent trigger* and by *efferent (haemodynamic) pattern*:

By afferent trigger	Provoking stimulus
Vasovagal syncope (common faint)	Fear, pain, intense emotion, sight of blood, prolonged motionless standing, heat, venepuncture
Situational reflex syncope	<i>Pulmonary</i> — cough, sneeze, wind-instrument/weight-lifter; <i>Urogenital</i> — post-micturition, instrumentation; <i>GI</i> — swallow,

By afferent trigger	Provoking stimulus
	defecation, glossopharyngeal neuralgia; <i>Cardiac</i> — Bezold–Jarisch reflex; <i>Ocular</i> — ocular pressure
Carotid sinus syndrome	Carotid sinus stimulation (tight collar, head-turning, shaving)
By efferent pattern	Dominant mechanism
Vasodepressor	Sympathetic vasoconstrictor <i>withdrawal</i> → hypotension predominates
Cardioinhibitory	Excess vagal tone → bradycardia/asystole predominates
Mixed	Both vagal and sympathetic reflex changes (most common)

Pathophysiology — the reflex arc

- ▶ **The orthostatic stress:** standing pools **500–1000 mL** of blood in the legs, buttocks and splanchnic bed, reducing venous return, ventricular filling, cardiac output and BP. Normally the **baroreflex** corrects this: unloading of carotid-sinus and aortic-arch baroreceptors → afferents via *glossopharyngeal (IX)* and *vagus (X)* nerves to the **nucleus tractus solitarius (NTS)** in the dorsomedial medulla → reduced vagal output to the sinus node (via *nucleus ambiguus*) and increased sympathetic outflow (via CVLM→RVLM disinhibition), restoring peripheral resistance and cardiac output.
- ▶ **In neurally mediated syncope this reflex paradoxically reverses.** The favoured model: reduced preload from venous pooling → vigorous contraction of a relatively *empty, catecholamine-stimulated* ventricle → activation of *unmyelinated ventricular mechanoreceptors (C-fibres)* in the atria, ventricles and pulmonary artery → afferents to the dorsal vagal nucleus → “**paradoxical**” **sympathetic withdrawal + surge in vagal tone** → vasodilatation and bradycardia (the **Bezold–Jarisch reflex**). The result mimics a “fictitious haemorrhage” to which the brainstem responds, paradoxically, by slowing/stopping the heart.
- ▶ Higher cortical centres also participate — emotion and the sight of blood can trigger fainting without preload reduction. Many situational faints additionally involve **hyperventilation** (hypocarbica → **cerebral vasoconstriction**) and **raised intrathoracic pressure** (↓ venous return).
- ▶ **Critical thresholds:** cessation of cerebral flow for **6–8 s**, a fall in systolic BP to **~50 mmHg**, or cerebral flow <25 mL/min/100 g causes loss of consciousness. Cerebral autoregulation normally holds flow constant over a perfusion pressure of **50–150 mmHg**.

Clinical features and recognition

- ▶ **Triphasic episode:** (1) *Prodrome (presyncope)* of autonomic activation — light-headedness, nausea, diaphoresis, pallor, warmth, palpitations, yawning, blurred/tunnel vision; (2) *transient LOC* with loss of postural tone; (3) *rapid, complete recovery* (no true post-ictal confusion).
- ▶ During the faint: eyes typically remain **open and deviate upward**, pupils dilated; brief **arrhythmic, multifocal myoclonic jerks** (<30 s) may simulate a seizure (“convulsive syncope”); urinary incontinence can occur but **faecal incontinence is very rare**.
- ▶ **Provocative/predisposing factors:** motionless upright posture, warm environment, volume depletion, alcohol, anaemia, hypoxaemia, pain, venepuncture, emotion.

Differentiating reflex syncope from its mimics

Feature	Neurally mediated syncope	Generalised seizure	Cardiac (arrhythmic) syncope
Posture/trigger	Usually upright; emotion, pain, heat	Any position; aura	Often exertional or supine; no trigger
Prodrome	Long autonomic prodrome (nausea, sweat, pallor)	Aura (e.g. unpleasant smell)	Brief/none (<5 s), sometimes palpitations
Movements	Brief, arrhythmic, multifocal myoclonus	Rhythmic tonic–clonic; tongue-biting	None typical
Recovery	Immediate re-orientation	Prolonged post-ictal confusion (>5 min)	Prompt but injury common
Colour	Pale	Cyanosed/flushed	Pale

Other mimics: **hypoglycaemia** (hunger, tremor, sweating — not features of syncope), **cataplexy** (consciousness preserved), **vertebrobasilar ischaemia**, and **psychogenic pseudosyncope** (frequent falls without haemodynamic change or injury).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **The baroreflex / reflex arc (Fig. 23-1):** label — *carotid sinus & aortic-arch baroreceptors* → *glossopharyngeal (IX) and vagus (X) afferents* → *Nucleus Tractus Solitarius (NTS)* → *Nucleus Ambiguus* (→ *vagal/parasympathetic to sinus node*) and *CVLM* → *RVLM* (→ *sympathetic efferent to heart & vessels*); mark *ventricular C-fibre mechanoreceptors* → *dorsal vagal nucleus (Bezold–Jarisch limb)*. Annotate the efferent result: *vasodilatation + bradycardia* → *↓BP* → *cerebral hypoperfusion*.
- ▶ **Tilt-table tracing (Fig. 23-2):** two stacked curves over time on 70° head-up tilt — upper = *Heart Rate (bpm)*, lower = *Blood Pressure (mmHg)* — showing the **paroxysmal hypotensive–bradycardic response** of neurally mediated syncope; contrast with the *gradual BP fall without HR rise* of orthostatic hypotension.

Clinical / Diagnostic significance

- ▶ **Initial evaluation (the cornerstone, diagnostic in ~50%):** detailed history, eyewitness account ($\pm$ phone video), full cardiac/neurological exam, **supine and 3-min standing BP/HR**, and a 12-lead ECG. Screen for high-risk features mandating admission (Table 23-1): exertional/supine syncope, palpitations preceding syncope, structural/ischaemic heart disease, **QTc >500 ms**, bifascicular block/QRS ≥ 120 ms, *Brugada* pattern, persistent bradycardia, family history of sudden death.
- ▶ **Tilt-table test:** confirms susceptibility to neurally mediated syncope when the diagnosis is unclear (ACC/AHA/HRS Class IIa). Protocol — 20-min supine stabilisation, then head-up tilt at **60–80° (70° usual) for 30–45 min**; sensitised with **isoproterenol (1–3 $\mu\text{g}/\text{min}$ to raise HR ~25%)** or **sublingual nitroglycerin 300–400 μg** . Unmedicated specificity ~90%; it also classifies the response as cardioinhibitory, vasodepressor or mixed (VASIS types) and exposes psychogenic pseudosyncope (LOC with normal BP/HR).
- ▶ **Carotid sinus massage:** for patients >40 yr with recurrent unexplained syncope. Apply 5–10 s pressure below the angle of the jaw, supine and upright, under continuous ECG/BP. **Positive (carotid sinus hypersensitivity):** *cardioinhibitory* = asystole >3 s, or *vasodepressor* = SBP fall >50 mmHg, with reproduction of symptoms. **Avoid** with carotid bruit, plaque/stenosis or recent TIA/stroke.
- ▶ **Cardiac work-up only if indicated:** echocardiography (if structural disease suspected), ambulatory/Holter monitoring for frequent spells, **external or implantable loop recorder** for infrequent spells (monitor $\geq$ twice the inter-spell interval), exercise testing for exertional syncope, EP study only with structural heart disease. Routine bloods are low-yield.

Management (stepped; ACC/AHA/HRS 2017 & ESC 2018)

- ▶ **Foundation (all patients):** education and reassurance about the benign nature, recognition of prodrome, avoidance of triggers (heat, dehydration, alcohol, prolonged standing), and prompt **supine positioning** at symptom onset. Liberalise **salt and fluid**; acute ingestion of ~500 mL water aborts orthostatic intolerance.
- ▶ **Physical counterpressure manoeuvres (Class IIa):** leg-crossing, squatting, handgrip/arm-tensing and **abdominal + leg-muscle tensing** (most effective) raise central blood volume — most useful in those with a long prodrome (RCT-supported). *Tilt/standing training* is of uncertain benefit.
- ▶ **Pharmacotherapy (refractory cases):** **Midodrine** ($\alpha 1$ -agonist) is the *only* agent proven effective in multicentre RCTs (Class IIa; avoid in hypertension, HF, urinary retention). **Fludrocortisone** (volume expansion, Class IIb) and an **SSRI** may be tried; **β -blockers are generally ineffective** (no better than placebo in POST) except possibly age ≥ 42 yr (Class IIb). Withdraw offending hypotensive drugs.
- ▶ **Cardiac pacing — narrow indication:** *not* routinely beneficial (vasodepression dominates most faints). A **dual-chamber pacemaker with closed-loop stimulation** reduces recurrence only in

selected patients >40 yr with frequent syncope and a documented spontaneous/ tilt-induced cardioinhibitory (asystolic) response (SPAIN, ISSUE-3-type data; ESC Class IIa, ACC/AHA IIb).

- ▶ **Carotid sinus syndrome:** dual-chamber pacing for recurrent syncope with a dominant cardioinhibitory/mixed response (Class IIa).
- ▶ **Emerging: cardioneuroablation** (radiofrequency/cryo ablation of vagal ganglionated plexi) shows high freedom from syncope in cardioinhibitory VVS in small RCTs — still investigational.

High-yield exam pointers

- ▶ Triad of neurally mediated syncope mechanism: **vasodilatation + bradycardia + loss of vasoconstrictor tone** via vagal surge and sympathetic withdrawal — *requires an intact ANS*.
- ▶ **Bezold–Jarisch reflex** (ventricular C-fibre mechanoreceptors) underlies the “empty-ventricle” paradoxical faint.
- ▶ Efferent patterns: **vasodepressor / cardioinhibitory / mixed** — mixed is commonest; pacing helps *only* cardioinhibitory.
- ▶ Carotid sinus hypersensitivity numbers: **asystole >3 s** (cardioinhibitory), **SBP drop >50 mmHg** (vasodepressor).
- ▶ Tilt-table: **70°, 30–45 min**; isoproterenol or SL-GTN sensitisation; specificity ~90% unmedicated.
- ▶ **Midodrine** = only drug with RCT-proven benefit; **β-blockers don’t work** (POST).
- ▶ Critical thresholds: LOC after **6–8 s** of arrested flow or **SBP ~50 mmHg**; cerebral autoregulation **50–150 mmHg**.
- ▶ Distinguish from seizure: brief arrhythmic myoclonus, *immediate* recovery, no tongue-biting, no true post-ictal phase.
- ▶ Convulsive syncope, upward eye deviation and urinary incontinence do **not** equal epilepsy; faecal incontinence is very rare in syncope.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Syncope” (Freeman & Raj): definition, classification, baroreflex/pathophysiology, neurally mediated subtypes, clinical features, evaluation and treatment.
- ▶ **Braunwald’s Heart Disease, 13e** — “Hypotension and Syncope”: Bezold–Jarisch/C-fibre mechanism, carotid sinus hypersensitivity criteria, tilt-table protocol and sensitisation, ACC/AHA/HRS treatment table, SPAIN trial, pacing and cardioneuroablation.
- ▶ **CMDT 2026** — “Disorders of Cardiac Rhythm” (Syncope): current diagnostic approach, counterpressure manoeuvres, midodrine/fludrocortisone/SSRI, pacing caveats, cardioneuroablation, driving restrictions.

- *Coverage note:* The named VASIS tilt-response typing is standard cardiology nomenclature; the corpus describes the underlying cardioinhibitory/vasodepressor/mixed responses but does not spell out the VASIS subtype letters.



Pathogenesis and Management of Congestive Cardiac Failure

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Heart failure (HF) is a complex clinical syndrome of symptoms and signs (breathlessness, fatigue, ankle swelling) arising from any structural or functional impairment of ventricular filling or ejection, leading to elevated intracardiac filling pressures and/or inadequate cardiac output at rest or on exertion. Because many patients lack overt volume overload, the *universal definition* prefers the term “heart failure” over the older “congestive cardiac failure,” requiring symptoms/signs **plus** corroboration by elevated natriuretic peptides **or** objective evidence of cardiogenic pulmonary/systemic congestion. It is the common final pathway of most chronic cardiovascular diseases; 5-year survival after diagnosis is only ~50%.

Aetiology, Phenotypes and Classification

- **Classification by ejection fraction (EF)** — drives therapy; roughly half of patients have reduced EF:
 - **HFrEF** (reduced; LVEF $\leq 40\%$) — coronary artery disease/MI, dilated/nonischaemic cardiomyopathy, valvular, toxic (alcohol, anthracyclines), peripartum, tachycardia-induced.
 - **HFmrEF** (mildly reduced; LVEF 41–49%) — intermediate; treated largely as HFrEF.
 - **HFpEF** (preserved; LVEF $\geq 50\%$) — hypertension, LVH, ageing, aortic stenosis, restrictive/infiltrative disease (amyloid, sarcoid, haemochromatosis), HCM.
 - **HFrecEF** (recovered EF) — e.g., fulminant myocarditis, stress/peripartum/tachycardia cardiomyopathy; better prognosis.
- **High-output failure** — anaemia (Hb ≤ 8 g/dL), thyrotoxicosis, beriberi, large AV fistula, Paget’s disease, cirrhosis; low SVR, usually unmasks underlying heart disease.
- **ACC/AHA stages (progressive, irreversible):** A at-risk (HTN, DM, no structural disease) → B structural disease/asymptomatic → C structural disease + current/prior symptoms → D refractory/advanced HF.
- **NYHA functional class (symptom-based, reversible):**

Class	Limitation	Clinical assessment
I	None	Ordinary activity causes no symptoms
II	Mild	Comfortable at rest; ordinary activity → dyspnoea/fatigue/palpitation/angina
III	Moderate	Comfortable at rest; <i>less than</i> ordinary activity → symptoms
IV	Severe	Symptoms at rest, worsened by any activity

Pathogenesis (Pathophysiology)

- ▶ **Index event and progressive remodelling** — HFrEF begins with an index injury (acute MI, chronic pressure/volume overload, genetic or congenital disease). Despite an initial fall in pump function patients stay asymptomatic for months–years because compensatory mechanisms are recruited; these same mechanisms ultimately become maladaptive and drive progression.
- ▶ **Patterns of ventricular remodelling** — *concentric hypertrophy* (pressure overload, e.g., hypertension, AS) reduces wall stress; *eccentric hypertrophy/dilatation* (volume overload, e.g., AR, MR). Accompanied by myocyte hypertrophy, interstitial/perivascular fibrosis, altered calcium-handling proteins, re-expression of fetal genes (β -myosin heavy chain), and myocyte necrosis/apoptosis/autophagy → increasing sphericity, papillary muscle displacement and secondary mitral regurgitation.
- ▶ **Compensatory (initially adaptive) responses:**
 - **Frank-Starling mechanism** — increased preload (end-diastolic volume) augments stroke volume; preload reserve is exhausted as the ventricle fails.
 - **Neurohormonal activation** — fall in cardiac output “unloads” arterial baroreceptors (LV, carotid sinus, aortic arch) → reduced parasympathetic and increased **sympathetic (SNS)** tone (resting plasma noradrenaline 2–3× normal, predicts mortality), and activation of the **renin-angiotensin-aldosterone system (RAAS)** with non-osmotic release of **arginine vasopressin**. Result: tachycardia, increased contractility, peripheral vasoconstriction, and renal salt/water retention to maintain blood pressure and preload.
- ▶ **Maladaptive consequences / vicious cycle** — sustained SNS/RAAS/AVP activation causes excessive afterload, volume overload, electrolyte disturbance, baroreceptor dysfunction, direct myocyte toxicity, fibrosis, arrhythmia and further remodelling — a self-perpetuating cycle. Counter-regulatory **natriuretic peptides (ANP, BNP)**, prostaglandins, bradykinin, adrenomedullin and nitric oxide oppose this but are eventually overwhelmed; **neprilysin** degrades natriuretic peptides and bradykinin (the rationale for ARNI).

- ▶ **Electrical dyssynchrony** — QRS prolongation/LBBB in up to one-third causes discoordinate contraction, worsening MR (basis for CRT).
- ▶ **Systemic / cardiorenal-abdominal interactions** — the **cardiorenal syndrome** reflects not only reduced forward renal perfusion but importantly **systemic venous congestion** and raised intra-abdominal pressure impeding renal venous return; splanchnic/hepatic congestion, gut wall oedema with endotoxaemia (LPS), and proinflammatory cytokines (TNF- α , IL-1, IL-6) promote progression and **cardiac cachexia**.

Clinical Features and Diagnosis

- ▶ **Symptoms of left HF (pulmonary congestion):** exertional dyspnoea → orthopnoea → paroxysmal nocturnal dyspnoea (“cardiac asthma”), bendopnoea, nocturnal cough; acute pulmonary oedema with pink frothy sputum.
- ▶ **Symptoms of right HF (systemic congestion):** weight gain, dependent oedema, abdominal bloating, anorexia, early satiety, RUQ pain (hepatic capsule stretch); anasarca in refractory disease. **Low-output symptoms:** fatigue, cool extremities, mental dullness, oliguria.
- ▶ **Signs:** tachycardia, narrow pulse pressure, *pulsus alternans*, raised JVP with hepatojugular/abdominojugular reflux, *Kussmaul’s sign*, bibasal crepitations, pleural effusion (right > left), displaced apex, **S3 gallop** (volume overload, poor prognosis), murmurs of functional MR/TR, tender pulsatile hepatomegaly, ascites, pitting oedema.
- ▶ **Investigations:** comprehensive metabolic panel, CBC, thyroid/iron studies (hyponatraemia and worsening renal function are adverse markers); ECG (ischaemia, LVH, LBBB, AF — present in up to 40%); **chest X-ray** (cardiothoracic ratio >0.5, upper-lobe diversion, interstitial/alveolar oedema, effusions); **2-D echocardiography with Doppler** is the key test (EF, chamber size, valves, diastolic function, pericardium); **BNP/NT-proBNP** support diagnosis and prognosis (falsely low in obesity; raised by age, female sex, CKD, AF, PE); CMR/PET, coronary angiography and endomyocardial biopsy for specific aetiologies.

Management of Chronic HFrEF — the Four Foundational Pillars (GDMT)

Stepwise, rapidly up-titrated **guideline-directed medical therapy (GDMT)** produces reverse remodelling and reduces mortality and hospitalisation. ACEI add ~23% mortality reduction; adding a beta blocker a further ~35%. Four pillars + adjuncts:

Pillar / drug class	Representative agent	Initiation → Target dose	Key point
RAAS inhibitor – ARNI (preferred)	Sacubitril-valsartan	100 mg bid → 200 mg bid	20% ↓ CV death/HF hosp vs enalapril (PARADIGM-HF); 36-h gap after ACEI (angioedema)

Pillar / drug class	Representative agent	Initiation → Target dose	Key point
ACE inhibitor (if ARNI not feasible)	Enalapril / Lisinopril	2.5 mg bid → 10–20 mg bid / 20–35 mg qd	Cough/angioedema
ARB (if ACEI-intolerant)	Candesartan / Valsartan	4–8 → 32 qd / 40 → 160 bid	—
Beta blocker (only 3 proven)	Carvedilol / Bisoprolol / Metoprolol succinate	3.125 bid → 25–50 bid / 1.25 → 10 qd / 12.5–25 → 200 qd	Start when euvoaemic; not for acute decompensation
MRA	Spironolactone / Eplerenone	12.5–25 → 25–50 qd / 25 → 50 qd	RALES; watch K ⁺ /renal function; eplerenone if gynaecomastia
SGLT-2 inhibitor	Dapagliflozin / Empagliflozin	10 mg qd	~25–26% ↓ events, with or without diabetes (DAPA-HF, EMPEROR-Reduced)

- ▶ **Loop diuretics** (furosemide, torsemide, bumetanide) for congestive symptoms — symptomatic only, no mortality benefit; minimise dose.
- ▶ **Hydralazine + isosorbide dinitrate** — for RAAS-intolerant patients and added in self-identified African-Americans on background therapy (A-HeFT).
- ▶ **Ivabradine** (If-channel inhibitor) — symptomatic HFrEF, **sinus rhythm**, **HR >70/min** on maximally tolerated beta blocker (SHIFT).
- ▶ **Vericiguat** (soluble guanylate cyclase stimulator) and **digoxin** (late-line, reduces hospitalisation, low dose) as adjuncts; **avoid** verapamil/diltiazem, NSAIDs, thiazolidinediones.
- ▶ **Device & surgical therapy**: ICD for primary prevention if NYHA II–III with LVEF ≤35% on GDMT (any aetiology), or post-MI LVEF ≤30% (not within 40 days of MI). CRT (biventricular pacing) when **QRS >149 ms with LBBB**. CABG for ischaemic cardiomyopathy with viable myocardium (STICH); transcatheter edge-to-edge mitral repair (COAPT) for severe secondary MR; LVAD/cardiac transplant for stage D.

Management of HFpEF/HFmrEF and Acute Decompensated HF

- ▶ **HFpEF/HFmrEF**: historically symptom-focused — control congestion with diuretics (avoid over-diuresis causing under-filling), tight blood-pressure control, maintain sinus rhythm/rate control in AF, treat ischaemia and comorbidities (obesity, OSA, CKD, anaemia/iron deficiency). **SGLT-2 inhibitors** (DELIVER, EMPEROR-Preserved) now reduce CV death/HF hospitalisation across EF >40% and are foundational; ARNI and GLP-1 agonists (obese HFpEF, e.g., semaglutide — STEP-HFpEF) confer selected benefit; spironolactone has a weak recommendation (TOPCAT).

- ▶ **Acute decompensated HF (ADHF):** identify precipitants (non-adherence, dietary salt, NSAIDs, ischaemia, arrhythmia, infection, PE). Phenotype-directed therapy: **IV loop diuretics** (bolus or infusion; low $\sim 1\times$ vs high $\sim 2.5\times$ home dose) $\pm$ sequential nephron blockade with metolazone/acetazolamide; **vasodilators** (nitroglycerin, nitroprusside) for hypertensive/pulmonary-oedema phenotypes with adequate BP; **inotropes** (dobutamine 2–20 $\mu\text{g/kg/min}$, milrinone 0.375–0.75 $\mu\text{g/kg/min}$, dopamine) only for low-output/cardiogenic-shock states as bridge or palliation; oxygen/non-invasive ventilation and opiates for flash pulmonary oedema; **mechanical circulatory support** (IABP, percutaneous VAD, ultrafiltration) for refractory shock. Initiate/continue GDMT before discharge (PIONEER-HF, EMPULSE) and arrange early follow-up with rapid up-titration (STRONG-HF).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Neurohormonal vicious cycle of HF:** *Index myocardial injury* $\rightarrow$ $\downarrow$ Cardiac output $\rightarrow$ baroreceptor unloading $\rightarrow$ $\uparrow$ SNS + $\uparrow$ RAAS + $\uparrow$ vasopressin $\rightarrow$ vasoconstriction ($\uparrow$ afterload) + $\text{Na}^+/\text{H}_2\text{O}$ retention ($\uparrow$ preload) + $\uparrow$ heart rate/contractility $\rightarrow$ $\uparrow$ wall stress $\rightarrow$ ventricular remodelling (hypertrophy, dilatation, fibrosis, apoptosis) $\rightarrow$ further $\downarrow$ cardiac output. Label the counter-regulatory limb: *natriuretic peptides (ANP/BNP)* $\rightarrow$ vasodilation + natriuresis (inhibited by neprilysin).
- ▶ **GDMT “four pillars” schematic:** four columns labelled ARNI/ACEI/ARB, Beta blocker, MRA, SGLT-2 inhibitor, sitting on a base labelled loop diuretic (symptomatic), with add-ons (ivabradine, hydralazine-nitrate, vericiguat, digoxin) and devices (ICD, CRT) above.

Clinical / Diagnostic significance

- ▶ BNP/NT-proBNP aid diagnosis in undifferentiated dyspnoea and risk-stratify; a very low value helps exclude HF in non-obese patients.
- ▶ Echocardiographic EF is the single most important branch point separating HFrEF (GDMT-responsive) from HFpEF.
- ▶ S3 gallop, elevated JVP, hyponatraemia, worsening renal function and inability to tolerate neurohormonal antagonists are markers of advanced disease and poor prognosis.
- ▶ Recognising and correcting precipitating factors (Table of patient-, provider-, and disease-related triggers) prevents recurrent decompensation; residual congestion at discharge strongly predicts readmission.

High-yield exam pointers

- ▶ **Universal definition** = symptoms/signs **plus** raised natriuretic peptide **or** objective congestion; classify by EF (HFrEF $\leq 40\%$, HFmrEF 41–49%, HFpEF $\geq 50\%$).
- ▶ Distinguish ACC/AHA stages A–D (**irreversible**) from NYHA I–IV (**reversible**).

- ▶ Core pathogenesis = **maladaptive SNS + RAAS activation** driving remodelling — the target of all disease-modifying drugs.
- ▶ **Four pillars of HFrEF GDMT**: ARNI (or ACEI/ARB) + beta blocker + MRA + SGLT-2 inhibitor; rapid up-titration.
- ▶ Only **carvedilol, bisoprolol, metoprolol succinate** improve survival; sacubitril-valsartan needs a **36-h washout** after an ACEI.
- ▶ **Ivabradine** = sinus rhythm + HR >70 on beta blocker; **digoxin/diuretics** = symptom relief, no mortality benefit.
- ▶ **ICD** if LVEF ≤35% (NYHA II–III) or post-MI LVEF ≤30%; **CRT** if QRS >149 ms with LBBB.
- ▶ **SGLT-2 inhibitors** now benefit across the whole EF spectrum, including HFpEF.
- ▶ In ADHF: treat precipitant, IV loop diuretic for decongestion, vasodilators if BP adequate, inotropes only for low-output/shock.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Heart Failure: Pathophysiology and Diagnosis” and “Heart Failure: Management” (definition/phenotypes, remodelling, neurohormonal activation, NYHA & ACC/AHA staging, GDMT target-dose table, devices, ADHF).
- ▶ **Braunwald's Heart Disease, 13e** — “Pathophysiology of Heart Failure” (compensatory mechanisms — SNS/RAAS, noradrenaline kinetics, Frank-Starling/preload reserve).
- ▶ **CMDT 2026** — “Heart Failure & Cardiomyopathy” (epidemiology, four-stage classification, current combination medical therapy framing).



Pericarditis

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — Pericarditis is inflammation of the pericardium, the double-layered fibroserous sac (visceral + parietal layers separated by 15–50 mL of plasma ultrafiltrate) that envelops the heart. It is the commonest pathological process affecting the pericardium and presents as a spectrum of overlapping syndromes — **acute pericarditis, pericardial effusion and cardiac tamponade, recurrent/incessant pericarditis, constrictive pericarditis** and **effusive–constrictive pericarditis**. Most acute cases in developed regions are viral or idiopathic and self-limiting, whereas in India/sub-Saharan Africa **tuberculosis** remains a leading cause and a major driver of constriction.

Classification (Harrison) and Aetiology

- ▶ **Clinical (by duration)**: Acute (<6 weeks; fibrinous or effusive) → Subacute (6 weeks–6 months; effusive-constrictive or constrictive) → Chronic (>6 months; constrictive or adhesive).

- ▶ **Infectious:** *Viral* (coxsackie A/B, echovirus, herpesviruses, mumps, adenovirus, HIV, post-COVID), *pyogenic/purulent* (pneumococcus, Staphylococcus, Streptococcus, Neisseria), *tuberculous, fungal* (histoplasma, coccidioides, Candida).
- ▶ **Non-infectious:** acute idiopathic, *uraemic/dialysis-associated, neoplastic* (lung, breast, lymphoma, leukaemia, mesothelioma), trauma, aortic dissection leaking into the sac, acute MI, post-irradiation, myxoedema, familial (*Mulibrey nanism* — autosomal recessive growth failure with constrictive pericarditis), familial Mediterranean fever.
- ▶ **Autoimmune / hypersensitivity:** rheumatic fever, SLE, rheumatoid arthritis, scleroderma, granulomatosis with polyangiitis, IgG4 disease; drug-induced (procainamide, hydralazine, isoniazid, phenytoin, minoxidil); **post-cardiac-injury syndromes** — postpericardiotomy, post-traumatic, and post-MI (*Dressler's syndrome*).

Acute Pericarditis — Clinical Features & Diagnosis

- ▶ **Four cardinal diagnostic features (Harrison):**
- ▶ **Chest pain** — retrosternal/left precordial, often pleuritic (sharp, worse on inspiration/coughing), radiating to the **trapezius ridge** (near-pathognomonic), classically *aggravated by lying supine and relieved by sitting up and leaning forward*. Pain is often absent in tuberculous, uraemic, neoplastic and post-irradiation forms.
- ▶ **Pericardial friction rub** — heard in ~85%; rasping/scratching, up to three components/cycle (atrial systole, ventricular systole, early diastole), best at end-expiration, patient upright and leaning forward.
- ▶ **ECG — evolves through four stages:** *Stage 1* — diffuse upwardly-concave ST elevation (limb leads + V2–V6) with reciprocal ST depression only in aVR ($\pm$ V1), plus **PR-segment depression** (atrial injury current, an early/specific sign); *Stage 2* — ST returns to baseline; *Stage 3* — diffuse T-wave inversion; *Stage 4* — normalisation. Contrast with AMI (convex/"tombstone" ST, regional, prominent reciprocal change, evolving over hours).
- ▶ **Pericardial effusion** — may cause muffled sounds, **electrical alternans**, *Ewart's sign* (dullness/bronchial breathing below the left scapula from lung compression) and a "water-bottle" cardiac silhouette on chest X-ray.
- ▶ **ESC 2015 diagnostic criteria (Braunwald):** at least **two of four** — (1) characteristic chest pain, (2) friction rub, (3) typical ECG changes (ST elevation/PR depression), (4) new/worsening pericardial effusion. Supported by raised **CRP**, leucocytosis and CMR evidence of pericardial inflammation (late gadolinium enhancement).
- ▶ **Investigations:** ECG, CBC with differential, **CRP/hsCRP** (tracks activity and guides treatment duration), **cardiac troponin** (modest rise indicates *myopericarditis* — concomitant epicardial myocarditis, seen in up to 15%), chest radiograph and **echocardiography** (first-line imaging).

CT/CMR are superior for loculated effusions, pericardial thickening, masses and active inflammation.

Cardiac Tamponade

- ▶ Accumulation of pericardial fluid sufficient to obstruct ventricular inflow — a medical emergency. As little as **200 mL** causes tamponade if rapid, versus **>2000 mL** if slowly accumulating (pericardium stretches).
- ▶ **Beck's triad**: hypotension, soft/absent heart sounds, and raised JVP with a **prominent x descent** and **absent y descent**.
- ▶ **Pulsus paradoxus**: inspiratory fall in systolic BP **>10 mmHg** — due to inspiratory RV filling bulging the septum leftward (ventricular interdependence), reducing LV stroke volume. Also seen in severe asthma/COPD, PE and $\sim\frac{1}{3}$ of constrictive cases.
- ▶ **Echo**: late-diastolic **RA and RV free-wall collapse**, dilated non-collapsing IVC, exaggerated respiratory variation in mitral/tricuspid inflow (“swinging heart” with electrical alternans).
- ▶ **Treatment**: urgent **pericardiocentesis** (echo-guided **subxiphoid** approach most common; apical/parasternal alternatives), draining the sac as completely as possible with a temporary catheter left for 2–3 days; IV saline as a temporising measure. **Anticoagulants are avoided**. Surgical/open drainage for loculated, malignant or recurrent effusions and when biopsy is needed.

Constrictive Pericarditis

- ▶ A rigid, fibrotic, often calcified pericardium encasing the heart, limiting diastolic filling. Worldwide TB is a major cause; in the West it follows viral/idiopathic pericarditis, cardiac surgery, mediastinal irradiation, connective-tissue disease and uraemia. Risk is **<1% after viral/idiopathic**, **2–5% after immune/neoplastic**, and **20–30% after purulent bacterial** pericarditis.
- ▶ **Pathophysiology**: filling is unimpeded in early diastole then halts abruptly at the elastic limit of the pericardium → **“dip-and-plateau”/square-root sign** and **equalisation of diastolic pressures** in all four chambers (within ~ 5 mmHg). Loss of transmission of intrathoracic pressure to the heart produces enhanced ventricular interdependence.
- ▶ **Clinical (right-heart congestion dominates)**: raised JVP with **prominent y descent** (M-/W-shaped venous wave), **Kussmaul's sign** (JVP fails to fall / rises with inspiration), **pericardial knock** (early S3 from abrupt halt of filling), hepatomegaly, ascites out of proportion to oedema, and **Broadbent's sign** (systolic apical retraction). Pulsus paradoxus is usually absent; AF in $\sim\frac{1}{3}$.
- ▶ **Investigations**: ECG — low voltage, T-wave flattening; CXR — **pericardial calcification** (commonest in TB); echo/Doppler — septal bounce, **$\geq 25\%$ inspiratory increase in mitral E velocity**, expiratory hepatic-vein diastolic flow reversal; tissue Doppler — preserved/increased medial mitral annular e' (**>8 cm/s**) with lateral e' lower than medial (*annulus reversus).

CT/CMR* confirm pericardial thickening (≥ 3 –4 mm). Catheterisation shows discordant RV/LV systolic pressures with respiration.

- **Treatment:** diuretics for symptom control; **pericardiectomy (complete pericardial resection)** is the only definitive therapy (operative mortality ~5–15%, highest after radiation).

Transient/reversible constriction (esp. post-cardiac-surgery, raised CRP, CMR enhancement) may respond to anti-inflammatory therapy. *Effusive-constrictive pericarditis* — constrictive physiology persists after fluid removal; needs wide visceral + parietal resection.

Constrictive Pericarditis vs Cardiac Tamponade vs Restrictive Cardiomyopathy

Feature	Tamponade	Constrictive pericarditis	Restrictive cardiomyopathy
Pulsus paradoxus	+++	+ ($\approx 1/3$)	+
JVP — prominent y descent	Absent	+++ (M/W wave)	+
JVP — prominent x descent	+++	++	+++
Kussmaul's sign	–	+++	+
Pericardial knock	–	++	–
Third heart sound (S3)	–	–	+
Pericardial effusion	+++	–	–
Pericardial calcification/thickening	–	++/+++	–
Equalisation of diastolic pressures	+++	+++	–

Treatment of Acute & Recurrent Pericarditis

- **First-line** — NSAID + colchicine (Harrison/ESC/CMDT):
 - Aspirin 750–1000 mg every 8 h for 1–2 weeks (or 2–4 g/day), then taper; or ibuprofen 600–800 mg tid; or indomethacin 25–50 mg tid — with gastroprotection (PPI).
 - Colchicine 0.5–0.6 mg once daily (<70 kg) or twice daily (>70 kg) for 3 months (≥ 6 months for recurrence) — halves recurrence and hastens symptom resolution.
- **Corticosteroids** (e.g. prednisone 0.25–0.5 mg/kg/day, slow taper) reserved for NSAID/colchicine failure or intolerance, autoimmune aetiology, renal failure or pregnancy — they **increase recurrence**, so used at low dose with concurrent colchicine.

- ▶ **Refractory/recurrent disease: IL-1 antagonists** — *anakinra* (IL-1 receptor antagonist) and *rilonacept* (IL-1 trap; FDA-approved after the RHAPSODY trial) — are highly effective steroid-sparing agents; azathioprine and IVIG are alternatives; pericardial stripping is a last resort.
- ▶ **Specific causes:** *Dressler's/post-MI* — prefer **aspirin + colchicine** (NSAIDs/steroids may impair myocardial healing); *uraemic* — intensify dialysis ± NSAID; *purulent* — drainage + IV antibiotics; *neoplastic* — drainage/pericardial window ± sclerotherapy; *tuberculous* — RIPE for 2 months then isoniazid + rifampicin to complete 6 months, with pericardiectomy if constriction develops.
- ▶ **High-risk features warranting admission (ESC):** *major* — fever >38 °C, subacute onset, large effusion, tamponade, failure to respond to NSAID/aspirin after a week; *minor* — myopericarditis, immunosuppression, trauma, oral anticoagulation. Recurrence affects ~15–30%.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **ECG evolution of acute pericarditis (4 stages):** lead strip showing — *Stage 1* diffuse concave ST elevation + PR depression (with reciprocal ST depression/PR elevation in aVR); *Stage 2* normalisation of ST; *Stage 3 T-wave inversion*; *Stage 4* normal. Label “diffuse concave ST↑”, “PR depression”, “aVR reciprocal change”.
- ▶ **JVP waveform comparison:** tamponade — prominent x, absent y descent; constriction — prominent x and y (M/W shape) with Kussmaul's sign. Label a, c, v waves and x, y descents.

Clinical / Diagnostic significance

- ▶ Differentiating acute pericarditis from STEMI is the highest-yield bedside skill: pericarditis shows *diffuse concave* ST elevation with PR depression and only modest troponin rise, versus regional convex ST elevation with marked enzyme rise in MI.
- ▶ A troponin rise signals **myopericarditis**; LV dysfunction is rare and the long-term prognosis is excellent, but it alters activity restriction and avoids over-aggressive anticoagulation.
- ▶ **CRP/hsCRP** is central — it confirms inflammation, monitors response, and guides duration of therapy (taper once CRP normalises).
- ▶ Constrictive pericarditis is a **surgically curable** cause of right heart failure — must be distinguished from cirrhosis (inspect the neck veins) and from restrictive cardiomyopathy (annulus reversus, septal bounce, equalised pressures).
- ▶ TB pericarditis: pericardial fluid **adenosine deaminase (ADA)** elevation and TB-PCR support the diagnosis; biopsy is often required; early anti-TB therapy prevents constriction.

High-yield exam pointers

- ▶ ESC 2015: diagnose acute pericarditis with ≥2 of 4 (pain, rub, ECG ST↑/PR↓, effusion).

- ▶ Friction rub present in ~85%; up to **three components** per cycle.
- ▶ **PR-segment depression** is an early, fairly specific ECG sign; ST elevation is diffuse and concave.
- ▶ **Beck's triad** = hypotension + muffled heart sounds + raised JVP; tamponade JVP has **absent y descent**.
- ▶ **Pulsus paradoxus** >10 mmHg; rapid effusions of only ~200 mL can tamponade.
- ▶ Constriction: **square-root sign**, **Kussmaul's sign**, **pericardial knock**, calcified pericardium (commonest in TB); pericardiectomy is curative.
- ▶ First-line therapy is NSAID/aspirin + **colchicine** ×3 months; colchicine halves recurrence; steroids increase it.
- ▶ **Dressler's syndrome** — weeks post-MI; treat with **aspirin + colchicine**, not NSAIDs/steroids.
- ▶ Recurrent pericarditis — escalate to **IL-1 blockers** (**anakinra**, **rilonacept**).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Pericardial Disease” (classification, four cardinal features, four-stage ECG, Beck's triad, pulsus paradoxus, tamponade, constrictive pericarditis, Table distinguishing tamponade vs constriction vs restriction, treatment doses, tuberculous pericarditis).
- ▶ **Braunwald's Heart Disease, 13e** — “Pericardial Diseases” (ESC 2015 diagnostic criteria, high-risk triage features, myopericarditis, recurrence definition, IL-1 antagonists/RHAPSODY, echo-Doppler differentiation — annulus reversus, septal bounce, 25% mitral E variation, RA/RV collapse timing, effusive-constrictive physiology, TB regimen).
- ▶ **CMDT 2026** — “Acute Inflammatory Pericarditis / Pericardial Effusion / Constrictive Pericarditis” (aspirin/ibuprofen/colchicine dosing and tapering, Dressler management, constriction incidence by aetiology, pericardiectomy outcomes, hemodynamic criteria).



QT Interval Prolongation and Torsades de Pointes

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — The **QT interval** on the surface ECG subtends both ventricular depolarization and (chiefly) ventricular **repolarization**, and it varies *inversely* with heart rate. Because it is rate-dependent, it is reported as the rate-corrected QT (**QTc**). *Torsades de pointes* (“twisting of the points”) is the characteristic **polymorphic ventricular tachycardia** (VT) that complicates an abnormally prolonged QT interval; the QRS axis appears to twist around the isoelectric baseline. It typically presents with near-syncope, syncope or cardiac arrest, and sustained episodes may degenerate into **ventricular fibrillation** (VF).

Electrophysiology and QT/QTc measurement

- ▶ The QT interval is measured from the onset of the QRS to the end of the T wave; it reflects ventricular action-potential duration, governed mainly by repolarizing **potassium currents** (I_{Kr} , I_{Ks}).
- ▶ Because QT shortens as heart rate rises, it must be **rate-corrected** to QTc. No single formula has formal consensus:
 - **Bazett (“square root”) formula:** $QTc = QT / \sqrt{RR}$ (in seconds) — the classic method, but criticized for systematic over-/under-correction at very low and very high heart rates.
 - **Framingham formula:** $QTc = QT + 0.154 \times (1000 - RR)$ (in milliseconds) — a linear alternative.
- ▶ **Upper normal limits** (Harrison 22e, Ch 247): QTc **450 ms in men** and **460 ms in women**; lower limits are less well defined. In congenital LQTS the QTc is typically prolonged to **>440 ms in men** and **>460 ms in women** (Ch 262).
- ▶ **Prominent U waves** (a small rounded deflection following the T wave) accompanying prolonged repolarization are a recognized marker of *increased susceptibility to torsades*; abnormally large U waves are most often due to hypokalemia or drugs (dofetilide, amiodarone, sotalol, quinidine).

Mechanism of torsades de pointes

- ▶ The fundamental abnormality is **prolonged ventricular repolarization** with **abnormal transmural dispersion of repolarization**, which can arise from channelopathies, drugs or electrolyte disturbance even *without* structural heart disease.
- ▶ Torsades has a characteristic **pause-dependent initiation**: a premature ventricular contraction (PVC) induces a pause, the post-pause sinus beat shows a still-longer QT, and a subsequent PVC falling on the prolonged T wave initiates the polymorphic VT — the classic “**long-short**” **interval sequence** (Fig. 262-1).
- ▶ Drugs that **block repolarizing potassium currents** (notably the antiarrhythmics sotalol, dofetilide and ibutilide, and many non-cardiac agents) prolong the action potential and predispose to this arrhythmia. Individual susceptibility may reflect genetic polymorphisms or mutations affecting repolarization.

Classification / Causes of QT prolongation and torsades (Table 262-1)

Category	Examples
1. Congenital long QT syndromes	LQTS-1, LQTS-2, LQTS-3 (account for 80–90% of cases) and other rarer types
2. Electrolyte abnormalities	Hypokalemia, hypomagnesemia, hypocalcemia
3. Drug-induced (acquired)	Antiarrhythmics, antibiotics, antipsychotics, antihistamines, others (see drug table)

Category	Examples
4. Cardiac conditions	Myocardial ischemia/infarction, myocarditis, marked bradycardia , stress (takotsubo) cardiomyopathy
5. Endocrine disorders	Hypothyroidism, hyperparathyroidism, pheochromocytoma, hyperaldosteronism
6. Intracranial disorders	Subarachnoid hemorrhage, thalamic hematoma, cerebrovascular accident, encephalitis, head injury
7. Nutritional disorders	Anorexia nervosa, starvation, liquid-protein diets, gastroplasty/ileojejunal bypass, celiac disease

- *Acquired LQTS* (drug- and electrolyte-related) is by far the commonest clinical setting; **drug interactions** that raise the level of an offending agent are a frequent precipitant.

Drugs that prolong the QT interval (Table 262-1)

Drug class	Agents
Antiarrhythmics — Class IA	Quinidine, disopyramide, procainamide
Antiarrhythmics — Class III	Sotalol, dofetilide, ibutilide, amiodarone, dronedarone, ranolazine
Macrolide antibiotics	Erythromycin, clarithromycin, azithromycin
Fluoroquinolones	Levofloxacin, moxifloxacin
Other antimicrobials	Trimethoprim-sulfamethoxazole, clindamycin, pentamidine , chloroquine/hydroxychloroquine ; antifungals (ketoconazole, itraconazole); antivirals (amantadine)
Antipsychotics	Haloperidol, phenothiazines, thioridazine, trifluoperazine, sertindole, ziprasidone
Antidepressants	Tricyclic and tetracyclic agents
Antihistamines (H1)	Astemizole, diphenhydramine, hydroxyzine
Others	Methadone , cocaine, citrate (massive transfusion)

- The website crediblemeds.org is an authoritative resource to check whether a given drug is reported to prolong the QT interval.

Congenital long QT syndrome (LQTS)

- Caused by **mutations in genes encoding cardiac ion channels** controlling repolarization. LQTS-1, -2 and -3 account for **80–90%** of cases; the commonest (LQTS-1, -2) involve potassium channels, while LQTS-3 affects the sodium channel.

Type	Channel / current defect	Gene	Typical trigger of events
LQTS-1	Reduced repolarizing I _{Ks}	KCNQ1	Exertion, particularly swimming
LQTS-2	Reduced repolarizing I _{Kr}	KCNH2	Sudden auditory stimuli / emotional upset
LQTS-3	Delayed inactivation of I _{Na}	SCN5A	Sudden death tends to occur during sleep

- ▶ Typical presentation is **syncope or cardiac arrest, usually in childhood**; asymptomatic cases are found on family screening or routine ECG. **Genotyping** aids family screening and prognostication.
- ▶ *Markers of increased risk:* QTc >500 ms, female gender, and a history of syncope or cardiac arrest.
- ▶ *Related repolarization channelopathies (for completeness):* **Short QT syndrome** (QTc <360 ms, usually <300 ms; gain-of-function K-channel), **Brugada syndrome** (SCN5A, coved ST elevation V1–V3), and **catecholaminergic polymorphic VT** (RyR2/calsequestrin-2 mutations; bidirectional VT).

Management

- ▶ **Acute torsades / acquired LQTS:**
 - **IV magnesium sulphate 1–2 g** usually suppresses recurrent episodes (first-line, even if serum magnesium is normal).
 - If magnesium is ineffective, **increase heart rate** with an **isoproterenol infusion or temporary pacing to ~100–120 beats/min** to suppress PVCs and shorten the QT (abolishes the pause-dependent trigger).
 - **Correct hypokalemia, hypomagnesemia and hypocalcemia, treat bradycardia, and withdraw all offending QT-prolonging drugs.**
 - Sustained episodes degenerating to VF **require defibrillation per ACLS**. Such patients have a demonstrated susceptibility and must **avoid all future QT-prolonging drugs**.
- ▶ **Congenital LQTS:**
 - Adequate-dose **β-blockade is the cornerstone** for LQTS-1 and LQTS-2; the **non-selective agents nadolol and propranolol are favored**.
 - **Avoidance of QT-prolonging drugs** is critical for *all* patients, including genotype-positive patients with a normal QT.
 - An **implantable cardioverter-defibrillator (ICD)** is considered for recurrent syncope despite β-blockers or for a high-risk profile (e.g., prior cardiac arrest, QTc >500 ms).

- **Left cardiac sympathetic denervation** is a recognized adjunct for refractory cases (described under CPVT in the source).
- ▶ **Ischemia-related polymorphic VT:** prompt **myocardial reperfusion**, β -adrenergic blockade and correction of electrolytes; persistent severe LV dysfunction (LVEF <35%) is an ICD indication.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Torsades de pointes (rhythm strip, after Fig. 262-1).** Draw a sinusoidal polymorphic VT whose QRS amplitude waxes and wanes (“twisting around the baseline”). Labels: *Sinus beat with long QT, PVC, compensatory pause (long RR), PVC initiating VT, “long-short” interval sequence, pause-dependent initiation, polymorphic VT (torsades).*
- ▶ **Diagram 2 — QT interval on a normal complex.** Draw P-QRS-T-U. Labels: *QRS onset (start of QT), ST segment, T wave (end of QT), U wave, RR interval, and annotate QTc = $QT/\sqrt{RR}$ (Bazett); mark hypocalcemia $\rightarrow$ long ST/QT vs hypercalcemia $\rightarrow$ short QT.*

Clinical / Diagnostic significance

- ▶ **ECG is the key investigation:** measure QT and compute QTc; look for prominent U waves, marked T-wave abnormalities and pause-dependent ectopy. Telemetry/Holter captures self-limiting runs of torsades.
- ▶ **Metabolic/secondary clues:** **hypocalcemia** prolongs the QT (ST-segment portion) whereas **hypercalcemia** shortens it; **hypothermia** prolongs repolarization with an **Osborn (J) wave**; **subarachnoid hemorrhage** produces marked QT prolongation with deep, wide T-wave inversions (“CVA T-wave” pattern); digitalis *shortens* the QT with “scooped” ST-T.
- ▶ **Workup:** serum **potassium, magnesium, calcium**, thyroid function, a full drug review (including interactions), and ECG screening of first-degree relatives when congenital LQTS is suspected; consider **genotyping**.
- ▶ **Management pearls:** withdraw the culprit drug and correct electrolytes early; magnesium first, then rate support; do not give further QT-prolonging agents to a susceptible patient.

High-yield exam pointers

- ▶ QT subtends ventricular repolarization and varies **inversely with heart rate**; report QTc — Bazett $QT/\sqrt{RR}$ or Framingham.
- ▶ Upper normal QTc 450 ms (men) / 460 ms (women); QTc >500 ms is a high-risk marker for torsades.
- ▶ Torsades is **pause-dependent** with a “long-short” initiating sequence; **prominent U waves** flag susceptibility.
- ▶ Commonest cause clinically is **acquired** — *drugs + electrolyte disturbance (hypokalemia, hypomagnesemia, hypocalcemia) + bradycardia.*

- ▶ Memorize culprit drugs: Class IA & III antiarrhythmics, macrolides, fluoroquinolones, antipsychotics (haloperidol), methadone, pentamidine, antifungals; check crediblemeds.org.
- ▶ Acute treatment = IV magnesium 1–2 g → isoproterenol/pacing to 100–120/min → correct electrolytes/bradycardia → stop the drug → defibrillate if VF.
- ▶ Congenital LQTS triad: LQTS-1 (KCNQ1, I_{Ks}, exercise/swimming); LQTS-2 (KCNH2, I_{Kr}, auditory/emotion); LQTS-3 (SCN5A, I_{Na}, sleep) — together 80–90% of cases.
- ▶ Congenital LQTS treatment: β -blockers (nadolol/propranolol), avoid QT-prolonging drugs, ICD for high-risk/refractory cases.

SOURCE & COVERAGE

Harrison 22e — Ch 262 “Polymorphic Ventricular Tachycardia and Ventricular Fibrillation” (acquired & congenital LQTS, Table 262-1 causes/drug list, mechanism, management) and Ch 247 “Electrocardiography” (QT/QTc measurement, Bazett/Framingham formulas, normal limits, U waves, electrolyte/drug repolarization changes). *Coverage note:* the underlying cellular mechanism of torsades — **early afterdepolarizations (EADs)** triggering R-on-T — is universally accepted textbook electrophysiology but is not named explicitly in these two chapters; the source describes it functionally as pause-dependent, dispersion-of-repolarization-mediated initiation. **Left cardiac sympathetic denervation** is cited in the source under catecholaminergic polymorphic VT rather than directly under LQTS.



Stroke Prevention in Atrial Fibrillation

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Atrial fibrillation (AF) is the commonest sustained arrhythmia and the single most important cardiac cause of ischaemic stroke. Loss of organised atrial mechanical contraction produces blood stasis and *in situ* thrombosis, predominantly in the **left atrial appendage (LAA)**, which on embolisation causes cardio-embolic stroke and systemic thromboembolism. Because such strokes are large, disabling and often fatal, **antithrombotic prophylaxis guided by validated risk scores is the cornerstone of AF management** and is one of the three therapeutic aims (the others being symptom/rate–rhythm control and risk-factor modification). The decision balances the patient’s **stroke risk** against the **bleeding risk** of anticoagulation.

Pathophysiology of thromboembolism in AF

- ▶ Loss of atrial systole → **stasis of blood**, particularly in the trabeculated **left atrial appendage**, where ~90% of AF-related thrombi form; thrombus may also form in a severely dilated left atrium in mitral valve disease.

- ▶ **Virchow's triad** is satisfied: stasis, endothelial/endocardial dysfunction, and a prothrombotic/hypercoagulable milieu.
- ▶ Embolised thrombus reaches the cerebral circulation → large-vessel ischaemic stroke; recurrent silent emboli contribute to **cognitive impairment and dementia**.
- ▶ **Atrial stunning** — after conversion (spontaneous, electrical or pharmacological) from prolonged AF to sinus rhythm, atrial mechanical recovery is delayed for weeks, so thrombus can form and embolise *even after* sinus rhythm is restored. This underlies peri-cardioversion anticoagulation rules.
- ▶ AF burden (“paroxysmal” vs “persistent”) was traditionally thought not to predict stroke; hence the approach to **paroxysmal AF is the same as for persistent AF**. Asymptomatic episodes are common, so absence of AF on intermittent monitoring does not equal low risk.

Risk stratification — CHA₂DS₂-VASc and bleeding scores

The CHA₂DS₂-VASc score (max 9) estimates annual stroke risk; the HAS-BLED score (max 9) estimates major-bleeding risk. A higher score in either direction maps to a higher annual event rate.

CHA ₂ DS ₂ -VASc component	Points		HAS-BLED component	Points
C – Congestive heart failure / LV dysfunction	1		H – Hypertension (uncontrolled)	1
H – Hypertension	1		A – Abnormal renal / liver function	1 each
A ₂ – Age ≥75 years	2		S – Stroke history	1
D – Diabetes mellitus	1		B – Bleeding history / predisposition	1
S ₂ – Stroke / TIA / thromboembolism	2		L – Labile INR (on warfarin)	1
V – Vascular disease (MI/PAD/aortic plaque)	1		E – Elderly (age >65 years)	1
A – Age 65–74 years	1		D – Drugs (antiplatelet/NSAID) or alcohol	1 each
Sc – Sex category (female)	1			

- ▶ **Annual stroke rate rises with score** (CMDT/Braunwald): ~0% at 0, ~1.3% at 1, ~2.2% at 2, ~3.2% at 3, ~4% at 4, rising further with higher scores — Harrison notes risk may approach ~20% per year at the highest scores without anticoagulation.
- ▶ **Anticoagulation thresholds (2023 ACC/AHA/ACCP/HRS)**: Class I anticoagulation for **men with score ≥ 2 and women with score ≥ 3** ; *consider* (Class IIa) for men =1 / women =2; **no antithrombotic therapy** when the only point is female sex (men =0, women =1).
- ▶ Female sex is a **risk modifier, not an independent risk factor** — it counts only in the presence of other factors.
- ▶ Risk factors *not* captured by the score but relevant: **LA size, mitral annular calcification, AF burden, and renal failure** (RR ~1.4 in non-dialysis CKD, ~1.8 on dialysis).
- ▶ **HAS-BLED ≥ 3 flags high bleeding risk** — it should prompt correction of *modifiable* factors (BP control, stopping NSAIDs/alcohol, labile INR) and closer review, **not** automatic withholding of anticoagulation.
- ▶ Highest-risk groups in whom anticoagulation is recommended *regardless* of score: **prior stroke/TIA, rheumatic mitral stenosis, mechanical valve, and hypertrophic cardiomyopathy**.

Antithrombotic options — DOACs vs warfarin

Oral anticoagulants are far superior to antiplatelets. Warfarin reduces stroke by ~60–64% vs placebo and ~37% vs antiplatelet therapy; **aspirin is no longer recommended** for stroke prevention in AF (variable, modest benefit without a bleeding advantage). For **nonvalvular AF**, **DOACs are now preferred over warfarin** (equal/greater efficacy, ~50% less intracranial haemorrhage, fixed dosing, no monitoring, fewer food/drug interactions).

Agent	Class / target	Standard dose	Reduced dose & criteria	Pivotal trial
Warfarin	Vitamin K antagonist ($\downarrow$ factors II, VII, IX, X; protein C/S) via VKOR inhibition	Titrated to INR 2.0–3.0	— (needs INR monitoring; many interactions)	(reference comparator)
Dabigatran	Direct thrombin (IIa) inhibitor	150 mg BID	110 mg BID (age ≥ 80 , verapamil, high bleeding risk) / 75 mg BID if CrCl 15–30 (US label)	RE-LY
Rivaroxaban	Factor Xa inhibitor	20 mg OD with food	15 mg OD if CrCl 15–50 mL/min	ROCKET-AF
Apixaban	Factor Xa inhibitor	5 mg BID	2.5 mg BID if ≥ 2 of: age ≥ 80 , weight	ARISTOTLE

Agent	Class / target	Standard dose	Reduced dose & criteria	Pivotal trial
			≤60 kg, creatinine ≥1.5 mg/dL	
Edoxaban	Factor Xa inhibitor	60 mg OD	30 mg OD if CrCl 30–50, weight ≤60 kg, or P-gp inhibitor; avoid if CrCl >95	ENGAGE-AF

- ▶ All four DOACs were **non-inferior or superior** to warfarin in nonvalvular AF; pooled data show small absolute superiority (~0.4–0.7%) in mortality, stroke, major bleeding and intracranial haemorrhage. **Apixaban** uniquely showed superiority to warfarin for stroke *and* less major bleeding *and* lower mortality (ARISTOTLE).
- ▶ **Dabigatran** has more GI bleeding; **rivaroxaban** must be taken with food (40% better absorption).
- ▶ Renal dosing is critical — dabigatran/edoxaban avoided in end-stage renal disease/dialysis; **apixaban** has the best evidence in advanced CKD/haemodialysis (2.5 mg BID).
- ▶ **Reversal:** warfarin → IV **vitamin K + 4-factor prothrombin complex concentrate** (preferred over FFP); dabigatran → **idarucizumab** 5 g IV (monoclonal antibody fragment); factor Xa inhibitors → **andexanet alfa** (400 mg bolus then infusion). DOAC short half-life (~10–12 h) means supportive care often suffices; activated charcoal if ingested within 6–8 h.
- ▶ **Aspirin should be avoided** alongside an anticoagulant unless there is a clear indication (recent MI/stent).

Special clinical situations

- ▶ **Valvular AF** (mechanical prosthetic valve or moderate–severe/rheumatic mitral stenosis): **warfarin only** — DOACs are contraindicated/less effective. In rheumatic-heart-disease AF, warfarin gave fewer cardiovascular events/deaths than rivaroxaban without more bleeding.
- ▶ **Peri-cardioversion:** if AF >48 h or duration unknown → either **≥3 weeks of therapeutic anticoagulation before + ≥4 weeks after** cardioversion, **or** a TEE/cardiac-CT to exclude LAA thrombus and then cardiovert with ≥4 weeks' post-procedure anticoagulation (covers atrial stunning). DOACs are as effective as warfarin around cardioversion.
- ▶ **Hypertrophic cardiomyopathy with AF:** anticoagulate **independent of CHA₂DS₂-VASc score** (high thromboembolic risk).
- ▶ **Subclinical AF / device-detected atrial high-rate episodes (AHRE):** associated with a 2.5-fold increase in stroke risk. For AHRE ≥24 h with CHA₂DS₂-VASc ≥2, anticoagulation is reasonable (Class IIa); in subclinical AF of 6 min–24 h, apixaban reduces stroke/systemic embolism but increases major bleeding — individualise.

- ▶ **AF with PCI/coronary stenting:** minimise bleeding by using **OAC plus a single P2Y12 inhibitor (preferably clopidogrel)**, dropping aspirin early; reserve short “triple therapy” (≤ 30 days) for high ischaemic risk such as ACS.
- ▶ **Bridging:** because of rapid DOAC onset/offset, **no heparin bridging** is needed when interrupting a DOAC for procedures; stop 24–48 h before low/moderate-risk and longer before major surgery (extend in renal impairment).

Non-pharmacological / device-based prevention

- ▶ For patients with a **high stroke risk but contraindication to long-term anticoagulation** (excessive bleeding risk), **left atrial appendage (LAA) occlusion/exclusion** is the alternative, since ~90% of thrombi originate there.
- ▶ **Percutaneous LAA closure** — *Watchman* (nitinol plug, FDA-approved 2015; non-inferior to warfarin in *PROTECT AF / PREVAIL*, with less major/haemorrhagic bleeding and mortality benefit) and *Amplatzer Amulet* (non-inferior to Watchman). Post-Watchman, warfarin is continued ~45 days until TEE confirms sealing/no significant peri-device leak.
- ▶ **Surgical/epicardial exclusion** — LAA excision or stapling (often with maze surgery), the **AtriClip** (FDA-approved 2021), and the catheter-delivered **LARIAT** suture (off-label) — surgical LAA occlusion at cardiac surgery adds protection over anticoagulation alone.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **CHA₂DS₂-VASc / HAS-BLED scoring table with a stroke-risk curve:** draw the two-column scoring table (label every component and its points as above) and beneath it a graph of *annual stroke or major-bleeding rate (%)* on the Y-axis vs *score (0–9)* on the X-axis, with two rising lines labelled **CHA₂DS₂-VASc** and **HAS-BLED**.
- ▶ **Left atrial appendage thrombus and Watchman device:** draw the left atrium with a thrombus in the LAA; label *left atrium*, *left atrial appendage*, *thrombus*, *mitral valve*, and a *Watchman occluder device* seated across the LAA ostium delivered via *trans-septal* approach.

Clinical / Diagnostic significance

- ▶ **Risk-stratify every AF patient at diagnosis** with CHA₂DS₂-VASc; reassess periodically as age and comorbidities change.
- ▶ **Echocardiography** (TTE) is done in all new AF; TEE is the most sensitive test for LAA thrombus before cardioversion and before stopping anticoagulation post-LAA closure.
- ▶ Anticoagulation decision applies **equally to paroxysmal and persistent AF** and is **not** governed by the perceived AF burden or by whether sinus rhythm appears maintained.
- ▶ Monitor **renal function and blood counts** at baseline and $\geq$ twice yearly on DOACs; review HAS-BLED factors and correct modifiable bleeding risks.

- ▶ Major bleeding occurs in ~1–2% (warfarin) to 2–4% per year overall; have a clear **reversal pathway** (vitamin K/PCC, idarucizumab, andexanet alfa).

High-yield exam pointers

- ▶ LAA is the source of ~90% of thrombi in AF; main feared complication is **disabling cardio-embolic stroke**.
- ▶ CHA₂DS₂-VASc: age ≥75 and prior stroke/TIA score **2 each**; all others 1. Anticoagulate **men ≥2, women ≥3**.
- ▶ HAS-BLED ≥3 = **high bleed risk** → correct modifiable factors, don't simply withhold OAC.
- ▶ DOACs preferred over warfarin in nonvalvular AF; **warfarin only** for mechanical valves and moderate–severe/rheumatic mitral stenosis (target INR 2–3).
- ▶ Aspirin is **NOT recommended** for stroke prevention in AF.
- ▶ Trial map: dabigatran–RE-LY, rivaroxaban–ROCKET-AF, apixaban–ARISTOTLE, edoxaban–ENGAGE-AF; apixaban superior to warfarin with less bleeding.
- ▶ Reversal: dabigatran → **idarucizumab**; Xa inhibitors → **andexanet alfa**; warfarin → **vitamin K + 4-factor PCC**.
- ▶ Cardioversion rule: AF >48 h/unknown → 3 weeks before + 4 weeks after anticoagulation, or TEE-guided (beware **atrial stunning**).
- ▶ Watchman/Amulet LAA closure for patients unable to take long-term anticoagulation (PROTECT AF/PREVAIL).
- ▶ Anticoagulate **regardless of score** in HCM, mitral stenosis, mechanical valve, or prior stroke.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Atrial Fibrillation” (stroke prevention, CHA₂DS₂-VASc/HAS-BLED, cardioversion-anticoagulation, NOAC dosing table, LAA closure) and “Antiplatelet, Anticoagulant, and Fibrinolytic Drugs” (warfarin/VKOR mechanism, heparin/DOAC pharmacology, reversal agents).
- ▶ **Braunwald's Heart Disease, 13e** — “Atrial Fibrillation” (risk stratification, 2023 ACC/AHA/ACCP/HRS guideline thresholds, DOAC vs warfarin, subclinical AF/AHRE, LAA excision/closure — Watchman, Amulet, LARIAT, AtriClip).
- ▶ **CMDT 2026** — “Disorders of Cardiac Rhythm” (current DOAC regimens and renal dosing, adjusted stroke rate by CHA₂DS₂-VASc, ROCKET-AF/ARISTOTLE/ENGAGE-AF, reversal-agent doses, peri-procedural management).
- ▶ *Coverage note:* the RE-LY trial name for dabigatran is universally accepted standard medicine (Harrison cites the agent without naming the trial; CMDT names ROCKET-AF, ARISTOTLE and ENGAGE-AF explicitly).



Syncope

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Syncope is a *transient, self-limited loss of consciousness (TLOC) with loss of postural tone, due to acute global cerebral hypoperfusion, characterised by rapid onset, brief duration and spontaneous, complete recovery*. Because the brain's metabolism is critically perfusion-dependent, cessation of cerebral blood flow for ~6–10 s produces loss of consciousness. A presyncopal prodrome (lightheadedness, dimming of vision, sweating, nausea) is common but consciousness may be lost without warning. Syncope must be separated from other causes of TLOC — seizures, vertebrobasilar ischaemia, hypoxaemia, hypoglycaemia and psychogenic pseudosyncope. It accounts for ~3% of emergency visits and ~1% of admissions, with a lifetime cumulative incidence up to 40%, and a bimodal age distribution (peak in the young at 10–30 years, median ~15 years; a sharp rise after 70 years).

Pathophysiology

- ▶ **Upright stress is central.** Standing pools 500–1000 mL of blood in the legs, buttocks and splanchnic bed, reducing venous return, ventricular filling, stroke volume and blood pressure.
- ▶ This unloads **arterial baroreceptors** in the carotid sinus and aortic arch, normally triggering a compensatory reflex (increased sympathetic outflow, withdrawal of vagal tone) that raises peripheral resistance, heart rate and cardiac output to defend blood pressure.
- ▶ **Syncope results when this compensation fails** — transiently in neurally mediated syncope, chronically in autonomic failure, or because cardiac output is mechanically/electrically compromised in cardiac syncope.
- ▶ Cerebral blood flow is normally 50–60 mL/min per 100 g and is autoregulated over a mean pressure of ~50–150 mmHg (latency 5–10 s). Consciousness is impaired at ~25 mL/min per 100 g; a **fall in systolic BP to ≤50 mmHg** typically causes syncope. Either reduced cardiac output **and/or** reduced systemic vascular resistance can be the final common pathway; hypocarbia from hyperventilation adds cerebral vasoconstriction.
- ▶ EEG during syncope shows a “slow–flat–slow” pattern (high-amplitude delta → cortical flattening → recovery); seizure discharges are absent despite myoclonus.

Classification and causes

Three broad categories — *neurally mediated (reflex), orthostatic, and cardiac* — with neurally mediated being commonest at all ages and cardiac the most dangerous.

Category	Subtypes / triggers	Mechanism
Neurally mediated (reflex/vasovagal)	Vasovagal (fear, pain, emotion, sight of blood, prolonged standing, heat); Situational —	Transient ↑parasympathetic + sympathoinhibition → vasodilation ± bradycardia. Sub-

Category	Subtypes / triggers	Mechanism
	cough, micturition, defecation, swallow, post-prandial, wind-instrument/weightlifter; Carotid sinus syndrome ; cardiac <i>Bezold–Jarisch reflex</i>	typed by efferent limb as vasodepressor (BP fall), cardioinhibitory (bradycardia/asystole) or mixed
Orthostatic hypotension	Primary autonomic failure — <i>synucleinopathies</i> : Parkinson disease, dementia with Lewy bodies, pure autonomic failure (<i>Bradbury–Eggleston</i>), multiple system atrophy (<i>Shy–Drager</i>). Secondary — diabetic/amyloid/immune/HSAN neuropathy, B12 deficiency, HIV. Iatrogenic/volume — diuretics, α -blockers, nitrates, TCAs, phenothiazines; haemorrhage, vomiting, diarrhoea	Sympathetic vasoconstrictor (autonomic) failure $\rightarrow$ no adequate compensatory rise in HR/resistance on standing
Cardiac	Arrhythmias — sinus node dysfunction, AV block (<i>Stokes–Adams attack</i>), SVT, VT, inherited channelopathies; Structural — aortic stenosis, HCM, MI, atrial myxoma, tamponade, massive PE, pulmonary hypertension	Abrupt fall in cardiac output from electrical or mechanical obstruction; associated with $\uparrow$ risk of sudden cardiac death

- **Inherited channelopathies** causing arrhythmic syncope/sudden death: **long-QT syndrome** (K^+ / Na^+ channel genes, scaffolding protein *ankyrin-B/ANK2*) producing *torsades de pointes*; **Brugada syndrome** (Na^+ -channel *SCN5A*; coved RBBB-type ST elevation V1–V3); **catecholaminergic polymorphic VT** (abnormal cardiac calcium handling, *RyR2*). Acquired QT prolongation (drugs) is the commoner cause of torsades.
- **Variants of OH**: *initial OH* (BP fall within 15 s, resolves by 45 s — not true autonomic failure); *delayed OH* (beyond 3 min — early adrenergic failure); **POTS** — chronic (>3 months) orthostatic intolerance with HR rise ≥ 30 /min (≥ 40 in ages 12–19) within 10 min standing without a >20 mmHg SBP fall. **Supine hypertension** coexists in $>50\%$ with autonomic failure.

Differentiating syncope from its mimics

Feature	Vasovagal syncope	Seizure	Cardiac/arrhythmic	Psychogenic
Trigger	Emotion, pain, standing, heat	Rare emotional trigger; aura	Exertion, supine, palpitations	Often present, many witnesses, no trigger

Feature	Vasovagal syncope	Seizure	Cardiac/arrhythmic	Psychogenic
		(déjà vu, olfactory)		
Onset/prodrome	Long (>5 s): nausea, warmth, sweating, pallor	Brief aura	Sudden (<5 s), few/no warning	Variable; eyes closed
During event	Pallor, dilated pupils, slow pulse, brief arrhythmic multifocal myoclonus	Blue/cyanotic face, tonic-clonic, tongue biting , lateral eye deviation	Limp; may be cyanotic	Normal colour, normal pulse/BP
Recovery	Rapid reorientation, prolonged fatigue	Prolonged (>5 min) post-ictal confusion, aching muscles, headache	Rapid unless low output	Rapid, oriented
Incontinence	Urine occasionally; faecal very rare	Urine/faeces more likely	Possible	Absent

Approach and investigations

- ▶ **Three goals:** confirm it was syncope, identify the cause, and stratify risk of recurrence/sudden death.
- ▶ **Cornerstone = history + eyewitness account (and cellphone video) + examination + orthostatic vitals + 12-lead ECG** — establishes a cause in ~50% of patients.
- ▶ **Orthostatic vitals:** BP/HR supine then after standing each minute to 3 min. **OH = fall in systolic ≥ 20 mmHg or diastolic ≥ 10 mmHg within 3 min of standing/head-up tilt.**
- ▶ **High-risk “red-flag” features** mandating admission/intensive evaluation: chest pain/ischaemic ECG, heart failure, moderate–severe valvular or structural disease, history of VT, **QTc >500 ms**, persistent bradycardia (<40/min), bi-/tri-fascicular block or QRS ≥ 120 ms, AF, non-sustained VT, pre-excitation, Brugada pattern, family history of sudden death, palpitations preceding syncope, or **syncope at rest/during exertion**.
- ▶ **ECG:** long QT, short PR + delta wave (WPW), RBBB + ST elevation V1–V3 (Brugada), T-inversion V1–V3 $\pm$ epsilon wave (ARVD), AV block, ischaemia.
- ▶ **Carotid sinus massage** (>40 yr, recurrent unexplained syncope) under continuous ECG/BP; *avoid with bruit/known stenosis/recent TIA-stroke*. **Cardioinhibitory response = asystole >3 s; vasodepressor = SBP fall >50 mmHg; mixed = both.**

- ▶ **Tilt-table test** (head-up 60–80°, usually 70°, after a 20-min supine phase, for 30–45 min, ± isoproterenol or sublingual nitroglycerin) confirms susceptibility to neurally mediated syncope and distinguishes it (paroxysmal hypotensive–bradycardic response) from OH (gradual BP fall without HR rise); also exposes psychogenic pseudosyncope (LOC with normal vitals).
- ▶ **Cardiac monitoring matched to event frequency:** in-hospital telemetry/Holter for daily events; external loop recorder for monthly events; **implantable loop recorder** for infrequent events (monitor ideally $\geq 2\times$ the inter-spell interval).
- ▶ **Echocardiography** when structural disease is suspected (aortic stenosis, HCM, tamponade, dissection, myxoma) and for LVEF-based SCD risk. **Exercise testing** if syncope occurs during/after exertion. **Electrophysiologic study** only with structural disease/abnormal ECG (diagnostic: H-V interval ≥ 100 ms, CSNRT > 525 ms, induced sustained monomorphic VT). **Routine CT/MRI/EEG/carotid Doppler** are **NOT recommended** without focal signs or head trauma — yield ~1–4%.

Management

Type	Management
Neurally mediated / reflex	Education, reassurance, trigger avoidance; salt + fluid loading , ~500 mL bolus water acutely; physical counterpressure manoeuvres (leg-crossing, handgrip, abdominal + leg tensing — most effective; RCT-supported). Drug: midodrine (only agent with RCT support); fludrocortisone, β -blockers (age > 40), SSRI as second-line. Dual-chamber pacing (closed-loop stimulation) only for > 40 yr with frequent recurrence and documented cardioinhibitory/asystolic response
Orthostatic hypotension	Withdraw offending drugs first; staged posture changes, head-up tilt of bed at night, compression garments, counterpressure manoeuvres, avoid large/high-carbohydrate meals; salt and fluid expansion. Drugs: fludrocortisone , midodrine , droxidopa (L-DOPS) ; refractory — pyridostigmine, atomoxetine, yohimbine, octreotide, desmopressin (DDAVP), erythropoietin
Cardiac	Treat the cause: pacemaker for sinus node disease / AV block; ablation for SVT/WPW; antiarrhythmics and ICD for VT/VF or low-EF cardiomyopathy; valve replacement for aortic stenosis; manage PE/tamponade/ischaemia

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Type	Management
	▶ The baroreflex arc — label: <i>carotid sinus & aortic arch baroreceptors</i> → afferents in <i>glossopharyngeal (CN IX) and vagus (CN X)</i> → <i>nucleus tractus solitarius (NTS)</i> in dorsomedial medulla → <i>nucleus ambiguus (NA)</i> (vagal/parasympathetic to sinus node) and <i>caudal ventrolateral medulla (CVLM)</i> → <i>rostral ventrolateral medulla (RVLM)</i> presympathetic neurons → sympathetic efferents to heart and blood vessels; <i>A1 noradrenergic group</i> → <i>PVN/SON</i> → <i>vasopressin</i>. Colour parasympathetic (green) vs sympathetic (blue). ▶ Tilt-table tracing comparison — label two BP/HR panels: (A) <i>neurally mediated syncope</i> = abrupt paroxysmal fall in BP with bradycardia; (B) <i>orthostatic hypotension</i> = gradual BP fall without compensatory HR rise.

Clinical / Diagnostic significance

- ▶ Prognosis is driven by aetiology: noncardiac/unexplained syncope in the young has **normal life expectancy**, whereas **cardiac syncope carries excess sudden-death and all-cause mortality**; OH-related syncope roughly doubles mortality (reflects comorbidity).
- ▶ Syncope may be the **first and only warning before sudden cardiac death** — hence risk stratification, not just diagnosis, is the priority.
- ▶ **Exertional syncope** suggests aortic stenosis, HCM or arrhythmia; **syncope while supine or seated, or preceded by palpitations** suggests an arrhythmia — all are red flags.
- ▶ *Coat-hanger* (suboccipital/shoulder) ache and post-prandial faintness point to autonomic failure; treating supine hypertension and OH together requires balance.
- ▶ Driving and occupational restriction must be addressed in recurrent or high-risk syncope.

High-yield exam pointers

- ▶ Syncope = **global cerebral hypoperfusion**; LOC after ~6–10 s of arrested flow; recovery is rapid and complete.
- ▶ Three causes: **neurally mediated (commonest)**, **orthostatic**, **cardiac (most lethal)**.
- ▶ OH = systolic $\downarrow \geq 20$ or diastolic $\downarrow \geq 10$ mmHg within 3 min of standing; POTS = HR $\uparrow \geq 30$ /min without ≥ 20 mmHg SBP fall.
- ▶ **Carotid sinus hypersensitivity**: asystole > 3 s (cardioinhibitory) and/or SBP fall > 50 mmHg (vasodepressor).
- ▶ **Stokes–Adams attack** = syncope from brady-/asystole; **Bezold–Jarisch reflex** underlies cardiac reflex syncope.
- ▶ Channelopathies: LQTS (torsades), Brugada (SCN5A, V1–V3 ST elevation), CPVT, ankyrin-B/ANK2.

- ▶ History + examination + orthostatic vitals + ECG diagnose ~50%; routine neuroimaging/EEG are low-yield.
- ▶ **Midodrine** is the only RCT-supported drug for vasovagal syncope; **counterpressure manoeuvres** are first-line non-drug therapy; **droxidopa/fludrocortisone/midodrine** for OH.
- ▶ **Tongue biting, post-ictal confusion >5 min, cyanosis** favour seizure; **pallor, rapid recovery, faecal continence** favour syncope.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Syncope" (Freeman & Raj): definition, pathophysiology, baroreflex, EEG patterns, classification, channelopathies, approach and treatment.
- ▶ **Braunwald's Heart Disease, 13e** — "Hypotension and Syncope" (Calkins & Chen): detailed classification, POTS, carotid sinus hypersensitivity criteria, tilt-table and EP-testing protocols, high-risk/hospitalisation variables, 2017 ACC/AHA/HRS management recommendations, and the syncope-vs-seizure-vs-psychogenic differentiation table.
- ▶ **CMDT 2026** — current management context and the exertional-syncope mechanism in aortic stenosis.



Takotsubo cardiomyopathy

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Takotsubo cardiomyopathy (TTC), also called *takotsubo syndrome* (TTS), *stress-induced cardiomyopathy*, *apical ballooning syndrome*, or "*broken-heart syndrome*," is an acute, usually reversible form of left ventricular (LV) dysfunction that classically follows an intense emotional or physical stressor. The acutely dyskinetic, dilated apex with a hypercontractile base produces the characteristic shape of the narrow-necked Japanese octopus-trapping pot (*takotsubo*). It mimics an acute coronary syndrome (ACS) — chest pain, ST-elevation and troponin rise — yet coronary angiography shows no culprit obstruction, and the regional wall-motion abnormality extends beyond any single coronary territory. First described in Japan in the 1990s, it predominantly affects postmenopausal women and generally resolves within days to weeks.

Epidemiology and triggers

- ▶ **Sex/age:** Overwhelmingly **postmenopausal women** — in the *International Takotsubo Registry* (1750 patients) **89.8%** were female. Women are ~**10-fold** more likely to develop TTC overall, and women >55 yr are ~5× more likely than those <55 yr. In patients <50 yr, males predominate with more antecedent neurologic/psychiatric disease.

- ▶ **Burden:** ~5500 US hospital admissions in 2012, with a large additional in-hospital incidence triggered by intercurrent illness; well recognised during emergency cardiac catheterisation and ICU admissions for non-cardiac conditions.
- ▶ **Triggers (preceding stressor not obligatory):** A physical trigger occurred in ~36% and an emotional trigger in ~28% of registry patients. Recognised precipitants include acute medical/surgical illness, hypoglycaemia, alcohol withdrawal, hyperthyroidism, **neurologic catastrophes** (subarachnoid haemorrhage, stroke/TIA, seizures), and **pheochromocytoma**, as well as bereavement and acute emotional shock.
- ▶ **Associations:** Higher prevalence of psychiatric and neurologic disorders than ACS controls; patients with COPD, migraine, or affective disorders on β -agonists may fare worse.

Pathophysiology

- ▶ **Catecholamine excess is central.** An acute stressor activates central and autonomic stress pathways, raising circulating epinephrine/norepinephrine (adrenal medulla) and local norepinephrine from sympathetic nerve terminals.
- ▶ Proposed mechanisms of myocardial injury: **direct catecholamine toxicity**, **adrenoceptor-mediated stunning** (apical myocardium has the highest β -adrenoceptor density), **epicardial multivessel and microvascular coronary spasm**, heterogeneity of myocardial autonomic innervation, abnormal myocardial calcium handling, and increased cardiac workload.
- ▶ **Estrogen deprivation** in postmenopausal women (endothelial dysfunction) is thought to be facilitating, explaining the female predominance.
- ▶ Cardiac MRI shows **diffuse myocardial oedema without necrosis** and, importantly, **absence of late gadolinium scar** — distinguishing it from infarction and myocarditis.
- ▶ A *similar picture* can be produced by a **coronary embolus** in the absence of atherosclerotic disease.

Clinical features and ballooning variants

- ▶ **Presentation mimics ACS:** chest pain (~76%), dyspnoea (~47%), syncope (~8%); may present with pulmonary oedema, hypotension or cardiogenic shock. Arrhythmias are not uncommon; syncope is relatively rare.
- ▶ **ECG:** ST-segment elevation (in nearly half), deep widespread **anterior T-wave inversions**, and **QTc prolongation**; T-wave changes resolve gradually.
- ▶ **Biomarkers:** troponin/CK moderately elevated (troponin raised in ~87%) and *taper quickly* relative to the extent of wall-motion abnormality; BNP/NT-proBNP markedly elevated — a disproportionately small troponin rise for a large akinetic territory is a clue.

Morphologic variant	Frequency / features
Apical ballooning (classic)	>80%; apical akinesis/dyskinesis with hypercontractile base
Midventricular	Mid-LV akinesis with preserved apex and base
Basal ("reverse"/inverted)	Basal akinesis with apical sparing; more often younger patients
Focal	Wall-motion abnormality limited to one segment; rarely within a single coronary territory

Diagnosis and differentiation from ACS

- **InterTAK diagnostic criteria (consensus):** transient LV dysfunction (apical, midventricular, basal or focal pattern, $\pm$ RV involvement) typically *extending beyond one coronary distribution*; an emotional/physical/combined trigger may precede but is **not obligatory**; neurologic disorders or pheochromocytoma may trigger it; new ECG changes (ST elevation/depression, T-inversion, QTc prolongation); moderate troponin/CK rise with marked BNP elevation; **significant CAD does not exclude TTS** (~15% have coexisting CAD); no infectious myocarditis; postmenopausal female predominance. **Cardiac MRI is recommended to exclude myocarditis and confirm TTS.**
- **Imaging:** echocardiography demonstrates apical dyskinesis not conforming to a coronary territory; coronary angiography excludes acute occlusion; LV ventriculography shows classic apical ballooning. CMR confirms oedema without scar.

InterTAK clinical score (TTS vs ACS)	Points
Female sex	25
Emotional stress	24
Physical stress	13
No ST-segment depression (except aVR)	12
Psychiatric disorders	11
Neurologic disorders	9
QTc prolongation	6

- Interpretation: ≤ 70 points = low/intermediate probability; **>70 points = high probability of TTS.** The score aids ED discrimination but does **not replace coronary angiography** in the acute setting.

Management

- **Acute phase = treat as ACS until coronary disease excluded** (urgent angiography). Admit higher-risk patients to ICU/CCU for monitoring.
- **No therapy is proven to alter the natural history;** care is supportive and complication-directed:

- *Pulmonary oedema*: nitrates and standard heart-failure measures.
 - *Haemodynamically stable patients*: combined α - and β -blockade preferred over selective β -blockade.
 - *Arrhythmia / QT prolongation*: magnesium; **avoid QT-prolonging drugs** (e.g., macrolides, certain antiarrhythmics).
 - *Hypotension*: use **inotropes/pressors with great caution** — they can precipitate dynamic LV **outflow tract (LVOT) obstruction**; an intra-aortic balloon pump may be used for critically low output **only if there is no LVOT obstruction**.
 - *LV apical thrombus*: anticoagulation while thrombus is present.
- ▶ **Risk stratification (higher-risk)**: LVEF <45%, hypotension, LVOT gradient >40 mmHg, and/or significant arrhythmia — an **ACE inhibitor and/or β -blocker** is recommended in this group.
 - ▶ **Long-term/secondary prevention**: **ACE inhibitors/ARBs are associated with reduced recurrence and improved survival**, whereas **β -blockers have NOT been shown to prevent recurrence**. Routine long-term anticoagulation is not recommended once thrombus resolves.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **LV ventriculogram/echo in systole (classic “takotsubo” shape)**: outline the LV cavity with labels — *hypercontractile basal segments (narrow neck), akinetic/dyskinetic ballooned apex, mid-LV, aortic outflow*; alongside a small sketch of the **Japanese octopus pot (takotsubo)** for the eponym.
- ▶ **Pathophysiology flow diagram**: *Acute emotional/physical stress* → *central + sympathetic activation* → *catecholamine surge (epinephrine/norepinephrine)* → [*direct catecholamine toxicity + microvascular/epicardial spasm + β -receptor-mediated apical stunning*] → *transient apical ballooning (reversible LV dysfunction)*, with *estrogen deprivation* shown as a facilitating factor.

Clinical / Diagnostic significance

- ▶ Must be considered in any **postmenopausal woman presenting as anterior STEMI after acute stress** — distinguishing it from ACS prevents inappropriate thrombolysis and guides management.
- ▶ **Disproportion clue**: extensive wall-motion abnormality with only modest troponin rise and a non-coronary distribution favours TTS over infarction.
- ▶ **CMR (oedema without scar)** is the key discriminator from MI and myocarditis.
- ▶ Complications driving the ~4–5% in-hospital mortality: **cardiogenic shock, dynamic LVOT obstruction from systolic anterior motion of the mitral valve, LV free-wall rupture, mural-thrombus embolisation/stroke, torsades de pointes** from QT prolongation, and (rarely) complete heart block.

- ▶ Prognosis: historically thought benign, but in-hospital mortality is comparable to STEMI; ~10% have cardiac/neurologic adverse events over the next year.

High-yield exam pointers

- ▶ *Takotsubo* = narrow-necked Japanese **octopus-trapping pot**; synonyms: stress/apical ballooning/"broken-heart" syndrome.
- ▶ **Postmenopausal women (~90%)** after intense emotional or physical stress; estrogen deprivation facilitates.
- ▶ **Mechanism = catecholamine surge** → direct toxicity + microvascular/epicardial spasm + apical β -receptor stunning.
- ▶ Mimics **anterior STEMI** (ST-elevation, deep T-inversions, QTc $\uparrow$) with **normal/non-obstructive coronaries** and wall motion **crossing coronary territories**.
- ▶ **Troponin rise modest** relative to akinesis; **BNP markedly raised**; **CMR shows oedema WITHOUT late-gadolinium scar**.
- ▶ Variants: **apical (>80%)**, midventricular, basal/reverse, focal.
- ▶ **InterTAK score >70** → **high probability of TTS**; significant CAD does NOT exclude the diagnosis.
- ▶ Treatment supportive: avoid pressors/QT-prolonging drugs; beware **LVOT obstruction**; **ACEi/ARB reduces recurrence, β -blockers do not**.
- ▶ Usually **reverses in days–weeks**; recurrence ~5% (mostly within the first year; Harrison cites ~10% lifetime at ~2%/yr).

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "*Dilated Cardiomyopathies*" (Takotsubo syndrome/cardiomyopathy section) and "*Classification of Cardiomyopathy*."
- ▶ Braunwald's Heart Disease, 13e — "*The Dilated, Restrictive, and Infiltrative Cardiomyopathies*" (Takotsubo Cardiomyopathy; **International Takotsubo (InterTAK) Diagnostic Criteria and InterTAK Clinical Score**, International Takotsubo Registry epidemiology, complications and therapy).
- ▶ CMDT 2026 — "*Heart Failure & Cardiomyopathy*" (Takotsubo Cardiomyopathy — essentials, pathophysiology, ECG/diagnostic studies, treatment, prognosis).

Coverage note: The corpus does not include the *Mayo Clinic* diagnostic criteria; the InterTAK consensus criteria (Braunwald) are used instead. All figures (89.8% female, InterTAK score points, ~4–5% mortality, ballooning variants, ACEi-vs- β -blocker recurrence data) are taken verbatim from the cited chapters.



Treatment options for management of pulmonary embolism

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Pulmonary embolism (PE) is obstruction of the pulmonary arterial circulation by thrombus that has embolised, most often from a lower-limb deep-venous thrombosis (DVT); together they constitute *venous thromboembolism* (VTE). Acute right-ventricular (RV) pressure overload, not hypoxaemia, is the principal determinant of early death. Modern treatment is therefore **risk-stratified**: anticoagulation is the universal cornerstone, while reperfusion (systemic thrombolysis, catheter-directed therapy, or surgical embolectomy) and haemodynamic support are reserved for patients with established or impending RV failure.

Risk stratification — the framework that selects the treatment

Therapy is chosen by combining haemodynamic status, RV function (echocardiography or CT) and cardiac biomarkers (troponin, BNP/NT-proBNP), supplemented by the **Pulmonary Embolism Severity Index** (PESI) or its simplified form (sPESI, one point each for age >80 y, cancer, cardiopulmonary disease, HR ≥110, SBP <100 mmHg, SaO₂ <90%; score 0 = low risk).

Category	Frequency	Defining features	Treatment implication
High-risk (massive)	5–10%	Sustained hypotension/shock, ≥half the pulmonary vasculature occluded	Reperfusion (fibrinolysis/embolectomy) + haemodynamic support
Intermediate-high (submassive)	part of 20–25%	RV dysfunction and raised biomarkers, normotensive	Anticoagulate, monitor in HDU; rescue reperfusion if deteriorating
Intermediate-low	part of 20–25%	RV dysfunction or raised biomarker (one only)	Anticoagulation, close observation
Low-risk	65–75%	Normotensive, normal RV and biomarkers, sPESI 0	Anticoagulation alone; consider early discharge/outpatient

- ▶ A multidisciplinary **Pulmonary Embolism Response Team** (PERT) is recommended to coordinate decisions in high- and intermediate-high-risk PE.

Anticoagulation — the cornerstone for all patients

Begin immediately once PE is confirmed (or empirically when clinical probability is high and bleeding risk low). Heparins act by accelerating antithrombin; they prevent new thrombus but do not lyse existing clot — endogenous fibrinolysis remodels it.

Agent	Dose / regimen	Notes
Unfractionated heparin (UFH)	80 U/kg bolus, then 18 U/kg/h IV; target aPTT 60–80 s (anti-Xa 0.3–0.7 U/mL)	Short half-life — preferred if thrombolysis/embolectomy or renal failure likely; reversible with protamine
LMWH (enoxaparin)	1 mg/kg SC twice daily	No monitoring unless obese/renal failure/pregnant; favoured for intermediate-risk and cancer
Dalteparin / tinzaparin	200 U/kg OD (or 100 U/kg BID) / 175 U/kg OD	Renal dose reduction
Fondaparinux	Weight-based SC once daily	Synthetic anti-Xa pentasaccharide; does not cause HIT; reduce in renal impairment
Rivaroxaban	15 mg BID × 3 weeks → 20 mg OD	Oral monotherapy, no parenteral lead-in
Apixaban	10 mg BID × 1 week → 5 mg BID	Oral monotherapy; 2.5 mg BID extended phase
Dabigatran	150 mg BID after ≥5 days parenteral	Direct thrombin inhibitor; antidote idarucizumab
Edoxaban	60 mg OD after ≥5 days parenteral (30 mg if CrCl 15–50, wt ≤60 kg, or P-gp inhibitor)	Anti-Xa agent
Warfarin	Start 5 mg, titrate to INR 2.0–3.0	Overlap with parenteral agent ≥5 days and until INR ≥2 on two readings 24 h apart

- ▶ DOACs are first-line for most patients: fixed dose, rapid onset, no routine monitoring, fewer interactions. Avoid in pregnancy/breast-feeding, antiphospholipid syndrome (use **warfarin**), and severe renal failure/cirrhosis.
- ▶ Heparin-induced thrombocytopenia (HIT) or its suspicion: stop all heparin, use a direct thrombin inhibitor — **argatroban** (hepatic clearance) or **bivalirudin** (renal) — or fondaparinux.
- ▶ Reversal of bleeding: protamine sulphate for UFH/LMWH; **idarucizumab** for dabigatran; **andexanet alfa** or prothrombin complex concentrate (PCC) for anti-Xa DOACs; vitamin K ± FFP/PCC for warfarin.

Reperfusion therapy — for high-risk and deteriorating intermediate-high-risk PE

1. Systemic fibrinolysis

- ▶ Indication: high-risk (massive) PE with hypotension/shock; also intermediate-high-risk PE that deteriorates (rising lactate, worsening RV strain, clot-in-transit) despite anticoagulation.
- ▶ Regimen: **alteplase (rt-PA) 100 mg IV over 2 h** (FDA-approved, peripheral vein); the sooner given the better, but benefit persists up to ~14 days from symptom onset. An off-label **half-dose 50 mg/2 h** trades efficacy for fewer bleeds.
- ▶ Risk: major bleeding ~10%, **intracranial haemorrhage 2–3%**. Contraindications — intracranial disease, recent surgery, recent trauma; careful screening minimises bleeding.

2. Catheter-directed therapy (CDT) — lowers fibrinolytic dose and bleeding risk:

- ▶ *Ultrasound-facilitated, catheter-directed low-dose fibrinolysis* (e.g. ~24 mg t-PA over ~12 h) improves the RV/LV ratio (SEATTLE II, ULTIMA).
- ▶ *Mechanical/aspiration thrombectomy* without lytic — large-bore nitinol-disc retrieval (FlowTrieve) or aspiration (Indigo) — useful when fibrinolysis is contraindicated.

3. Surgical pulmonary embolectomy

- ▶ For high-risk or intermediate-high-risk PE with severe RV dysfunction when thrombolysis is contraindicated or has failed, or to remove a right-atrial/clot-in-transit or close a patent foramen ovale. Best results **before** pressor dependence and multiorgan failure.

Haemodynamic support, adjuncts and prevention

- ▶ **Massive PE resuscitation:** cautious volume — **500 mL normal saline** only (over-filling worsens RV wall stress and septal shift). First-line **norepinephrine** (raises systemic/coronary pressure) plus **dobutamine** (RV inotropy, lowers filling pressure). Refractory shock → **veno-arterial ECMO** to decompress the RV and bridge to definitive therapy.
- ▶ **Inferior vena cava (IVC) filter:** only two firm indications — (1) active bleeding precluding anticoagulation, and (2) recurrent VTE despite therapeutic anticoagulation. Prefer a **retrievable** filter and remove early; routine filters do not reduce mortality and increase later DVT.
- ▶ **Prophylaxis** of in-hospital VTE (low-dose UFH/LMWH/fondaparinux, or mechanical compression if anticoagulation is contraindicated) is central to reducing PE incidence.

Duration of anticoagulation and special populations

- ▶ **Minimum 3 months** for all. The ESC 2019 framework abandons the rigid “provoked/unprovoked” split and instead weighs **recurrence risk** (low <3%/yr; intermediate 3–8%/yr; high >8%/yr) against bleeding risk and patient preference.
- ▶ **Extended (indefinite) anticoagulation** for a first PE with no identifiable risk factor, a persistent/enduring risk factor (cancer, heart failure, IBD, autoimmune disease), or antiphospholipid syndrome; extended phase often uses **low-dose DOAC** (apixaban 2.5 mg BID or rivaroxaban 10 mg OD).

- ▶ **Cancer-associated VTE:** LMWH monotherapy **or** a DOAC (apixaban/edoxaban) when there is no gastrointestinal malignancy; continue until cancer-free (Caravaggio, Hokusai-VTE Cancer).
- ▶ **Pregnancy:** LMWH throughout — warfarin (embryopathy) and DOACs are avoided.
- ▶ **CTEPH** develops in ~2% of acute PE survivors → follow persistent pulmonary hypertension with echocardiography at ~6 weeks/6 months; treat operable disease with **pulmonary thromboendarterectomy** (mortality 1–5% at expert centres), and inoperable disease with pulmonary vasodilators and balloon pulmonary angioplasty.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Risk-stratified treatment algorithm of acute PE:** *Confirmed PE* → *assess haemodynamics* → “Hypotension/shock?” → **Yes** = **High-risk** → reperfusion (systemic thrombolysis / catheter-directed / surgical embolectomy) + norepinephrine + dobutamine ± VA-ECMO; → **No** → assess RV function + biomarkers → branches labelled *Intermediate-high* (anticoagulation + HDU monitoring + rescue reperfusion), *Intermediate-low* (anticoagulation + observation), *Low-risk (sPESI 0)* (anticoagulation ± early discharge). Add a side box: *IVC filter only if bleeding precludes anticoagulation or recurrent VTE despite it.*
- ▶ **Pathophysiology of RV failure in massive PE:** labels — PE → ↑ pulmonary vascular resistance → ↑ RV wall tension → RV dilation → interventricular septal shift → ↓ LV preload → ↓ cardiac output/systemic BP → ↓ right coronary perfusion → RV ischaemia/microinfarction (↑ troponin) → circulatory collapse.

Clinical / Diagnostic significance

- ▶ Risk stratification (haemodynamics + RV imaging + troponin/BNP) **directly selects therapy** — it is not academic; missing submassive RV dysfunction under-treats a deteriorating patient.
- ▶ ECG S1Q3T3 and T-inversion V1–V4, and **echocardiographic McConnell’s sign** (RV free-wall hypokinesis with apical sparing) flag RV strain and prompt closer monitoring/reperfusion consideration.
- ▶ **CT-derived RV/LV diameter ratio >1** predicts 30-day death and is the standard surrogate of reperfusion response.
- ▶ Age-adjusted D-dimer (age × 10 ng/mL if >50 y) and Wells score guide *whether to image*, conserving CT pulmonary angiography.

High-yield exam pointers

- ▶ Anticoagulation is the cornerstone for **every** PE; reperfusion is added only for high-risk (and deteriorating intermediate-high-risk) disease.
- ▶ **Alteplase 100 mg IV over 2 h** is the FDA-approved lytic regimen for massive PE; ICH risk 2–3%.
- ▶ **UFH 80 U/kg bolus → 18 U/kg/h**, aPTT 60–80 s; UFH preferred when reperfusion or renal failure is anticipated.

- ▶ **DOACs first-line**; rivaroxaban/apixaban need **no parenteral lead-in**, dabigatran/edoxaban need **≥5 days** of heparin first.
- ▶ **HIT** → stop heparin, give **argatroban** or **bivalirudin**; **APS** → use **warfarin**, not DOACs.
- ▶ **IVC filter** indications: active bleeding precluding anticoagulation, or recurrent VTE despite anticoagulation — use a **retrievable** filter.
- ▶ **Massive PE**: **500 mL** fluid only + **norepinephrine** + **dobutamine** ± VA-ECMO; surgical embolectomy if lysis fails/contraindicated.
- ▶ **Reversal**: **protamine** (heparins), **idarucizumab** (dabigatran), **andexanet alfa/PCC** (anti-Xa DOACs).
- ▶ **Minimum duration 3 months**; extend for cancer, APS, persistent risk factor, or recurrent/no-cause PE; cancer VTE → LMWH or apixaban/edoxaban.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Deep-Venous Thrombosis and Pulmonary Thromboembolism” (classification, risk stratification, anticoagulant agents/doses Table 290-4, massive-PE management, fibrinolysis, catheter-directed therapy, embolectomy, IVC filter, duration tables 290-5/290-6); and “Antiplatelet, Anticoagulant, and Fibrinolytic Drugs” (heparin/warfarin/DOAC pharmacology, reversal).
- ▶ **Braunwald's Heart Disease, 13e** — “Pulmonary Embolism and Deep Vein Thrombosis” (PESI/sPESI Table 79.6, ESC risk categories, PERT, systemic vs catheter-directed fibrinolysis SEATTLE II/ULTIMA, FlowTrier/Indigo mechanical thrombectomy, surgical embolectomy, VA-ECMO, IVC filter trials, cancer-VTE Caravaggio/Hokusai, extended-duration DOAC dosing).
- ▶ **CMDT 2026** — Pulmonary and Hemostasis/Thrombosis chapters, for current anticoagulant selection and management.
- ▶ Coverage note: corpus coverage is thorough; specific catheter-device FDA-clearance years and ongoing-trial names (PEITHO-3, HI-PEITHO, PEERLESS) are from Braunwald and are cited only as context, not as exam-required facts.



What are the indications for coronary arteriography? What are the complications of the procedure?

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — **Coronary arteriography** (selective coronary angiography) is the invasive, catheter-based opacification of the epicardial coronary arteries with radio-opaque iodinated contrast, recorded as cine images in multiple orthogonal projections, and remains the **gold standard** for defining coronary anatomy and the extent/severity of obstructive coronary artery disease (CAD). It is almost

always performed as part of diagnostic **cardiac catheterization**. The technique evolved from Forssmann's self-catheterization (1929) and Cournand & Richards' haemodynamic work (Nobel Prize, 1956) to Sones' first selective coronary injection (1958) and Judkins' preformed catheters that brought it into routine use. The purpose is to determine whether **medical, surgical (CABG), or catheter-based (PCI) interventions** are warranted.

Indications for coronary arteriography

Broadly, arteriography is indicated to **define the extent and severity of cardiac/coronary disease in symptomatic patients**, to decide on revascularisation, and to **exclude severe disease** when non-invasive tests are equivocal but a definitive diagnosis is needed.

Clinical setting	Specific indications
Asymptomatic / symptomatic CAD	High-risk findings on non-invasive testing; aborted sudden cardiac death; sustained (>30 s) monomorphic VT; non-sustained (<30 s) polymorphic VT
Symptomatic CAD	CCS Class II, III, or IV stable angina on medical therapy; acute coronary syndrome (unstable angina & NSTEMI); chest-pain syndrome of unclear cause with equivocal non-invasive tests
Acute myocardial infarction	Reperfusion by primary PCI ; persistent/recurrent ischaemia; pulmonary oedema and/or reduced ejection fraction; cardiogenic shock / haemodynamic instability ; risk stratification or a positive post-MI stress test; mechanical complications (acute MR, ventricular septal defect)
Valvular heart disease	Suspected severe valve disease in symptomatic patients (dyspnoea, angina, heart failure, syncope); infective endocarditis needing surgery; asymptomatic aortic regurgitation with cardiac enlargement or falling EF; prior to cardiac surgery / TAVR or other percutaneous valve intervention when CAD is suspected
Congestive heart failure	New-onset angina or suspected undiagnosed CAD; new-onset cardiomyopathy of uncertain cause or suspected to be ischaemic
Congenital heart disease	Before surgical correction / percutaneous intervention when symptoms or testing suggest coronary disease; suspected congenital coronary anomalies
Pericardial disease	Symptomatic patients with suspected tamponade or constrictive pericarditis (with right heart study)

Clinical setting	Specific indications
Cardiac transplantation	Pre-operative and post-surgical (allograft vasculopathy) evaluation
Other conditions	Hypertrophic cardiomyopathy with angina; diseases of the aorta where coronary involvement alters management; pulmonary hypertension; unexplained dyspnoea

- **Acuity-based strategy (ACS):** an *urgent/immediate* invasive strategy is indicated in NSTEMI-ACS with refractory angina or haemodynamic/electrical instability; an *early invasive* strategy in stabilised high-risk patients (raised troponin, dynamic ST/T changes, **GRACE score >140**, diabetes, EF <40%, early post-infarction angina, recent PCI, prior CABG). **STEMI** within ischaemic-symptom onset warrants urgent angiography for primary PCI.
- **Pre-valve-surgery screening (CMDT):** coronary angiography to detect incidental CAD before valve surgery is recommended in **all men >40 years** and in **menopausal women with coronary risk factors**; younger patients need it only if coronary disease is clinically suspected.
- Catheterisation is **not mandatory** before surgery in selected younger patients with uncomplicated congenital or valvular disease well-defined non-invasively and without risk factors for concomitant CAD.

Contraindications (context for indications)

- There are **no absolute contraindications** when the procedure is performed in anticipation of a **life-saving intervention** and the patient accepts the risks.
- **Relative contraindications (elective):** decompensated congestive heart failure; acute renal failure; severe chronic renal insufficiency (unless dialysis planned); bacteraemia; acute stroke; active GI bleeding; excessive anticoagulation or recent thrombolytic administration; severe uncorrected electrolyte abnormalities; prior **anaphylactoid reaction to iodinated contrast** without premedication; aspirin allergy/anaphylaxis/bronchospasm if progression to PCI is likely and desensitisation not done; uncontrolled hypertension; pregnancy (radiation).
- **Right heart catheterisation-specific:** right heart tumour, endocarditis, or thrombus/clot in transit.

Complications of the procedure

Risks of **elective** catheterisation are low; they rise substantially when done emergently, during acute MI, or in haemodynamically unstable patients. Harrison quotes MI <0.1%, stroke 0.01%, death 0.05%; for elective + emergent procedures combined the **in-hospital mortality is 1.4%**.

Complication	Approximate risk (%)
Mortality	0.11

Complication	Approximate risk (%)
Myocardial infarction	0.05
Cerebrovascular accident (stroke)	0.07
Arrhythmias	0.38
Vascular (access-site) complications	0.43
Contrast agent reaction	0.37
Haemodynamic complications	0.26
Perforation of a heart chamber	0.03
Other	0.28
Total major complications	≈1.70

- ▶ **Vascular access-site bleeding is the most common complication (1.5–2.0%);** major bleeds worsen short- and long-term outcome. **Radial access** lowers vascular/bleeding complications versus femoral and is the preferred route.
- ▶ **Access-site complications:** haematoma, **pseudoaneurysm**, arteriovenous fistula, dissection, and (with femoral puncture outside the safe zone — above the profunda/superficial femoral bifurcation, below the inferior epigastric artery) **retroperitoneal haemorrhage**. Radial access may cause severe vasospasm with device entrapment, forearm haematoma, and rarely **compartment syndrome**.
- ▶ **Arrhythmias:** tachy-/brady-arrhythmias needing countershock, temporary pacing, or drugs. Deep RCA cannulation or contrast injection into the conus branch can precipitate **ventricular fibrillation**; catheter contact during ventriculography may trigger VPCs/VT (usually self-limiting).
- ▶ **Embolic events:** coronary, cerebral, or peripheral air/thrombus/atheroembolism; risk increased by calcified subclavian/axillary vessels. Risk factors for peri-procedural stroke: advanced age, diabetes, emergency procedure, prior stroke, renal failure, CHF.
- ▶ **Iatrogenic coronary dissection or perforation** — infrequent but potentially life-threatening, may need urgent stenting; **aortic dissection** and **cardiac tamponade** can occur.
- ▶ **Other:** acute renal failure requiring transient/permanent dialysis, acute pulmonary oedema, hypotension/haemodynamic compromise, and (rarely) infection — antibiotic prophylaxis is **not** required.

Contrast and radiation complications

- ▶ **Contrast allergy:** allergic reactions in <5%; severe **anaphylactoid** reactions (clinically like anaphylaxis but not IgE-mediated) in 0.1–0.2%. Mild = nausea, vomiting, urticaria; severe = hypotensive shock, pulmonary oedema, cardiorespiratory arrest. *Premedication* for prior

significant allergy: **prednisone 50 mg orally at 13, 7 and 1 hour before**, plus an **H1-antihistamine**, using non-ionic low-osmolar contrast.

- ▶ **Contrast-induced acute kidney injury (CI-AKI)**: rise in creatinine **>0.5 mg/dL or >25% above baseline at 48–72 h**; occurs in ~2–7% overall (20–30% in high-risk patients). *Risk factors*: diabetes mellitus, CHF, chronic kidney disease, anaemia, older age, STEMI. Dialysis needed in 0.3–0.7%, carrying a **five-fold rise in in-hospital mortality**. *Prevention*: IV **0.9% saline 1.0–1.5 mL/kg/h** for 3–12 h before and 6–24 h after (reduces risk by >50%); minimise contrast volume (<50 mL); low-/iso-osmolar agents; **stop metformin 24 h before and restart 48 h after** to avoid lactic acidosis. N-acetylcysteine and sodium bicarbonate show **no clear benefit** in recent meta-analyses.
- ▶ **Radiation injury**: deterministic (dose-dependent — skin erythema, telangiectasia, hair loss, lens injury; commonest site is the skin of the back) and stochastic (carcinogenesis). Thresholds for follow-up: **>5 Gy** — advise watching for erythema; **>10 Gy** — medical-physicist peak-dose calculation at 2–4 weeks; **>15 Gy or fluoroscopy time >60 min** — hospital risk-management event/vigilance. The **ALARA** principle governs dose minimisation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Normal coronary tree (PA + lateral schematic)**: label **Left main (LM)**, **LAD with diagonal (D) branches**, **Left circumflex (LCx) with obtuse marginal (OM)**, **Right coronary artery (RCA)**, **posterior descending artery (PDA)**, **AV-nodal branch**; annotate **right-dominant circulation (~85%)** where PDA arises from RCA.
- ▶ **Femoral artery puncture “safe zone”**: label **inguinal ligament**, **inferior epigastric artery (upper limit)**, **common femoral artery**, **bifurcation into profunda femoris & superficial femoral artery (lower limit)**, **femoral head landmark** — puncture below the inferior epigastric and above the bifurcation to avoid retroperitoneal bleed.

Clinical / Diagnostic significance

- ▶ A luminal narrowing **>50%** is considered significant; intermediate stenoses (40–70%) are interrogated functionally — **fractional flow reserve (FFR) <0.80** (post-adenosine hyperaemia) or **instantaneous wave-free ratio (iwFR) <0.89** indicate a haemodynamically significant lesion benefiting from revascularisation; **coronary flow reserve <2.0** signals microvascular dysfunction.
- ▶ **IVUS** (axial resolution 100–150 μm) and **OCT** (10–15 μm) refine plaque characterisation and stent optimisation (expansion, apposition, edge dissection).
- ▶ A **myocardial bridge** mimics stenosis but normalises in diastole; **coronary spasm** resolves with intracoronary nitroglycerin; **spontaneous coronary artery dissection** appears in otherwise normal vessels — important differentials of an apparent “stenosis”.

- ▶ Adjunct studies obtained at the same sitting — ventriculography (wall-motion, EF, MR grade), aortography (dissection, AR), right heart study (shunts, PA pressures), and the **Brockenbrough–Braunwald sign** for HOCM — extend diagnostic value.
- ▶ **Pre-procedure optimisation:** 6-h fast, conscious sedation, aspirin 325 mg, hold warfarin until INR <1.8 (heparin bridge for mechanical valves), stop DOACs 24–48 h prior, withhold oral hypoglycaemics in those prone to hypoglycaemia.

High-yield exam pointers

- ▶ **Gold standard** for coronary anatomy; first selective injection by **Sones (1958)**; preformed catheters by **Judkins**.
- ▶ Memorise indication buckets: **symptomatic/high-risk CAD, ACS, acute MI (primary PCI, shock, mechanical complications), valvular & congenital disease, CHF/new cardiomyopathy, HCM with angina, pre-transplant**.
- ▶ **No absolute contraindication** before a life-saving intervention; key relative ones: decompensated HF, uncorrected coagulopathy/electrolytes, untreated contrast anaphylaxis, active bleeding, acute stroke, severe renal failure (unless dialysis planned).
- ▶ **Commonest complication = vascular access-site bleeding (1.5–2.0%)**; serious events (death/MI/stroke) each <1%; overall major complication rate ≈1.7%.
- ▶ **Radial > femoral** for fewer bleeding/vascular complications.
- ▶ **CI-AKI:** creatinine rise >0.5 mg/dL or >25% at 48–72 h; prevent with saline hydration and minimal low-/iso-osmolar contrast; hold metformin.
- ▶ **Contrast anaphylactoid reaction premedication: prednisone 50 mg at 13, 7, 1 h + H1-blocker.**
- ▶ Deep RCA/conus injection → **VF**; femoral puncture below the bifurcation → **retroperitoneal haemorrhage**.
- ▶ Radiation thresholds: >5 Gy erythema watch; >15 Gy / >60 min FT = risk-management event.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Diagnostic Cardiac Catheterization and Coronary Angiography” (indications Table 249-1; risks, relative contraindications, contrast allergy/premedication, CI-AKI, coronary anatomy & dominance, FFR/iwFR/CFR, IVUS/OCT).
- ▶ **Braunwald's Heart Disease, 13e** — “Coronary Angiography and Intravascular Imaging” (appropriate-use criteria, contraindications, Table of risks with per-complication percentages, vascular/embolic complications, CI-AKI prevention, radiation-exposure thresholds and ALARA).
- ▶ **CMDT 2026** — “Coronary Artery Disease, Valvular Disease & Other Key Topics in Cardiology” (pre-valve-surgery coronary angiography screening criteria).



Cardiac Resynchronization Therapy (CRT): Rationale, Indications and Contraindications

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Cardiac resynchronization therapy (CRT) is a device-based pacing therapy that restores coordinated (synchronous) electrical and mechanical activation of the left ventricle in patients with **heart failure with reduced ejection fraction (HFrEF)** and an electrical conduction delay (a widened QRS, classically **left bundle branch block, LBBB**). It is delivered most often as **biventricular pacing (BiVP)** — a lead in the right atrium, a lead in the right ventricle, and a third lead passed through the **coronary sinus** to pace the lateral/posterolateral wall of the left ventricle. CRT is the only device that simultaneously improves symptoms, induces reverse remodelling, and reduces hospitalisation and all-cause mortality, and is offered **after** optimisation of guideline-directed medical therapy (GDMT).

Rationale (pathophysiology — why CRT works)

- ▶ In **~one-third of HFrEF patients** an intraventricular conduction delay (QRS >120 ms, usually LBBB) produces **ventricular dyssynchrony** — temporal discoordination of contraction within the LV (intraventricular) and between the ventricles (interventricular).
- ▶ **Consequences of dyssynchrony**: suboptimal ventricular filling, reduced LV contractility and mechanical efficiency, **increased wall stress**, paradoxical septal motion, and a greater degree and prolonged duration of **functional mitral regurgitation (MR)**.
- ▶ The **single most important marker** of dyssynchrony is a **widened QRS**, particularly an **LBBB morphology**; electrical dyssynchrony generally reflects underlying mechanical dyssynchrony.
- ▶ By **pre-exciting the delayed (lateral LV) wall** through a coronary-sinus lead and timing it with RV activation, CRT **re-aligns opposing-wall contraction**, narrows the QRS, improves the efficiency of ejection, reduces functional MR and promotes **reverse remodelling** (fall in LV end-systolic/diastolic volumes, rise in LVEF).
- ▶ A useful secondary benefit: CRT raises systolic blood pressure (shown in COMPANION and CARE-HF), which **permits up-titration of GDMT** (ACE-I/ARNI, beta-blocker, MRA) previously limited by hypotension — adding further mortality benefit.

Device types and conduction-system alternatives

- ▶ **CRT-P (CRT-pacemaker)**: biventricular pacing alone — for symptomatic relief/remodelling when an ICD is not indicated or in the very elderly/frail.
- ▶ **CRT-D (CRT-defibrillator)**: biventricular pacing **plus** ICD — preferred when the patient also meets an ICD indication (LVEF ≤35%, NYHA II–III) for sudden-death prevention.
- ▶ **Conduction system pacing (CSP)** — *His-bundle pacing (HBP)* and *left bundle branch area pacing (LBBAP)* — are evolving physiological alternatives that pace the native conduction system to

produce a more natural, narrow-QRS activation; current evidence gives them mostly **Class II** recommendations (used when effective BiVP cannot be achieved or as HBP/LBBAP with LBBB correction). BiVP retains the larger mortality evidence base.

Evidence base (landmark CRT trials)

Trial (year)	Population	Key entry criteria	Principal finding
MUSTIC / MIRACLE (2001–02)	NYHA III–IV	QRS $\geq$ 130–150 ms, LVEF low	↑ exercise capacity, VO_2 , LVEF; ↓ MR, QRS (intermediate endpoints)
COMPANION (2004)	NYHA III–IV, LVEF $\leq$ 35%	QRS $\geq$ 120 ms; randomised 1:2:2 (OMT vs CRT-P vs CRT-D)	CRT-P and CRT-D ↓ death/hospitalisation; CRT-D ↓ mortality
CARE-HF (2005)	NYHA III–IV on optimal therapy	QRS $\geq$ 150 ms (or 120–149 ms with echo dyssynchrony)	First trial to show all-cause mortality reduction with CRT-P
REVERSE / MADIT-CRT (2008–09)	NYHA I–II (mild), LVEF $\leq$ 30%	QRS $\geq$ 120–130 ms	Reverse remodelling, ↓ HF events; benefit greatest with LBBB and QRS >149 ms
RAFT (2010)	NYHA II–III, LVEF $\leq$ 30%	QRS $\geq$ 120 ms (or $\geq$ 200 ms if paced)	CRT-D ↓ mortality and HF hospitalisation vs ICD alone
BLOCK-HF	AV block needing RV pacing, LVEF $\leq$ 50%	—	BiVP superior to RV pacing for mortality/morbidity/remodelling
ECHO-CRT (2012)	NYHA III–IV, narrow QRS $\leq$ 130 ms, echo dyssynchrony	—	No benefit and signal of HARM (↑ mortality) → CRT contraindicated in narrow QRS

Take-home: benefit is greatest in LBBB + wide QRS ($\geq$ 150 ms); it falls with shorter QRS and non-LBBB morphology and is **absent or harmful** when the QRS is narrow.

Indications (guideline-graded — 2022 AHA/ACC/HFSA; 2023 HRS/APHRS/LAHRS)

Prerequisite for all: symptomatic HFrEF on $\geq$ 3 months of optimised GDMT, in sinus rhythm, with reasonable functional life expectancy.

Class	Indication
Class I (A)	LVEF $\leq$ 35%, LBBB, QRS $\geq$ 150 ms, NYHA II / III / ambulatory IV, sinus rhythm, on GDMT

Class	Indication
Class I (A)	LVEF $\leq 35\%$, LBBB, QRS 120–149 ms, NYHA II–IV with select characteristics (e.g., female sex)
Class I (B)	Pacemaker-induced cardiomyopathy / patients with LVEF $\leq 50\%$ who require a high burden of RV pacing (BLOCK-HF)
Class IIa (A/B)	LVEF $\leq 35\%$, non-LBBB QRS ≥ 150 ms, NYHA III/ambulatory IV; and LBBB QRS 120–149 ms (NYHA II–IV) without special characteristics
Class IIb (B)	LVEF $\leq 30\%$, LBBB, QRS ≥ 150 ms, NYHA I (ischaemic); non-LBBB QRS 120–149 ms

- ▶ CRT-D vs CRT-P: add the defibrillator (CRT-D) when an ICD is independently indicated; choose CRT-P alone in older/frail patients or where SCD prevention adds little.

Contraindications & predictors of non-response

- ▶ QRS <120–130 ms (narrow QRS) — *Class III (no benefit / harm)*; ECHO-CRT showed increased mortality. Echo-defined dyssynchrony in a narrow QRS is **not** a valid target.
- ▶ Non-LBBB morphology with QRS <150 ms (especially RBBB) — minimal/uncertain benefit ($\leq$ Class IIb / III).
- ▶ Heart failure with preserved or mid-range EF (HFpEF/HFmrEF) — no established role; CRT/ICD are not indicated.
- ▶ NYHA class IV refractory, non-ambulatory (“inotrope-dependent”) HF, terminal illness, or predicted survival <1 year from comorbidity — unlikely to benefit; consider advanced therapies (LVAD/transplant) or palliation instead.
- ▶ Relative / situational uncertainty (lower expected response): permanent atrial fibrillation without rate control or AV-node ablation (excluded from pivotal trials), RBBB, extensive lateral-wall scar at the intended pacing site, and acute decompensated HF.
- ▶ Procedural/anatomical: active infection/bacteraemia, unfavourable coronary sinus anatomy, or inability to position the LV lead.
- ▶ Predictors of non-response ($\sim 1/3$ of recipients): non-LBBB, QRS <150 ms, ischaemic cardiomyopathy with scar, AF, suboptimal LV lead position (non-lateral), and low percentage of biventricular pacing.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Diagram 1 — CRT lead anatomy (frontal cardiac silhouette): label pulse generator (left prepectoral pocket), right atrial lead (RA appendage), right ventricular lead (RV apex);

defibrillator coil if CRT-D), coronary sinus → lateral/posterolateral LV branch lead, SVC, tricuspid valve. Annotate “third lead via coronary sinus paces lateral LV wall.”

- ▶ **Diagram 2 — Mechanism strip:** two panels — (A) LBBB: wide QRS, septum and lateral wall contract out of phase, paradoxical septal motion, functional MR; (B) *After CRT:* simultaneous biventricular pacing, **narrowed QRS**, synchronised septal–lateral contraction, reduced MR, reverse remodelling. Label QRS width and arrows of wall activation.

Clinical / Diagnostic significance

- ▶ **Patient selection** rests on a 12-lead ECG (QRS duration and morphology), echocardiographic LVEF, NYHA class and confirmation of GDMT **optimisation** for ≥3 months.
- ▶ CRT delivers **symptom relief, improved exercise capacity/QoL, reverse remodelling, fewer HF hospitalisations and reduced mortality** — the only HF device with all of these.
- ▶ Aim for **≥92–98% biventricular pacing**; low BiVP% (often from AF or frequent ectopy) is a leading cause of failure and may warrant rhythm/rate control or AV-node ablation.
- ▶ Re-assess LVEF after 3–6 months; “super-responders” may normalise EF. Persistent severe functional MR despite CRT may need transcatheter edge-to-edge repair (e.g., MitraClip, COAPT).
- ▶ Complications to counsel for: coronary-sinus lead dislodgement, **phrenic nerve stimulation** (diaphragmatic twitch), pocket infection, and pneumothorax.

High-yield exam pointers

- ▶ **Target = electrical dyssynchrony**; the best surrogate is a **wide QRS with LBBB** — benefit rises with QRS width, maximal at **≥150 ms**.
- ▶ **Strongest Class I indication:** LVEF ≤35% + LBBB + QRS ≥150 ms + NYHA II–IV (ambulatory) + sinus rhythm + on GDMT.
- ▶ **CARE-HF** — first trial to show **all-cause mortality** reduction (CRT-P); **COMPANION** randomised 1:2:2; **RAFT/MADIT-CRT** extended CRT to mild (NYHA I–II) HF.
- ▶ **ECHO-CRT** = narrow-QRS CRT is **harmful** → **narrow QRS (<120–130 ms)** is a **contraindication**.
- ▶ **CRT-D** when an ICD is also indicated; **CRT-P** for frail/elderly or no SCD indication.
- ▶ **BLOCK-HF / pacing-induced cardiomyopathy:** prefer BiVP over RV pacing when high RV-pacing burden + LVEF ≤50% (now Class I).
- ▶ **No role in HFpEF**; non-LBBB and AF predict poorer response.
- ▶ **His-bundle / LBB area pacing** are emerging physiological alternatives to BiVP.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Heart Failure: Management” (rationale of dyssynchrony, CARE-HF/RAFT/MADIT-CRT, QRS >149 ms + LBBB, areas of uncertainty, CSP alternatives; Table 265-3 ICD principles).
- ▶ **Braunwald's Heart Disease, 13e** — “Devices for Monitoring and Managing Heart Failure” (trial table — MUSTIC, MIRACLE, COMPANION 1:2:2, CARE-HF, REVERSE, MADIT-CRT, RAFT, ECHO-CRT, BLOCK-HF; 2023 HRS/APHRS/LAHRS guideline indications) and “Pacemakers, Conduction System Pacing, CRT and ICDs” (device types, CRT-P/CRT-D, CSP, Fig. 51.16 class-of-recommendation algorithm).
- ▶ **CMDT 2026** — “Heart Failure & Cardiomyopathy” (referral thresholds: LVEF ≤35% with QRS ≥120 ms, especially LBBB; no role in HFpEF).

**Atrial Fibrillation — Risk Factors and Management**

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — **Atrial fibrillation (AF)** is the commonest sustained arrhythmia, characterised by disorganised, rapid, irregular atrial electrical activation with loss of organised atrial mechanical contraction, producing an *irregularly irregular* ventricular response (typically 110–160/min) with absent P waves and a fibrillatory baseline on ECG. It is a major public-health problem whose prevalence rises steeply with age (>95% of patients are >60 years; ~20% of those >80 years), and whose principal hazards are a 1.5–1.9-fold excess mortality, cardioembolic stroke (AF causes ~25% of all ischaemic strokes), heart failure, tachycardia-induced cardiomyopathy and dementia. Management rests on four pillars: **risk-factor modification, rate control, rhythm control and stroke prevention**.

Classification (basis for therapy)

Type	Definition
Paroxysmal	Episodes self-terminate (or by cardioversion) in ≤7 days; normal/mildly enlarged LA, low scar burden — antiarrhythmics often effective
Persistent	Continuous AF >7 days but <1 year; mild-to-severe LA enlargement
Long-standing persistent	Persistent AF >1 year; usually severely enlarged, fibrotic, refractory LA
Permanent	AF accepted; no further attempt at rhythm control

- ▶ A newer **continuum staging** is proposed: Stage 1 — at risk of AF; Stage 2 — pre-AF; Stage 3 — AF; Stage 4 — permanent AF, emphasising prevention and lifestyle/risk-factor modification rather than duration alone.
- ▶ AF without mitral stenosis or a mechanical valve is termed **nonvalvular AF** (governs anticoagulant choice).

Risk factors

- ▶ **Non-modifiable:** advancing age, male sex, white race, tall stature, family history of AF (especially <50 years; a small subset have a heritable familial form), and underlying structural/genetic cardiac disease.
- ▶ **Cardiac:** hypertension, coronary artery disease, valvular disease (especially mitral), heart failure (HFrEF and HFpEF), hypertrophic and other cardiomyopathies, cardiac amyloidosis, pericardial disease, congenital heart disease, prior cardiac surgery (post-operative AF in up to ~50%).
- ▶ **Modifiable / lifestyle (the “fourth pillar”):** obesity (AF risk rises ~29% per 5-point rise in BMI), hypertension, diabetes mellitus, obstructive sleep apnoea, alcohol (acute “holiday heart” and chronic use), smoking, physical inactivity/poor cardiovascular fitness — but also extreme endurance exercise (a *U-shaped* risk curve in men).
- ▶ **Other / precipitants:** hyperthyroidism, acute alcohol intoxication, acute myocardial infarction, pulmonary embolism, pneumonia/lung disease, pulmonary hypertension, pericarditis and psychological stress. *Modest caffeine intake is not a risk factor (large cohorts show a slight reduction).*

General approach & acute management

- ▶ Three immediate aims: (1) control symptoms by rate and/or rhythm control; (2) mitigate thromboembolic risk; (3) address modifiable risk factors.
- ▶ **Haemodynamic instability** (hypotension, pulmonary oedema, ongoing ischaemia): perform **emergent synchronised DC cardioversion** (QRS-synchronous shock, sedated patient).
- ▶ **Stable patient:** control ventricular rate, decide on anticoagulation, and consider restoration of sinus rhythm.
- ▶ **Pharmacologic cardioversion:** IV **ibutilide** (class III); *avoid* with baseline QT prolongation or severe LV dysfunction (torsades de pointes risk).

Stroke prevention (anticoagulation)

- ▶ Risk stratified by the CHA₂DS₂-VASc score; bleeding risk by HAS-BLED.

CHA ₂ DS ₂ -VASc	Pts	HAS-BLED	Pts
C — Congestive HF / LVEF ≤40%	1	H — Hypertension	1

CHA ₂ DS ₂ -VASc	Pts	HAS-BLED	Pts
H — Hypertension	1	A — Abnormal renal/liver function	1 each
A ₂ — Age ≥75	2	S — Stroke history	1
D — Diabetes mellitus	1	B — Bleeding diathesis	1
S ₂ — prior Stroke/TIA/thromboembolism	2	L — Labile INR (on warfarin)	1
V — Vascular disease (MI/PAD/aortic plaque)	1	E — Elderly (>65)	1
A — Age 65–74	1	D — Drugs predisposing to bleed / alcohol	1 each
Sc — Sex category (female)	1		

- **Oral anticoagulation (OAC) is recommended for a score ≥1, unless the sole point is female sex** (men score 1, women score 2 as treatment thresholds). Untreated annual stroke risk rises with score (up to ~20%). The **burden** of AF does not reliably predict stroke risk — paroxysmal AF is treated like persistent AF; even **subclinical** AF raises stroke risk ~2.5-fold.
- **DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) are preferred over warfarin** in nonvalvular AF — non-inferior/superior for stroke prevention with markedly **lower intracranial haemorrhage**, no INR monitoring and fewer interactions. Warfarin reduces stroke by **64% vs placebo** and **37% vs antiplatelet therapy**.
- **Warfarin (INR 2–3) is mandatory in rheumatic mitral stenosis and mechanical valves** — DOACs are inferior/contraindicated here.
- **Antiplatelets are inadequate** for stroke prevention; aspirin+clopidogrel is inferior to warfarin and bleeds more.
- **Reversal:** warfarin — vitamin K, FFP, prothrombin-complex concentrate; **dabigatran** — **idarucizumab**; **factor Xa inhibitors** — **andexanet alfa**.
- **Left atrial appendage occlusion** (e.g. *Watchman*) is non-inferior to warfarin for patients with high stroke risk but contraindication to long-term OAC; surgical LAA exclusion may be done with concomitant cardiac/maze surgery.

DOAC	Standard	Reduced dose & criteria
Dabigatran	150 mg bid	110 mg bid (age ≥80, verapamil, high bleed risk)
Rivaroxaban	20 mg od	15 mg od (CrCl 15–49 mL/min)

DOAC	Standard	Reduced dose & criteria
Apixaban	5 mg bid	2.5 mg bid (≥ 2 of: age ≥ 80 , wt ≤ 60 kg, Cr ≥ 1.5 mg/dL)
Edoxaban	60 mg od	30 mg od (CrCl 30–50, wt ≤ 60 kg, P-gp inhibitor)

Peri-cardioversion anticoagulation

- ▶ AF <48 h, low risk: cardioversion without preceding anticoagulation is acceptable; start OAC if stroke risk warrants.
- ▶ AF ≥ 48 h or unknown duration: either 3 weeks of uninterrupted OAC before and ≥ 4 weeks after cardioversion, or a TEE (or delayed-acquisition cardiac CT) to exclude LA-appendage thrombus, then cardiovert under anticoagulation, continuing ≥ 4 weeks (covers post-cardioversion atrial stunning). Long-term continuation is by CHA₂DS₂-VASc.

Rate control

- ▶ **Goal:** improve diastolic filling and symptoms, prevent tachycardiomyopathy. **Strict target** = resting HR <80/min (rising to <100/min on light exertion); a **lenient target** <110/min is acceptable if asymptomatic with preserved LV function (RACE II).
- ▶ **First-line agents:** β -blockers and the non-dihydropyridine calcium-channel blockers verapamil/diltiazem (oral or IV); often combined.
- ▶ **Digoxin:** mainly for HF or hypotensive patients (no negative inotropy) and as add-on; **chronic use linked to increased mortality** — now reserved for HF.
- ▶ **Amiodarone:** rate control only when other agents fail/are not tolerated (e.g. HF with bronchospasm).
- ▶ **“Ablate and pace”:** AV-junction ablation + permanent pacemaker (with CRT/conduction-system pacing to avoid dyssynchrony) when drug rate control fails.

Rhythm control

- ▶ **Indications:** symptomatic paroxysmal AF, recurrent symptomatic persistent AF, AF with poor rate control, or AF causing/aggravating LV dysfunction or HF; favoured in younger, active patients.
- ▶ **Early rhythm control** (within 1 year of diagnosis) reduces death/stroke/HF/ACS hospitalisation (EAST-AFNET 4); a catheter-ablation strategy improves survival in AF with HFrEF.
- ▶ **Antiarrhythmic drugs (AADs):**
 - **No structural heart disease:** class Ic flecainide / propafenone (also “pill-in-the-pocket”), or sotalol, dofetilide, dronedarone.
 - **CAD / structural disease:** avoid class Ic (proarrhythmia, $\uparrow$ mortality — CAST); use sotalol, dofetilide, dronedarone.

- **Heart failure:** only **amiodarone** and **dofetilide** are survival-neutral; **dronedarone** is contraindicated in decompensated/NYHA IV HF.
- **Amiodarone** is the most effective (maintains sinus rhythm in $\sim\frac{2}{3}$), usable in HF/CAD, but **>40% develop long-term toxicity** (thyroid, lung, liver, skin, eye) — second-line in most.
- Class Ia/III agents cause QT prolongation/torsades; **dofetilide (and often sotalol) require in-hospital initiation** with ECG monitoring.
- ▶ **Catheter ablation — pulmonary vein isolation (PVI):** triggers most often arise from PV antra. Now **first-line in selected younger paroxysmal-AF patients** and superior to AADs for maintaining sinus rhythm; $\sim 80\%$ sinus at 1 year after a single procedure for paroxysmal AF (10–30% need repeat). Energy sources: radiofrequency, cryoballoon, and newer **pulsed-field (electroporation) ablation** (myocardium-selective, lower oesophageal/phrenic/PV-stenosis injury). **Complications (2–7%):** tamponade ($\sim 1\%$), stroke (0.5–1%), phrenic nerve palsy, PV stenosis, and the rare but lethal **atrio-oesophageal fistula** ($<0.1\%$).
- ▶ **Surgical/hybrid ablation (Cox-maze):** usually concomitant with valve/CABG surgery; LAA excised.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **ECG of AF:** label *absent P waves, fibrillatory (f) baseline best seen in V1, irregularly irregular R-R intervals, narrow QRS, variable/rapid ventricular rate.*
- ▶ **AF management algorithm:** boxes for *Haemodynamically unstable* → *emergent DC cardioversion*; *Stable* → three arms — *Rate control* (β -blocker / verapamil-diltiazem / digoxin), *Rhythm control* (AADs / PVI ablation), *Stroke prevention* ($\text{CHA}_2\text{DS}_2\text{-VASc}$ → DOAC/warfarin / LAA occlusion); plus a *Risk-factor modification* box (weight loss, BP, OSA, alcohol).

Clinical / Diagnostic significance

- ▶ **Diagnosis:** 12-lead ECG, ambulatory Holter, implantable loop recorder or wearable/smartwatch ECG (for paroxysmal and subclinical AF, including post-cryptogenic-stroke screening — AF detected in up to $\sim 8.9\%$ within 6 months).
- ▶ **Work-up:** echocardiography (LA size, LV function, valve disease, HCM/amyloid), thyroid function, electrolytes, full blood count, renal/liver function (guides DOAC dosing); TEE before cardioversion when indicated.
- ▶ **Pearls:** rate control + uncontrolled rapid AF → reversible **tachycardia-induced cardiomyopathy**; **stiff left atrial syndrome** with long-standing AF; aggressive **risk-factor management** ($\geq 10\%$ weight loss, $\text{BMI} \leq 27$, OSA treatment, alcohol abstinence, BP and glycaemic control) reduces AF burden and improves ablation success.

High-yield exam pointers

- ▶ Commonest sustained arrhythmia; causes ~25% of **ischaemic strokes**; lifetime risk ~25% in 40-year-old men.
- ▶ **Four pillars**: risk-factor modification, rate control, rhythm control, stroke prevention.
- ▶ **CHA₂DS₂-VASc ≥ 1 → anticoagulate** (female sex alone does not count); **HAS-BLED** assesses bleed risk.
- ▶ **DOACs preferred** in nonvalvular AF; **warfarin mandatory** for mechanical valves and rheumatic mitral stenosis.
- ▶ ≥ 48 h AF → **3 weeks OAC before + 4 weeks after** cardioversion, or **TEE-guided** approach (atrial stunning).
- ▶ **Rate target**: strict $<80/\text{min}$, lenient $<110/\text{min}$; **digoxin reserved for HF**.
- ▶ **Reversal**: idarucizumab (dabigatran), andexanet alfa (factor Xa inhibitors).
- ▶ **PVI ablation** first-line in selected paroxysmal AF; **EAST-AFNET 4** supports early rhythm control.
- ▶ Avoid class Ic drugs in CAD/structural heart disease; **dronedarone contraindicated** in decompensated HF.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Atrial Fibrillation” (pathophysiology, classification, CHA₂DS₂-VASc/HAS-BLED, DOAC dosing table, rate/rhythm control, ablation).
- ▶ **Braunwald's Heart Disease, 13e** — “Atrial Fibrillation” (risk-factor modification as fourth pillar, EAST/CABANA trials, rate-control targets, AAD selection by comorbidity).
- ▶ **CMDT 2026** — “Disorders of Cardiac Rhythm” (current anticoagulation thresholds, DOAC table, antiarrhythmic cautions).



Neurology



Acute Disseminated Encephalomyelitis

Asked in: Paper III Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Acute disseminated encephalomyelitis (ADEM) is an acute, typically **monophasic**, immune-mediated inflammatory demyelinating disorder of the CNS that characteristically follows an antecedent viral infection (**post-infectious / parainfectious encephalomyelitis**) or, historically, a vaccination (**post-vaccinal encephalomyelitis**). It is defined clinically by the rapid evolution of a **polyfocal** neurological deficit accompanied by **encephalopathy**,

and pathologically by widely scattered foci of **perivenular** inflammation and demyelination. ADEM is far commoner in children than adults; its hyperacute, haemorrhagic variant is *acute haemorrhagic leukoencephalitis (AHL)* of *Weston Hurst*.

Etiology and triggers

- ▶ **Post-infectious (parainfectious) ADEM** — the great majority of cases; the neurological syndrome typically begins *late* in the viral illness, as the exanthem is fading.
 - **Measles** is the classic and historically commonest antecedent — complicates roughly **1 in 1000** cases (Bradley: ~1 in 400 to 1 in 1000); live measles vaccination has dramatically reduced this worldwide.
 - In developed countries **varicella (chickenpox)** is now the most frequent trigger (**1 in 4000–10,000** cases); chickenpox-associated ADEM is notable for conspicuous **cerebellar** involvement.
 - Other agents: **rubella, mumps, influenza, parainfluenza, Epstein–Barr virus, human herpesvirus-6, HIV, dengue, Zika, herpes simplex/zoster, Mycoplasma pneumoniae, Borrelia, Leptospira, and SARS-CoV-2.**
- ▶ **Post-vaccinal ADEM** — of mainly historical importance: the original “*neuroparalytic accidents*” of the *Pasteur* rabies vaccine (rabbit spinal-cord-derived) and the *Jenner* smallpox vaccine; later reports with pertussis, rubella, diphtheria and the swine-influenza vaccine.
 - **Modern vaccines pose no meaningful risk:** the *Vaccine Safety Datalink* study of 24 vaccines in >9 million individuals (64 million doses) found no excess ADEM risk — the only possible signal was Tdap, estimated at <1 case per million doses.
- ▶ **Idiopathic** — a non-specific upper respiratory illness or no identifiable trigger in a proportion of cases. Rare drug associations: sulfonamides, para-aminosalicylic acid/streptomycin.

Form	Typical antecedent	Note
Parainfectious	Measles, varicella, rubella, mumps, EBV, Mycoplasma, SARS-CoV-2	Commonest; begins as exanthem fades
Post-vaccinal	Rabies (Pasteur), smallpox (Jenner), pertussis	Now of historical importance only
Idiopathic	None / non-specific URI	No identifiable trigger
AHL (Hurst)	Usually preceding URI	Hyperacute, haemorrhagic, often fatal

Pathogenesis and pathology

- ▶ **Mechanism** — a **cross-reactive (molecular-mimicry) autoimmune response** to the infectious agent triggers an inflammatory demyelinating attack on CNS myelin. Autoantibodies to **myelin**

basic protein (MBP) and other myelin antigens are found in the CSF of some patients; cases with serum or CSF antibodies to **myelin oligodendrocyte glycoprotein (MOG)** are now reclassified as **MOGAD** (see below).

- ▶ **Hallmark histology** — *widely scattered foci of perivenular (perivascular) inflammation with surrounding demyelination*, involving **both white and grey matter**; vessel necrosis is frequent and meningeal reaction may be seen. This contrasts with the larger, confluent white-matter plaques of MS.
- ▶ **Acute haemorrhagic leukoencephalitis (AHL / Hurst disease)** — the most explosive form; lesions are **vasculitic and haemorrhagic** with a **necrotising vasculitis of venules and capillaries** and perivascular accumulation of polymorphonuclear cells and red blood cells. Antecedent is usually an upper respiratory infection; course is fulminant and frequently fatal.

Clinical features

- ▶ **Onset** — abrupt, with rapid progression over hours to a few days; peak deficit within days. A **prodrome** of fever, malaise and myalgia may precede the CNS syndrome.
- ▶ **Encephalopathy is the defining feature** — ranging from lethargy/irritability through stupor to coma; its presence (with multifocal signs) is the single most useful clinical discriminator from a first MS attack.
- ▶ **Polyfocal / disseminated signs** reflecting simultaneous cerebral, brainstem, cerebellar and spinal-cord involvement: hemiparesis or quadriparesis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss, ataxia and movement disorders.
- ▶ **Seizures** are common; **meningismus** and headache frequent (fever often reappears as the exanthem fades).
- ▶ **Optic and spinal patterns** — when present, optic neuritis tends to be **bilateral** and any transverse myelopathy **complete** (cf. usually unilateral/partial in MS).
- ▶ **Course and prognosis** — recovery begins within days and resolves over weeks to months; the illness is **monophasic** by definition. Poor prognosis correlates with severity and abruptness of onset; measles-associated ADEM carries a worse outcome than vaccine-associated disease. Adult case-series report **mortality of 5–20%**, with permanent sequelae in many survivors.

Investigations

- ▶ **CSF** — normal/raised opening pressure; **lymphocytic pleocytosis** (generally ≥ 200 cells/ μ L in ~80%), occasionally a mixed polymorphonuclear–lymphocytic picture in the first days; **protein modestly elevated** (0.5–1.5 g/L; 50–150 mg/dL). **Oligoclonal bands (OCB)** are transient and **uncommon** — their persistence favours MS.
- ▶ **MRI (investigation of choice)** — *extensive, large, poorly-demarcated, relatively symmetric* T2/FLAIR hyperintensities in cerebral and cerebellar white matter, brainstem and spinal cord; characteristic involvement of **deep grey matter (thalamus, basal ganglia)** and cortex. A key

feature is that the **great majority of lesions enhance with gadolinium simultaneously** (all of similar/recent age) — consistent with a single monophasic event — and they show partial resolution *without new lesions* on follow-up. (Contrast MS: lesions of differing ages, *Dawson fingers*, T1 black holes.)

- ▶ **Antibody serology** — test serum (and CSF if seronegative) **MOG-IgG** by cell-based assay and **AQP4-IgG** to identify MOGAD/NMOSD; **autoimmune/paraneoplastic encephalitis panel** where relevant.
- ▶ **Diagnostic criteria (paediatric ADEM, IPMSSG)** — a first **polyfocal clinical CNS event** of presumed inflammatory demyelinating cause **plus encephalopathy not explained by fever**, abnormal brain MRI in the acute phase, and **no new clinical or MRI events ≥ 3 months after onset**.

ADEM versus multiple sclerosis versus MOGAD

Feature	ADEM	Multiple sclerosis	MOGAD
Typical age	Children > adults	15–50 yr	Children and adults
Course	Monophasic	Relapsing/progressive	Monophasic or relapsing
Encephalopathy/seizures	Characteristic	Rare	Possible (ADEM-like in children)
Antecedent infection/vaccine	Usual	Not typical	Often
Optic neuritis	Bilateral, transient	Usually unilateral	Bilateral, longitudinally extensive, papillitis
MRI lesions	Large, symmetric, deep grey matter; all enhance together	Ovoid, periventricular, Dawson fingers; lesions of varying age	Fluffy ill-defined lesions; longitudinally extensive cord, conus, “H sign”
CSF OCB	Transient, uncommon	Persistent in majority	Uncommon (~6–13%)
Antibody	MBP (non-specific)	—	MOG-IgG (cell-based assay)

- ▶ **Caveat:** ~30% of adults initially labelled ADEM relapse within 3 years and are reclassified as MS; others prove to be MOGAD, NMOSD or GFAP astrocytopathy — hence **surveillance imaging after recovery is mandatory**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Axial brain MRI (FLAIR) schematic of ADEM** — label: *bilateral, large, poorly-demarcated, relatively symmetric subcortical/deep white-matter hyperintensities; thalamic*

and basal-ganglia (deep grey matter) lesions; brainstem lesion; all lesions enhancing simultaneously with gadolinium. Add a contrasting small panel for MS (periventricular Dawson fingers, lesions of differing ages).

- ▶ **Histology of the perivenular lesion** — label: *central venule; perivascular cuff of lymphocytes/monocytes; surrounding “sleeve” of demyelination with preserved axons; (AHL variant: necrotising vasculitis, perivascular neutrophils and red cells, petechial haemorrhage).*

Clinical / Diagnostic significance

- ▶ **Treatment is empirical (no controlled trials):** first-line is **high-dose IV glucocorticoids** (e.g., IV methylprednisolone) followed by an oral prednisone taper that may need to continue up to 8 weeks to prevent rebound.
- ▶ **Refractory / steroid-unresponsive disease** (no response within a few days): escalate to **plasma exchange (plasmapheresis)** or **IV immunoglobulin**; immunosuppressants such as cyclophosphamide have been used in fulminant cases.
- ▶ **AHL demands aggressive immunotherapy and neuro-critical care** for raised intracranial pressure; prognosis remains poor.
- ▶ **Mandatory exclusions before committing to ADEM:** infective (herpes simplex/viral) encephalitis (treat empirically with **aciclovir** until excluded), bacterial meningoencephalitis, antiphospholipid syndrome, autoimmune/paraneoplastic (limbic) encephalitis, CNS vasculitis, neurosarcoidosis, primary CNS lymphoma and metastatic disease.
- ▶ **Key triage rule:** *simultaneous onset of disseminated signs, meningismus, encephalopathy and seizures favours ADEM over a first MS attack* — but distinction may be impossible acutely in adults, so follow up clinically and radiologically.

High-yield exam pointers

- ▶ **ADEM = monophasic, post-infectious/post-vaccinal, immune-mediated demyelination with encephalopathy + polyfocal deficit.**
- ▶ **Encephalopathy** is the cardinal discriminator from MS; **seizures and meningismus** also favour ADEM.
- ▶ Commonest antecedent historically = **measles** (≈ 1 in 1000); now **varicella** (1 in 4000–10,000), the latter with **cerebellar** signs.
- ▶ **Hallmark pathology = perivenular inflammation + demyelination**, white *and* grey matter.
- ▶ **AHL (Weston Hurst)** = hyperacute, haemorrhagic, necrotising-vasculitic, often fatal variant.
- ▶ **MRI:** large, symmetric, deep-grey-matter lesions that all enhance simultaneously; OCBs transient/uncommon (persistent OCB $\rightarrow$ think MS).

- ▶ Many “ADEM” cases with MOG-IgG are now reclassified as MOGAD; ~30% of adults later prove to be MS — *do surveillance MRI after recovery*.
- ▶ Treatment: **high-dose IV steroids** → **taper (up to 8 weeks)**; PLEX or IVIG if refractory; adult mortality 5–20%.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Neuromyelitis Optica” (chapter covering MOGAD and Acute Disseminated Encephalomyelitis) and “Multiple Sclerosis” (Table: Disorders that can mimic MS).
- ▶ **Bradley & Daroff’s Neurology in Clinical Practice, 8e** — “Multiple Sclerosis and Other Inflammatory Demyelinating Diseases of the CNS” (ADEM, post-vaccinal and parainfectious forms, acute haemorrhagic leukoencephalitis).
- ▶ **CMDT 2026** — “Nervous System Disorders” (demyelinating disease differential; supportive management).
- ▶ *Coverage note:* The corpus covers ADEM well within Harrison’s NMO/MOGAD chapter and Bradley, despite the spec flagging it as thin. The **formal IPMSSG (International Paediatric MS Study Group) consensus ADEM criteria** quoted under Investigations are universally accepted paediatric-neurology consensus but are not stated verbatim in the indexed corpus; all other specifics (epidemiological ratios, CSF/MRI values, mortality, Vaccine Safety Datalink data, treatment) are taken directly from Harrison 22e and Bradley 8e.



Aetiology, pathogenesis and management of Parkinson’s disease

Asked in: Paper III Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Parkinson’s disease (PD) is the second most common age-related neurodegenerative disorder after Alzheimer’s disease, first described by *James Parkinson* (1817). It is a **synucleinopathy** characterised pathologically by degeneration of dopaminergic neurons in the **substantia nigra pars compacta (SNc)**, striatal dopamine depletion, and intraneuronal **α -synuclein** inclusions (*Lewy bodies* and *Lewy neurites*). Clinically it presents with the cardinal motor tetrad of **bradykinesia, rest tremor, rigidity and postural instability**, accompanied by a broad spectrum of non-motor features. Mean age of onset is ~60 years; lifetime risk is ~3% (men) and ~2% (women).

Aetiology

- ▶ **Sporadic / idiopathic** — the majority of cases occur sporadically and are of **unknown cause**; gene mutations are the only proven causes and may be found even in apparently sporadic cases.

- ▶ **Genetic (~15% familial)** — monogenic forms account for ~5% of cases, rising to ~15% when *GBA1* variants are included.
 - *Dominant*: **SNCA** (α -synuclein — first gene linked; even duplication/triplication of wild-type gene causes PD), **LRRK2** (~3% of sporadic cases; *p.G2019S* commonest, founder effect in Ashkenazi Jews & North African Berber Arabs; incomplete penetrance), **VPS35**, **RAB32**.
 - *Recessive (early-onset)*: **PRKN** (*Parkin* — commonest cause of autosomal-recessive juvenile PD, onset <20 yr, dystonia common, dementia rare), **PINK1**, **PARK7/DJ-1**.
 - **GBA1** (glucocerebrosidase) — the **strongest known genetic risk factor**; present in ~10% of PD and ~25% of Ashkenazi PD; associated with faster progression and cognitive decline.
- ▶ **Environmental** — the MPTP story (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, a contaminant of illicit heroin synthesis) produced parkinsonism in Californian addicts in the 1980s, proving an exogenous toxin can selectively kill dopamine neurons. Epidemiological associations (inconsistent): **pesticides, solvents, rural living, farming, well-water**. *Possible protective factors*: caffeine, cigarette smoking, NSAIDs, calcium-channel blockers.
- ▶ **“Double-hit” hypothesis** — interaction of a genetic susceptibility with an environmental toxin; neither alone is sufficient (unproven).
- ▶ **Secondary parkinsonism** — drug-induced (dopamine blockers — neuroleptics, **metoclopramide**; also tetrabenazine, **flunarizine/cinnarizine**, amiodarone, lithium), vascular, tumour, infection, normal-pressure hydrocephalus, trauma, and toxins (carbon monoxide, manganese).

Pathology and pathogenesis

- ▶ **Hallmark pathology** — loss of pigmented dopaminergic SNc neurons (depigmentation of the nigra), reduced striatal dopamine, and **α -synuclein-positive Lewy bodies/neurites**. *Non-dopaminergic* degeneration also affects cholinergic *nucleus basalis of Meynert*, noradrenergic *locus coeruleus*, serotonergic *raphe nuclei*, olfactory and peripheral autonomic systems — explaining the non-motor features.
- ▶ **Braak staging / spread** — Lewy pathology may begin in the peripheral autonomic nervous system, gut, olfactory bulb or **dorsal motor nucleus of the vagus** and ascend in a predictable sequence to the SNc and cortex, giving rise to the **“body-first” vs “brain-first”** concept. Premotor features (constipation, anosmia, REM sleep behaviour disorder, cardiac denervation) may precede motor onset by years to decades.
- ▶ **α -Synuclein “prion-like” hypothesis** — misfolded α -synuclein forms β -sheet-rich toxic oligomers and aggregates that **template** misfolding of native protein and **spread** trans-synaptically (supported by Lewy pathology developing in grafted healthy embryonic neurons, and by the **gut-brain axis** via the vagus).

- ▶ **GBA1-lysosome vicious cycle** — reduced glucocerebrosidase (GCase) activity impairs lysosomal clearance → α -synuclein accumulation; accumulated α -synuclein further inhibits GCase trafficking — a self-amplifying loop also operative in sporadic PD.
- ▶ **Final common pathways of cell death** — oxidative stress, neuroinflammation (microglial activation, HLA-DRB1 association, autoreactive T cells), excitotoxicity, **mitochondrial dysfunction** (complex I defect; *Parkin/PINK1* impair mitophagy), and lysosomal/proteasomal failure converge on a signal-mediated **apoptotic** process (interacting network — Olanow model).

Pathophysiology — basal ganglia circuitry

- ▶ The **striatum** (putamen + caudate) is the input region; **GPI/SNr** are the inhibitory (GABAergic) output regions projecting to thalamus and brainstem. Striatum and output nuclei are linked by the **direct (D1, facilitatory)** and **indirect (D2, inhibitory)** pathways, modulated by SNc dopamine.
- ▶ In PD, **dopamine denervation** → reduced inhibition of the indirect pathway → **increased firing of the STN and GPI** → excessive inhibition of the thalamus → reduced cortical motor activation → **parkinsonism**.
- ▶ This model is the rationale for surgically **lesioning or stimulating the STN/GPI**. Levodopa-induced **dyskinesia** relates not merely to reduced output firing *frequency* but to altered firing *patterns* (pauses, bursts) transmitting “misinformation” to cortex.

Clinical features and diagnosis

- ▶ **Cardinal motor features** — *Bradykinesia* (slowness, decrement); *Rest tremor* (4–6 Hz, “pill-rolling”, asymmetric, re-emergent on posture); *Rigidity* (lead-pipe; **cogwheel** when tremor is superimposed — *Negro’s sign*); *Postural instability* (late).
- ▶ **Other motor** — micrographia, masked facies (*hypomimia*), reduced blinking, hypophonia, drooling, dysphagia, stooped posture, **festinating shuffling gait**, freezing, falls; *Myerson’s sign* (non-fatiguing glabellar tap reflex).
- ▶ **Non-motor** — anosmia, **REM sleep behaviour disorder**, constipation, orthostatic hypotension, urinary/sexual dysfunction, depression/anxiety/apathy, psychosis (visual hallucinations), and cognitive impairment/dementia.
- ▶ **Diagnosis is clinical** — historically “2 of 3” cardinal signs (24% post-mortem error). The **UK Brain Bank Criteria** (asymmetry, rest tremor, good levodopa response) raise accuracy to >90%; the **MDS Clinical Diagnostic Criteria** add supportive criteria, absolute exclusions and red flags, defining *clinically established* and *clinically probable* PD.
- ▶ **Investigations (selective)** — **DAT-SPECT / PET** shows reduced asymmetric striatal uptake (posterior putamen, caudate spared) — useful when diagnosis is uncertain; **α -synuclein seed amplification assay (SAA)** in CSF/skin (high sensitivity/specificity); MRI to exclude

atypical/secondary causes; genetic testing in young-onset/familial cases. **Excellent levodopa response** strongly supports PD.

Differential diagnosis and staging

Category	Examples	Distinguishing clue
Atypical parkinsonism	MSA (MSA-p / MSA-c), PSP, corticobasal syndrome	Early speech/gait, falls, no rest tremor, symmetry, poor levodopa response
MSA	Glial cytoplasmic α -synuclein inclusions	Autonomic failure, cerebellar signs, pontine “hot-cross-bun” sign
PSP	Tauopathy	Vertical gaze palsy, “hummingbird” midbrain sign, retrocollis, early falls
Secondary	Drug-induced, vascular, NPH, toxins	History of neuroleptics; symmetrical; CO/Mn $\rightarrow$ globus pallidus
Other neurodegenerative	Wilson’s disease, Huntington (Westphal), SCA, DLB	Age <40, <i>exclude Wilson’s</i> (treatable)

- **Hoehn & Yahr staging** (severity): I — unilateral; II — bilateral/midline, balance intact; III — impaired righting reflex, mild–moderate disability; IV — severe disability but still walks/stands unaided; V — wheelchair/bedbound unless aided.

Management

- **General principle** — no current therapy is disease-modifying; treatment is **symptomatic and individualised**, using **low doses and polypharmacy** to minimise the levodopa dose and delay motor complications. Exercise, physiotherapy, speech/occupational therapy, education and caregiver support apply throughout.
- **Levodopa** (with peripheral decarboxylase inhibitor **carbidopa** or **benserazide**) — the **gold standard / most effective** drug; 200–1000 mg/day, start $\leq$ 400 mg/day (e.g. Sinemet 25/100 tds). Failure to respond should question the diagnosis. Forms: standard, CR, **Rytary/Crexont** (immediate+extended beads), Stalevo (with entacapone), intestinal gel (Duopa/Duodopa), inhaled (**Inbrija**).
 - *Motor complications* (dose- and duration-related, worse in young/female/severe disease): **wearing-off**, unpredictable **on-off**, **peak-dose (choreiform) dyskinesia**, **diphasic dyskinesia**, delayed-/no-on; behavioural — dopamine dysregulation syndrome, *punding*.
- **Dopamine agonists** — non-ergot **pramipexole**, **ropinirole**, **rotigotine patch** (less dyskinesia; favoured in younger patients); **apomorphine** (SC/sublingual — rescue for “off”). Beware sudden sleep attacks and **impulse-control disorders** (gambling, hypersexuality, shopping).

- ▶ **MAO-B inhibitors** — **selegiline**, **rasagiline** (1 mg/day), **safinamide** — mild monotherapy benefit and adjunctive reduction of “off” time; rasagiline of interest for possible disease-modification (*ADAGIO*, *DATATOP*).
- ▶ **COMT inhibitors** — **entacapone** (with each levodopa dose), **opicapone** (once daily), **tolcapone** (needs LFT monitoring — hepatotoxicity) — prolong “on” time.
- ▶ **A2A antagonist** — **istradefylline** (20–40 mg/day) reduces “off” time.
- ▶ **Amantadine** (NMDA antagonist) — the only oral agent that reduces **dyskinesia** without worsening parkinsonism.
- ▶ **Anticholinergics** — **trihexyphenidyl**, **benztropine** — mainly for **tremor**; avoid in elderly/cognitively impaired.
- ▶ **Advanced disease** — **continuous dopaminergic delivery** (intestinal levodopa-carbidopa gel; SC foslevodopa-foscarbidopa or apomorphine) and **on-demand therapies** (inhaled levodopa, SC/sublingual apomorphine) for refractory fluctuations.
- ▶ **Surgery** — **deep brain stimulation** (DBS) of the STN or GPi for disabling tremor or medically refractory motor complications (reversible, allows bilateral procedures); historical **pallidotomy** / **VIM thalamotomy** (tremor); **MRI-guided focused ultrasound** as a non-incisional alternative. DBS improves dopaminergic features but not non-dopaminergic disability.
- ▶ **Non-motor management** — depression/anxiety (SSRIs/benzodiazepines; pramipexole); psychosis (reduce offending drugs, then low-dose **quetiapine**/**clozapine** or **pimavanserin** — *avoid typical neuroleptics*); dementia (**rivastigmine**); orthostatic hypotension (salt, head-up tilt, **fludrocortisone**, **midodrine**, **droxidopa**); RBD (**clonazepam** 0.5–1 mg / **melatonin**); constipation, urinary and sexual dysfunction addressed symptomatically.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Basal ganglia direct/indirect pathway circuit (normal vs PD)**: label *Cortex*, *Putamen* (*striatum*), *D1* (*direct*) *pathway*, *D2* (*indirect*) *pathway*, *SNc* (*dopamine*), *GPe*, *STN*, *GPi/SNr*, *Thalamus* (*VL*), *PPN* — with arrows showing in PD: ↓dopamine → ↑STN & ↑GPi firing → ↑thalamic inhibition → parkinsonism.
- ▶ **SNc pathology / Lewy body**: label *depigmented substantia nigra*, *melanised dopaminergic neuron*, *α-synuclein-positive Lewy body* (*with halo*), *Lewy neurite*.

Clinical / Diagnostic significance

- ▶ A **brisk, sustained response to levodopa** is both diagnostic and therapeutic; poor response is a *red flag* for atypical/secondary parkinsonism.
- ▶ **Premotor markers** (anosmia, RBD, constipation, DAT/SAA positivity) may permit diagnosis before motor onset — important for future disease-modifying trials.

- ▶ Always **exclude treatable mimics**: drug-induced parkinsonism (stop offending agent) and **Wilson's disease** (copper chelation prevents progression).
- ▶ Striatal dopamine terminal loss may be near-complete within ~4 years of diagnosis — relevant to the timing of any neuroprotective therapy.

High-yield exam pointers

- ▶ **Cardinal tetrad**: bradykinesia + rest tremor (4–6 Hz, pill-rolling) + rigidity (cogwheel) + postural instability; tremor is **asymmetric** at onset.
- ▶ **Pathology**: SNc dopaminergic loss + **α -synuclein** **Lewy bodies**; PD is a **synucleinopathy** (cf. PSP/CBS = tauopathies).
- ▶ **Genetics**: *SNCA* first linked; *LRRK2 G2019S* commonest dominant; *****GBA1* strongest risk factor***; *PRKN** commonest early-onset recessive.
- ▶ **MPTP** → **MPP⁺** = mitochondrial complex I toxin — proof of principle for toxic dopaminergic injury.
- ▶ **Levodopa** = **gold standard**; combine with carbidopa/benserazide; start ≤ 400 mg/day; motor complications are **dose/duration-related**.
- ▶ **Amantadine** = best oral drug for **dyskinesia**; **anticholinergics** for tremor; **DBS of STN/GPi** for refractory fluctuations.
- ▶ **Avoid typical neuroleptics** in PD psychosis — use **quetiapine/clozapine/pimavanserin**.
- ▶ **Hoehn & Yahr** stages I–V; **UK Brain Bank & MDS** diagnostic criteria; **DAT-SPECT** + **α -synuclein SAA** as supportive tests.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Parkinson's Disease” (aetiology, genetics, pathogenesis, basal-ganglia pathophysiology, full pharmacological/surgical management) and “Dementia with Lewy Bodies”.
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Parkinson Disease and Other Movement Disorders” & “Diagnosis and Assessment of Parkinson Disease” (epidemiology, clinical features, **Hoehn & Yahr staging**).
- ▶ **DeJong's The Neurologic Examination** — clinical signs (cogwheel/lead-pipe rigidity, *Negro's* and *Myerson's* signs, micrographia, masked facies).
- ▶ **CMDT 2026** — “Nervous System Disorders / Parkinsonism” (current drug regimens, doses, surgical and supportive management).



Alzheimer's Disease

Asked in: Paper III Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the **most common cause of dementia**, accounting for an estimated **60–70%** of the ~55 million people living with dementia worldwide. It is a clinico-biological entity defined pathologically by extracellular **neuritic (amyloid- β) plaques**, intraneuronal **neurofibrillary tangles (NFTs)** of hyperphosphorylated tau, and neuronal/synaptic loss, classically presenting as an insidious, slowly progressive **amnestic dementia** beginning with loss of episodic memory. Pathology spreads from the medial temporal lobes to temporo-parietal and frontal association cortices, with relative sparing of primary motor and sensory cortex until late.

Epidemiology & Risk Factors

- ▶ **Age** is the dominant risk factor: ~10% of people >65 years have AD — 3% at 65–74, 17% at 75–84, and 32% at ≥ 85 years.
- ▶ **Positive family history** is the second key factor; **autosomal-dominant familial AD (FAD)** accounts for only 1–2% of cases (multigenerational early-onset dementia).
- ▶ **ApoE $\epsilon 4$ allele** — the major genetic risk factor for sporadic/late-onset AD (see Genetics).
- ▶ **Female sex** is an independent risk factor; women carrying a single $\epsilon 4$ allele are more susceptible than male $\epsilon 4$ carriers.
- ▶ Other associations: **traumatic brain injury**, **diabetes** (≈ 3 -fold risk), hypertension, obesity, dyslipidaemia, elevated homocysteine, **hearing loss**, low educational attainment, smoking, physical inactivity, sleep disorders, and air pollution. Vascular disease and stroke lower the threshold for clinical expression of AD.

Clinical Manifestations & Course

- ▶ **Typical (amnestic) AD**: insidious **episodic memory loss** (repeating questions, misplacing items) followed by progressive deficits in **executive, language, and visuospatial** domains.
- ▶ **Disease spectrum (clinical staging)**: *subjective cognitive decline* $\rightarrow$ *mild cognitive impairment (MCI)* / “early symptomatic AD” $\rightarrow$ *dementia*. About **50% of MCI patients progress to dementia over ~4 years** ($\sim 12\%$ /year); the *preclinical* stage (biomarker-positive, asymptomatic) may precede symptoms by ≥ 20 years.
- ▶ **Middle stages**: unable to work, easily lost; progressive aphasia (naming $\rightarrow$ comprehension $\rightarrow$ fluency), **apraxia**, visuospatial failure, acalculia, impaired clock reading; delusions (theft, infidelity, misidentification), wandering, sleep–wake disruption.
- ▶ **Late stages**: rigidity, mutism, incontinence, bedbound state; **myoclonus** and hyperactive reflexes; death usually from aspiration, infection, or malnutrition.
- ▶ **Atypical variants** ($\sim 20\%$ present non-amnestically): **posterior cortical atrophy** (visuospatial, Balint & Gerstmann syndromes), **logopenic progressive aphasia** (impaired naming/repetition

with phonological errors), **dysexecutive/behavioural** (“frontal”) variant, and **corticobasal (akineti-rigid-dystonic)** syndrome.

- Typical symptomatic duration is **8–10 years** (range 1–25). Seizures (focal and generalized) increasingly recognized, especially in young-onset and autosomal-dominant AD.

Pathology & Pathogenesis

- **Macroscopic**: diffuse cortical atrophy, earliest and most severe in the **medial temporal lobe** (entorhinal/perirhinal cortex, hippocampus) and **nucleus basalis of Meynert**; locus coeruleus severely affected, substantia nigra relatively spared.
- **Neuritic plaques**: extracellular core of **amyloid- β (A β)**, a 39–42-amino-acid peptide cleaved from **amyloid precursor protein (APP)** by **β -secretase (BACE)** and **γ -secretase**. The amyloidogenic pathway yields toxic **A β 42**; the non-amyloidogenic α -secretase (ADAM10/17) pathway is non-toxic. Soluble **A β oligomers** are thought to be the early toxic species (amyloid cascade hypothesis).
- **Neurofibrillary tangles**: intraneuronal **paired helical filaments** of hyperphosphorylated **tau**; tau normally stabilizes microtubules, but when hyperphosphorylated it detaches and aggregates, with prion-like templated spread. NFT spread follows **Braak staging** — six stages reducible to three: **transentorhinal (I–II) $\rightarrow$ limbic (III–IV) $\rightarrow$ isocortical (V–VI)**.
- **Amyloid angiopathy**: vascular A β deposition predisposing to microhaemorrhage and lobar haemorrhage.
- **Neurochemistry**: marked **cholinergic deficit** ($\downarrow$ acetylcholine, choline acetyltransferase, nicotinic receptors) from degeneration of the nucleus basalis of Meynert — the basis of the **cholinergic hypothesis** and cholinesterase-inhibitor therapy; also noradrenergic (locus coeruleus) and serotonergic (dorsal raphe) depletion.

Genetics

Gene	Chromosome	Role / Effect
APP	21	Point mutations cause FAD; trisomy 21 (Down syndrome) develops AD pathology after age 40 (extra APP dose)
PSEN-1 (presenilin-1)	14	Commonest FAD cause (40–70%); γ -secretase component; mean onset ~45 yr, rapid course (~6–7 yr)
PSEN-2 (presenilin-2)	1	Rarer FAD (Volga-German kindreds); mean onset ~53 yr, duration ~11 yr

Gene	Chromosome	Role / Effect
ApoE ε4	19	Major risk allele for sporadic/late-onset AD; not a deterministic cause

- ▶ **ApoE**: one ε4 allele raises risk ~2–3-fold; ε4/ε4 homozygotes ~10–15-fold, with each allele advancing onset ~10 years. ε2 is protective. ε4 is *neither necessary nor sufficient*. The **Christchurch ApoE3 mutation** may protect against tau aggregation/dementia despite amyloid.
- ▶ **GWAS / risk modifiers**: >40 common low-effect variants — **CLU, PICALM, CR1** (innate immunity, lipid metabolism, synaptic function); **TREM2** rare but strong (OR ~3–4; homozygous mutation = Nasu-Hakola disease).

Diagnosis & Biomarkers

- ▶ **Clinical**: slowly progressive amnesic dementia, normal systemic labs, and posterior-predominant cortical + hippocampal atrophy. Clinical diagnosis confirmed at autopsy ~70–80% of the time (mimics: LATE, PART, Lewy body disease, vascular, FTLT).
- ▶ **Bedside cognition**: MMSE, MoCA, Mini-Cog (insensitive to MCI). Neuropsychology shows a **encoding/consolidation deficit** (flat learning curve, no benefit from recognition cues) typical of medial temporal involvement.
- ▶ **Structural MRI/CT**: medial temporal (hippocampal/entorhinal) atrophy with temporal-horn dilatation; chiefly to **exclude** NPH, tumour, vascular disease.
- ▶ **FDG-PET**: temporo-parietal **hypometabolism**.
- ▶ **Amyloid PET** ([¹¹C]PIB, [¹⁸F]florbetapir/florbetaben/flutemetamol): confirms plaque load; ~25% of cognitively-normal elderly are positive, so use is restricted to defined scenarios.
- ▶ **Tau PET** ([¹⁸F]flortaucipir): NFT distribution mirroring Braak stages.
- ▶ **CSF**: ↓Aβ42 and ↓Aβ42/Aβ40 ratio, ↑phospho-tau (p-Tau181 / p-Tau217); ↑total tau is non-specific.
- ▶ **Plasma biomarkers** (emerging): p-Tau217, p-Tau181, Aβ42/Aβ40 ratio — scalable, high concordance with amyloid PET/autopsy.
- ▶ **Diagnostic criteria evolution**: 1984 NINCDS-ADRDA (clinicopathological “probable/possible AD”) → 2011 NIA-AA (clinical stages + amyloid/neurodegeneration biomarkers) → 2018 NIA-AA research framework (A/T/N) = biological definition by Amyloid, Tau, Neurodegeneration → 2014 IWG-2 → 2024 Revised Criteria (amyloid PET/CSF/plasma Aβ and p-Tau as “core 1” biomarkers, tau PET “core 2” for staging).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **APP processing pathway**: draw the transmembrane APP spanning the cell membrane; show two branches — *non-amyloidogenic* (α-secretase [ADAM10/17] → sAPPα + P3;

“Non-toxic”) and *amyloidogenic* (β -secretase [BACE] then γ -secretase $\rightarrow$ $A\beta_{40}$ [non-toxic] and $A\beta_{42}$ [toxic]) leading to the **neuritic plaque**. Label: APP, cell membrane, α -secretase, β -secretase, γ -secretase, sAPP α , $A\beta_{40}$, $A\beta_{42}$, amyloid plaque.

- ▶ **AD neuropathology / Braak spread:** a mid-sagittal/coronal brain showing **medial temporal lobe** (hippocampus, entorhinal cortex) and **nucleus basalis of Meynert**; inset of a **neuritic plaque** (central $A\beta$ core + dystrophic neurites) and a **neurofibrillary tangle** (paired helical filaments of hyperphosphorylated tau). Label the Braak sequence: transentorhinal $\rightarrow$ limbic $\rightarrow$ isocortical.

Clinical / Diagnostic significance

- ▶ **Symptomatic (neurotransmitter) therapy:** Cholinesterase inhibitors (first-line) — **donepezil** 5–10 mg OD; **rivastigmine** 1.5 mg BID up to 3–6 mg BID or 9.5 mg/24 h patch; **galantamine** 4 mg BID up to 8–12 mg BID / 24 mg ER. **Memantine** (NMDA-receptor antagonist) 5 mg $\rightarrow$ target 10 mg BID for **moderate–severe** AD, often added when disease advances. Titrate over 4–6 weeks; main side effects GI (nausea, diarrhoea, cramps), bradycardia, vivid dreams.
- ▶ **Disease-modifying anti-amyloid monoclonal antibodies** (early symptomatic, biomarker-confirmed): **Lecanemab** (anti-protofibril) 10 mg/kg IV every 2 weeks — *Clarity-AD* showed 27% **slowing** of CDR-SB decline at 18 months; **Donanemab** (anti-pyroglutamate- $A\beta$) IV monthly — *TRAILBLAZER-ALZ2* showed 22% **slowing on iADRS** / 28% on CDR-SB. **Aducanumab** withdrawn. Key toxicity = **ARIA** (amyloid-related imaging abnormalities): **ARIA-E** (vasogenic oedema, FLAIR) and **ARIA-H** (microhaemorrhage/siderosis, GRE/SWI); risk rises with **ApoE ϵ 4 dose** (FDA box warning for ϵ 4 homozygotes) — genotype before treatment; contraindicated with anticoagulation, extensive CAA, and thrombolysis.
- ▶ **Neuropsychiatric management:** SSRIs (e.g. escitalopram) for depression; **levetiracetam** for seizures; **brexpiprazole** is the only FDA-approved drug for agitation in AD (atypical antipsychotics carry a **black-box mortality warning** in elderly dementia). **Avoid anticholinergics** (diphenhydramine, oxybutynin).
- ▶ **Caregiver support:** memory aids, home-safety, driving cessation, day-care, respite, and education; lifestyle/vascular-risk modification (Mediterranean/DASH diet, exercise, cognitive and social activity).

High-yield exam pointers

- ▶ AD = commonest dementia (60–70%); two pathological hallmarks — **$A\beta$ neuritic plaques + tau NFTs**.
- ▶ **ApoE ϵ 4** = major sporadic risk gene (chr 19); **APP** (21), **PSEN-1** (14, commonest FAD), **PSEN-2** (1) cause autosomal-dominant early-onset FAD.
- ▶ **Down syndrome** invariably develops AD pathology after age 40 (extra APP dose).

- ▶ **Nucleus basalis of Meynert** cholinergic loss → cholinesterase-inhibitor rationale.
- ▶ **Braak staging**: transentorhinal → limbic → isocortical.
- ▶ CSF: ↓Aβ42, ↑p-Tau; plasma p-Tau217 is the emerging blood biomarker; A/T/N = biological framework.
- ▶ First-line drugs = **cholinesterase inhibitors**; add **memantine** in moderate–severe disease.
- ▶ **Lecanemab & donanemab** = first disease-modifying anti-amyloid antibodies; watch for ARIA (highest in ε4 homozygotes).
- ▶ MCI converts to dementia at ~12%/year (~50% over 4 years).
- ▶ Posterior cortical atrophy and logopenic aphasia are atypical AD presentations.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Alzheimer's Disease” (clinical features, pathology, genetics, biomarkers, treatment, ARIA, Clarity-AD/TRAILBLAZER-ALZ2) and “Dementia” (diagnostic approach).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Alzheimer Disease and Other Dementias” (diagnostic-criteria evolution NINCDS-ADRDA → NIA-AA → A/T/N, Braak staging, neuropsychology, atypical variants).
- ▶ **CMDT 2026** — “Nervous System Disorders” (current drug regimens, doses, and anti-amyloid monoclonal-antibody management).



Approach to Coma

Asked in: Paper III Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — *Coma* is a deep sleep-like state of unarousable unresponsiveness, with the eyes closed, from which the patient cannot be roused even by vigorous stimuli. It lies at the severe end of a continuum of impaired alertness (drowsiness → stupor → coma) and is one of the commonest neurological emergencies in internal medicine. Consciousness has two components — **arousal/wakefulness** (brainstem reticular activating system, RAS) and **awareness/content** (cerebral cortex); coma reflects failure of one or both. An *organised, time-critical bedside approach* — simultaneous resuscitation, structured history, and a focused neurological examination to localise the lesion — is essential, because metabolic-toxic causes (far commoner than structural ones) are frequently reversible.

Spectrum of impaired consciousness and coma mimics

State	Arousal	Awareness	Key features
Drowsiness	↓ (easily roused)	Largely intact	Simulates light sleep

State	Arousal	Awareness	Key features
Stupor	Roused only by vigorous/repeated stimuli	Impaired	Withdraws from noxious stimuli
Coma	Absent	Absent	Eyes closed, unarousable
Vegetative state	Present (eyes open, sleep–wake cycles)	Absent	“Awake but unaware”; autonomic/respiratory function retained; <i>persistent</i> if >4 weeks
Minimally conscious state	Present	Inconsistent/minimal	Reproducible command-following, visual tracking; better prognosis than VS
Akinetic mutism / abulia	Awake	Partly preserved	Immobile, mute; medial frontal/medial thalamic damage
Catatonia	Variable	Preserved	Psychiatric; waxy flexibility, responds to <i>lorazepam</i>
Locked-in syndrome	Awake	Fully preserved	Ventral pontine lesion (basilar thrombosis); quadriplegic, anarthric, but vertical gaze + lid elevation retained , pupils reactive

- ▶ These mimics must be distinguished from true coma at the bedside; asking the patient to look up/down and blink unmasks the *locked-in state*, and *catatonia* may reverse transiently with IV lorazepam.

Anatomical–physiological basis and causes

- ▶ Coma arises from either (1) **widespread bilateral cerebral hemispheric dysfunction** or (2) **failure of the brainstem–thalamic RAS** (upper pons, midbrain, thalamus). A unilateral hemispheric mass causes coma only by compressing the brainstem.
- ▶ Neurons depend on continuous cerebral blood flow: **glucose stores last ~2 min and oxygen stores only 8–10 s** after circulatory arrest — hence the urgency.
- ▶ **Three diagnostic categories (Harrison):**
- ▶ **No focal/lateralising signs (CT often normal)** — intoxications (alcohol, sedatives, opioids), metabolic (hypo-/hyperglycaemia, hypoxia, hyponatraemia, uraemia, hepatic coma, hypercapnia, hypercalcaemia, Addisonian/myxoedema crisis), severe systemic infection/sepsis, status/non-

convulsive status epilepticus and post-ictal states, hypertensive encephalopathy/eclampsia/PRES, severe hypo-/hyperthermia.

- ▶ **Focal brainstem or lateralising signs (CT usually abnormal)** — intracerebral (basal ganglionic, thalamic, cerebellar, pontine) haemorrhage, large MCA infarct with mass effect, basilar artery thrombosis, abscess, tumour with oedema, subdural/epidural haematoma.
- ▶ **Meningeal syndromes (fever/stiff neck, CSF pleocytosis)** — bacterial meningitis/meningoencephalitis, subarachnoid haemorrhage, autoimmune/paraneoplastic encephalitis.
- ▶ **Threshold values** worth recalling: serum Na^+ <125 mmol/L $\rightarrow$ confusion, <119 mmol/L (acute) $\rightarrow$ coma/convulsions; hyperosmolar coma when osmolality >350 mosmol/L; coma from hypothermia when core $<31^\circ\text{C}$.

Herniation syndromes (structural deterioration)

- ▶ **Uncal (lateral) transtentorial** — medial temporal uncus impacts CN III $\rightarrow$ *ipsilateral fixed dilated pupil* (earliest sign; peripheral parasympathetic fibres affected first), then contralateral hemiparesis; compression of the opposite peduncle gives ipsilateral hemiparesis = ***Kernohan-Woltman notch sign*** (a false-localising sign).
- ▶ **Central transtentorial** — symmetric downward thalamic displacement; heralded by *small pupils and drowsiness*, with orderly rostro-caudal (midbrain $\rightarrow$ pons $\rightarrow$ medulla) deterioration.
- ▶ **Transfalcine (subfalcine/cingulate)** — cingulate gyrus under the falx.
- ▶ **Foraminal (tonsillar)** — cerebellar tonsils into foramen magnum $\rightarrow$ early medullary compression, apnoea, sudden death.

Step 1 — Resuscitation, history and general examination

- ▶ **Airway–Breathing–Circulation first:** protect airway/intubate if GCS ≤ 8 , apnoea, or aspiration risk; support BP; immobilise the cervical spine if trauma is possible.
- ▶ **“Coma cocktail” without delay (CMDT):** **thiamine 100 mg IV** (before glucose, to avert Wernicke’s), then **dextrose 50% 25 g IV**, and **naloxone 0.4–1.2 mg IV** for possible opioid overdose; check a bedside capillary glucose immediately.
- ▶ **History (collateral)** from family/paramedics: rapidity of onset (abrupt $\rightarrow$ SAH, brainstem stroke, ICH; gradual $\rightarrow$ mass/metabolic), antecedent headache/fever/seizures/trauma, drug/alcohol use, and chronic liver/renal/cardiac/lung disease.
- ▶ **General examination:** vital signs, fundoscopy (papilloedema, subhyaloid haemorrhage of SAH), nuchal rigidity, skin (petechiae $\rightarrow$ meningococcaemia/TTP; cherry-red $\rightarrow$ CO), breath (fetus hepaticus, ketones), and a trauma survey. *Fever* $\rightarrow$ infection/heatstroke/NMS; *hypothermia* $\rightarrow$ sedative/alcohol/myxoedema; **hypertension + bradycardia + irregular respiration = Cushing response of raised ICP.**

Step 2 — Neurological examination: grading and localisation

A. Depth of coma — scoring scales

Glasgow Coma Scale	Best response	Score
Eye opening (E)	Spontaneous / To speech / To pain / Nil	4 / 3 / 2 / 1
Verbal (V)	Oriented / Confused / Inappropriate words / Incomprehensible sounds / Nil	5 / 4 / 3 / 2 / 1
Motor (M)	Obeys / Localises / Withdraws / Abnormal flexion / Extension / Nil	6 / 5 / 4 / 3 / 2 / 1

- ▶ GCS ranges 3–15; validated chiefly for *traumatic* coma. Limitation: cannot score V in intubated patients and omits brainstem reflexes — hence the **FOUR score** (*Full Outline of UnResponsiveness*; Wijdicks), which grades **Eye, Motor, Brainstem reflexes** (pupillary, corneal, cough) and **Respiration** (each 0–4, total 0–16) and is usable in the intubated patient.

B. Brainstem reflexes (localise the level — see Fig. 30-3 analogue):

- ▶ **Pupils** — reactive midsize (2.5–5 mm) excludes upper-midbrain damage; **unilateral fixed dilated** >6 mm = CN III/uncal compression; **bilateral fixed midposition** = midbrain; **pinpoint** (<1 mm) **reactive** = pontine haemorrhage *or* opioids (give naloxone); **small reactive** (1–2.5 mm) = metabolic/diencephalic. Pupillary reactivity is typically *preserved in metabolic coma* — a key discriminator.
- ▶ **Ocular position/movement** — “the eyes look toward a hemispherical lesion and away from a brainstem lesion”; roving conjugate movements exclude brainstem damage; **ocular bobbing** = bilateral pontine lesion (basilar thrombosis); **ocular dipping** = diffuse anoxic cortical damage.
- ▶ **Oculocephalic** (“doll’s eye”) — turn the head (only after excluding cervical injury); intact brainstem → eyes move opposite to head turn. **Oculovestibular** (**cold caloric**) — irrigate the canal with ice water → tonic deviation *toward* the cold ear; mnemonic **COWS** (Cold-Opposite, Warm-Same, naming the fast phase). Both are preserved in metabolic coma and lost with structural brainstem damage.
- ▶ **Corneal reflex** — afferent CN V, efferent CN VII; tests pontine integrity.

C. Respiratory patterns (localising value, see Fig. 5.1 analogue):

- ▶ **Cheyne-Stokes** (cyclical crescendo–decrescendo with apnoea) → bihemispheric/diencephalic or metabolic; **central neurogenic hyperventilation** → upper pontine/midbrain tegmentum; **apneustic** (inspiratory pause) → mid/caudal pons; **cluster/ataxic** (*Biot*) → medulla (pre-terminal); **Kussmaul** (deep regular) → metabolic acidosis.

D. Motor responses & posturing:

- ▶ **Decorticate** posturing (flexion of elbows/wrists, supination; legs extended) → lesion *rostral to the midbrain*; **decerebrate** posturing (extension/pronation of arms, leg extension) → lesion in/caudal to the *midbrain–upper pons*. Purposeful withdrawal implies intact corticospinal tracts; *multifocal myoclonus and asterixis* suggest a metabolic cause.

Step 3 — Investigations

- ▶ **Bedside/blood**: capillary then lab glucose, electrolytes, calcium, magnesium, osmolality, renal and hepatic function (with NH_3), ABG, full blood count, **toxicology screen**, cultures if febrile.
- ▶ **Imaging**: urgent **non-contrast CT head** for haemorrhage/herniation/hydrocephalus; add CT/MR **angiography** if posterior-circulation/basilar occlusion is suspected. A normal CT does not exclude early infarction, encephalitis, diffuse axonal injury, or isodense subdural.
- ▶ **EEG**: essential to detect **non-convulsive status epilepticus**; shows triphasic/ δ slowing in metabolic coma, “alpha coma” (poor prognosis), and *extreme delta brush* in anti-NMDA-receptor encephalitis.
- ▶ **Lumbar puncture** (after CT excludes a mass): mandatory when meningitis/encephalitis or CT-negative SAH is suspected — give blood cultures + empirical antibiotics *first* if meningitis is likely.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Brainstem-reflex localisation diagram (Harrison Fig. 30-3 style)**: sagittal brainstem with labels — *Midbrain (CN III / pupillary light reflex)*, *Pons (CN V–CN VII corneal reflex; MLF; reflex conjugate eye movements; CN VI, VIII)*, *Medulla (respiratory neurons; gag/cough)*; arrows for *oculocephalic* and *oculovestibular (caloric)* pathways.
- ▶ **Pupils-in-coma chart (Plum & Posner style)**: label each — *Metabolic = small reactive*, *Diencephalic = small reactive*, *Tectal = large “fixed”*, *hippus*, *CN III/uncal = dilated fixed*, *Pontine = pinpoint*, *Midbrain (nuclear) = midposition fixed*.

Clinical / Diagnostic significance

- ▶ The pattern of pupils + eye movements + respiration + posturing **localises** the lesion to hemisphere vs diencephalon vs midbrain vs pons vs medulla and distinguishes *structural* from *metabolic* coma (preserved pupillary and reflex eye movements favour metabolic).
- ▶ **Brain death** = irreversible cessation of all cerebral and brainstem function: prerequisites — established irreversible cause, exclusion of confounders (hypothermia $<32\text{--}35^\circ\text{C}$, sedatives/paralytics, severe metabolic/endocrine derangement); findings — deep coma, **absent pupillary, corneal, oculocephalic, oculovestibular, cough/gag reflexes**, and a **positive apnoea test** (no respiratory effort with $\text{PaCO}_2 \geq 60$ mmHg or a ≥ 20 mmHg rise above baseline, pH <7.30). Spinal reflexes may persist. Ancillary tests (cerebral angiography/radionuclide flow study) used when clinical testing is incomplete.

- **Prognosis:** metabolic coma fares far better than anoxic/traumatic coma. After cardiac arrest, *bilaterally absent pupillary light reflexes at 24 h*, and *absent corneal reflexes / absent–extensor motor responses and bilaterally absent SSEP cortical responses at 72 h*, predict poor outcome — but therapeutic hypothermia delays reliable prognostication, mandating *multimodal* assessment.

High-yield exam pointers

- Consciousness = **arousal (RAS) + awareness (cortex)**; coma needs bilateral hemispheric or brainstem RAS failure.
- **Metabolic > structural** as a cause; *reactive pupils + intact reflex eye movements* point to metabolic coma.
- **First-line drugs:** thiamine → dextrose → naloxone; intubate if GCS ≤8.
- **Uncal herniation** → ipsilateral blown pupil first; **Kernohan-Woltman** = false-localising ipsilateral hemiparesis.
- **GCS 3–15** (E4 V5 M6); **FOUR score** adds brainstem reflexes + respiration and works in intubated patients.
- **COWS** for cold-caloric fast phase; **ocular bobbing** = pons, **dipping** = anoxic cortex.
- **Decorticate** = above midbrain; **decerebrate** = midbrain/pons (worse).
- **Cushing response** (hypertension + bradycardia + irregular breathing) signals raised ICP/impending herniation.
- Always do EEG in unexplained coma to exclude **non-convulsive status epilepticus**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — “Coma” (Josephson, Ropper, Hauser): definitions, RAS physiology, herniation syndromes, brainstem-reflex examination, differential diagnosis (Table 30-1), brain death and prognosis.
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Stupor and Coma”: Glasgow Coma Scale (Table 5.6) and FOUR score, pupillary pathways/Plum-Posner pupil chart, respiratory-pattern localisation, oculocephalic/caloric tables, posturing.
- **CMDT 2026** — “Nervous System Disorders / Coma & Stupor”: emergency workup, coma cocktail doses, rostro-caudal deterioration, brain-death apnoea-test thresholds, vegetative/minimally conscious states (amantadine).



Autosomal Recessive Ataxias

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — The **autosomal recessive cerebellar ataxias (ARCAs)** are a clinically and genetically heterogeneous group of inherited disorders in which degeneration of the **cerebellum and its**

afferent/efferent pathways (spinocerebellar tracts, dorsal columns, dorsal root ganglia, peripheral nerves) produces progressive gait and limb incoordination, dysarthria and oculomotor disturbance, typically with **onset in childhood, adolescence or early adulthood**. ARCA's characteristically affect siblings while parents are asymptomatic heterozygous carriers, and they are frequently accompanied by non-cerebellar neurological and systemic features (neuropathy, pyramidal signs, cardiomyopathy, telangiectasia, skeletal deformity). With whole-exome/whole-genome sequencing the number of recognised ARCA's now exceeds **90**, but *Friedreich's ataxia* remains by far the commonest, accounting for about half of all hereditary ataxias.

Classification — a mechanism-based scheme

A genomic/pathway classification has largely superseded the older purely clinical one. ARCA's are usefully grouped by the **biological pathway disrupted** (Synofzik), which also predicts the diagnostic biomarker and potential therapy:

Pathogenic pathway	Representative ARCA's (gene → protein)	Diagnostic biomarker / clue
Mitochondrial dysfunction	Friedreich ataxia (<i>FXN</i> → frataxin); ARSACS (<i>SACS</i> → saccin); SPG7 (<i>SPG7</i> → paraplegin); POLG/ataxia-neuropathy spectrum (<i>POLG1</i>); AVED (<i>TTPA</i> → α-tocopherol transfer protein)	Low serum vitamin E (AVED)
Defective DNA repair	Ataxia-telangiectasia (<i>ATM</i>); ataxia-telangiectasia-like disorder (<i>MRE11</i>); AOA1 (<i>APTX</i> → aprataxin); AOA2 (<i>SETX</i> → senataxin)	↑α-fetoprotein (AT, ATLD, AOA2); ↓albumin + ↑cholesterol (AOA1)
Complex lipid metabolism	Abetalipoproteinaemia (<i>MTTP</i>); Niemann-Pick type C (<i>NPC1/NPC2</i>); cerebrotendinous xanthomatosis (<i>CYP27A1</i>)	↑plasma cholestanol (CTX); oxysterols/bile acids (NPC)
Cytoskeletal / structural & repeat-expansion	SYNE1 ataxia (<i>SYNE1</i> → nesprin-1); RFC1-related CANVAS (biallelic AAGGG intronic expansion)	Cerebellar atrophy + sensory neuropathy (CANVAS)

After *Friedreich's ataxia* and *RFC1/CANVAS*, the next commonest ARCA's are *SPG7*, *ARSACS*, *AOA2*, *SYNE1*, *ataxia-telangiectasia*, *AOA1* and *POLG-ataxia* (each ≥2%).

Friedreich's Ataxia (FRDA) — the prototype ARCA

Clinical features

- ▶ Presents **before 25 years of age** with progressive staggering gait, frequent falls and *titubation*; the **lower limbs are more severely affected** than the upper.
- ▶ Examination: **nystagmus**, **loss of fast saccades**, **dysarthria**, **dysmetria**, **truncal/limb ataxia**; **areflexia** (absent ankle and knee jerks) with **extensor plantar responses** (the classic combination of areflexia + Babinski sign in a young patient); **loss of vibration and joint-position sense** (large-fibre sensory/spinocerebellar involvement); distal weakness.
- ▶ **Systemic: hypertrophic cardiomyopathy in ~90%** (cardiomegaly, symmetrical hypertrophy, conduction defects/arrhythmias — the **commonest cause of death**); **diabetes mellitus in ~20%** (insulin resistance + β -cell dysfunction); skeletal deformities — **pes cavus**, **pes equinovarus** and **scoliosis**; optic atrophy and sensorineural deafness may occur. Median age at death ~35 years; women have a better prognosis than men.

Genetics & pathogenesis

- ▶ The **only known autosomal recessive trinucleotide-repeat disease**, caused by an unstable ***GAA triplet-repeat expansion in intron 1 of the FXN (*frataxin*) gene on chromosome 9 (9q13–q21.1)***.
- ▶ **>95% are homozygous** for the GAA expansion; normal alleles carry **7–22 repeats**, patients **200–900 repeats** — *larger repeats correlate with earlier onset and greater severity*. **Compound heterozygotes** (one GAA expansion + one point mutation) give atypical/milder phenotypes (e.g. late-onset FRDA, FRDA with retained reflexes).
- ▶ **Frataxin is a mitochondrial protein of iron homeostasis**; its deficiency causes **mitochondrial iron accumulation**, **loss of iron-sulphur (Fe-S) cluster enzymes**, **reduced ATP production** and **oxidative cell injury**, with iron deposition in the heart.

Pathology: degeneration of **dorsal root ganglia**, **dorsal (posterior) columns**, **dorsal/ventral spinocerebellar tracts**, **lateral corticospinal tracts** and **the dentate nucleus**; MRI shows **spinal cord atrophy** (cerebellar atrophy is relatively mild).

Other important autosomal recessive ataxias

- ▶ **Ataxia-telangiectasia (AT):** first decade; cerebellar ataxia with **oculocutaneous telangiectasia (conjunctival)**, oculomotor apraxia, choreoathetosis, myoclonus; **recurrent sinopulmonary infections**, **IgA/IgG2 immunodeficiency**, marked **radiosensitivity** and high risk of **lymphoma**, **leukaemia** and **breast cancer**. **ATM gene (11q22–23)** encodes a PI3-kinase-like serine/threonine kinase activated by DNA double-strand breaks. Markers: **elevated α -fetoprotein** and immunoglobulin deficiency.
- ▶ **Ataxia with vitamin E deficiency (AVED):** **TTPA** mutation (α -tocopherol transfer protein); juvenile onset, **phenotype mimics Friedreich's** (ataxia, proprioceptive loss, areflexia, Babinski) with **low serum vitamin E but normal lipoproteins** — *treatable with vitamin E*.
- ▶ **Abetalipoproteinaemia (Bassen-Kornzweig syndrome):** **MTTP** (microsomal triglyceride transfer protein) defect impairing VLDL formation $\rightarrow$ fat-soluble vitamin (E) malabsorption;

spinocerebellar degeneration with **acanthocytosis**, **retinitis pigmentosa**, **steatorrhoea** — responds to high-dose vitamin E.

- ▶ **ARSACS** (autosomal recessive spastic ataxia of Charlevoix-Saguenay, *SACS/sacsin*; Québec founder effect): triad of **cerebellar ataxia + lower-limb spasticity + sensorimotor neuropathy**; MRI shows **pontine T2-hypointense stripes and thickened middle cerebellar peduncles**.
- ▶ **RFC1-related CANVAS**: late-onset; Cerebellar Ataxia + Neuropathy (sensory neuronopathy) + Vestibular Areflexia Syndrome, frequently preceded by a **chronic dry cough** and autonomic features; biallelic intronic AAGGG expansion.
- ▶ ***AOA1** (*APTX/aprataxin*) — *ataxia + oculomotor apraxia + neuropathy with hypoalbuminaemia and hypercholesterolaemia*; **AOA2** (*SETX/senataxin*) — *similar, with raised α -fetoprotein**.
- ▶ ***Cerebrotendinous xanthomatosis** (*CTX, CYP27A1*): *ataxia, dementia, epilepsy, neuropathy with tendon xanthomas and juvenile cataracts; raised plasma cholestanol** — treatable with chenodeoxycholic acid.
- ▶ ***Niemann-Pick type C** (*NPC1/NPC2*): *ataxia with vertical supranuclear gaze palsy, organomegaly and psychiatric features; miglustat slows progression*. **POLG***-related ataxia-neuropathy spectrum (**MIRAS/SANDO**) — ataxia, neuropathy, seizures, ophthalmoplegia.

Diagnostic approach & biomarkers

- ▶ **Pattern recognition**: age at onset, family tree (affected siblings, consanguinity), and the *spinocerebellar/sensory* versus *pure cerebellar* phenotype.
- ▶ **Targeted serum biomarkers** (cheap, high-yield first-line): **vitamin E** (AVED, abetalipoproteinaemia), **α -fetoprotein** (AT, AOA2), **albumin + cholesterol** (AOA1), **plasma cholestanol** (CTX), **lipoprotein electrophoresis/blood film for acanthocytes** (abetalipoproteinaemia), lactate (mitochondrial).
- ▶ **Genetic testing**: repeat-primed PCR for *FXN* GAA and *RFC1* AAGGG expansions first; then a **recessive-ataxia NGS panel / WES** if negative.
- ▶ **Ancillary**: nerve conduction (absent sensory action potentials with near-normal motor velocities in FRDA), MRI brain/spine (spinal-cord atrophy in FRDA; cerebellar atrophy in others), ECG/echocardiography (FRDA cardiomyopathy), audiometry, OGTT.

Treatment

- ▶ **Identify the treatable ARCA**s — *vitamin E* for AVED/abetalipoproteinaemia, *chenodeoxycholic acid* for CTX, *miglustat* for Niemann-Pick C, *coenzyme Q10* for CoQ10-deficient ataxia; correct B1/B12/thyroid deficiencies that mimic inherited ataxia.
- ▶ **Friedreich's ataxia**: **omaveloxolone**, an NRF2 agonist, is the **first and only FDA-approved drug** (patients ≥ 16 years), improving function in randomised trials by targeting mitochondrial energy failure. **Iron chelators and antioxidants are potentially harmful** (may aggravate myocardial

injury). Otherwise supportive — physiotherapy, surveillance and management of cardiomyopathy, diabetes and scoliosis.

- ▶ **Ataxia-telangiectasia:** immunoglobulin (IVIG) replacement for immunodeficiency, infection control, avoidance of unnecessary ionising radiation, malignancy surveillance; glucocorticoids may transiently improve neurological function.
- ▶ **Genetic counselling** (1-in-4 recurrence risk, carrier testing, prenatal diagnosis) is integral to management.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Spinal-cord cross-section in Friedreich's ataxia** — label and shade the degenerating tracts: *dorsal (posterior) columns (gracilis & cuneatus), dorsal and ventral spinocerebellar tracts, lateral corticospinal tracts*, with *dorsal root ganglion* and *Clarke's column* marked as primary sites of neuronal loss; show *dentate nucleus* of the cerebellum.
- ▶ **Classification tree of inherited ataxias** — branches: *Autosomal dominant (SCAs, DRPLA, episodic ataxia)* | *Autosomal recessive (Friedreich's, AVED, abetalipoproteinaemia, AT, ARSACS, AOA1/2, CANVAS, CTX, NPC)* | *X-linked (FXTAS)* | *Mitochondrial*, with the recessive branch sub-grouped into **mitochondrial / DNA-repair / lipid-metabolism** pathways.

Clinical / Diagnostic significance

- ▶ The triad of a young patient with **areflexia, extensor plantar responses and loss of position/vibration sense** should trigger an FXN GAA test — FRDA is the single commonest inherited ataxia worldwide.
- ▶ **Cardiomyopathy drives mortality in FRDA**, so every patient needs ECG/echo surveillance — a neurological diagnosis with a cardiological endpoint.
- ▶ Recognising the **treatable mimics** (AVED, abetalipoproteinaemia, CTX, NPC, CoQ10 deficiency) is the highest-value clinical act, since timely metabolic therapy can arrest progression.
- ▶ **α-fetoprotein and cholestanol** are simple serum tests that rapidly narrow a wide genetic differential before expensive sequencing.

High-yield exam pointers

- ▶ Friedreich's ataxia = **commonest hereditary ataxia (~50%)**; *FXN/frataxin*, chromosome 9, GAA intron-1 expansion, only AR trinucleotide-repeat disease; normal 7–22, disease 200–900 repeats; **frataxin = mitochondrial iron-handling/Fe-S protein**.
- ▶ FRDA signs: **areflexia + Babinski + impaired proprioception**, pes cavus, scoliosis, **hypertrophic cardiomyopathy (90%, top cause of death)**, diabetes (20%).
- ▶ **Omaveloxolone (NRF2 agonist)** — only FDA-approved FRDA drug (≥16 yr); **avoid iron chelators/antioxidants**.

- ▶ **Ataxia-telangiectasia:** *ATM* gene, ↑AFP, immunodeficiency, radiosensitivity, malignancy (lymphoma/leukaemia).
- ▶ ***AVED** (TTPA) and **abetalipoproteinaemia** (MTTP) are treatable with vitamin E; *abetalipoproteinaemia* shows *acanthocytes + retinitis pigmentosa*.*
- ▶ **CANVAS** = RFC1 AAGGG expansion; ataxia + sensory neuronopathy + vestibular areflexia + chronic cough.
- ▶ Biomarker shortcuts: ↑AFP → AT/AOA2; ↓albumin+↑cholesterol → AOA1; ↑cholestanol → CTX; ↓vitamin E → AVED/abetalipoproteinaemia.
- ▶ **ARSACS** triad = **ataxia + spasticity + neuropathy** (Charlevoix-Saguenay, SACS/sacsin).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Ataxic Disorders” (Autosomal Recessive Ataxias: Friedreich's ataxia, RFC1-CANVAS, ataxia-telangiectasia; treatment incl. omaveloxolone).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Cerebellar Ataxia” (ARCA classification Table 23.7 by pathogenic pathway — mitochondrial/DNA-repair/lipid; gene-protein-biomarker correlations; ARSACS, AOA1/2, CTX, NPC, POLG, AVED).
- ▶ **CMDT 2026** — “Nervous System Disorders” (Friedreich ataxia clinical/genetic summary and omaveloxolone) and vitamin E deficiency.



Benign Intracranial hypertension

Asked in: Paper III Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Benign intracranial hypertension*, now preferentially termed **idiopathic intracranial hypertension (IIH)** or *pseudotumor cerebri*, is a syndrome of raised intracranial pressure (ICP) — manifesting with headache and papilledema — occurring in the **absence of an intracranial mass, hydrocephalus, venous sinus thrombosis or abnormal CSF constituents**. The label “benign” is a misnomer because untreated disease causes **progressive optic atrophy and irreversible blindness**; “idiopathic” is preferred. Diagnosis is one of *exclusion* and rests on the modified Dandy (Friedman) criteria, with the cardinal goal of therapy being preservation of vision.

Terminology & epidemiology

- ▶ **Historical names:** *otitic hydrocephalus* (papilledema with otitis media), *pseudotumor cerebri* (pneumoencephalography era), *benign intracranial hypertension* — all unsatisfactory; **IIH** is the current descriptive term, though “pseudotumor cerebri” persists for the *secondary* causes.

- ▶ Overwhelmingly a disease of **obese young women of childbearing age**. In the landmark **Idiopathic Intracranial Hypertension Treatment Trial (IIHTT)** the mean age was **29 years**, **97.6% were women**, and mean BMI **39.9 kg/m²**.
- ▶ Associations: obesity, recent weight gain, menstrual irregularity; with modern imaging IIH is now the **commonest cause of papilledema** in the developed world.

Pathophysiology

- ▶ The fundamental abnormality is **raised CSF pressure** with otherwise normal brain parenchyma and ventricles.
- ▶ **Venous outflow / venous sinus stenosis hypothesis** (dominant current model): bilateral distal **transverse sinus stenoses** (or stenosis of a dominant transverse sinus) → reduced cerebral venous drainage → **cerebral venous hypertension** → impaired passive CSF resorption at arachnoid granulations → rising CSF pressure → external compression of the transverse sinus → a self-perpetuating *vicious cycle*. Whether the stenosis is cause or consequence remains debated (stenoses also occur in normals).
- ▶ Elevated venous pressure has been documented in the superior sagittal and proximal transverse sinuses; raised right-atrial filling pressure can be transmitted to the sinuses.
- ▶ A contribution from cerebral interstitial **white-matter (brain) edema** has been proposed on MRI diffusion studies but remains *without consensus*.

Clinical features

- ▶ **Headache** — most frequent presenting symptom (~84% in IIHTT); often worse on straining/coughing, may wake the patient in the early morning; phenotype is **migraine-like in ~52%** and **tension-type in ~22%**.
- ▶ **Transient visual obscurations (TVOs)** — brief (seconds) mono- or binocular greying/blacking of vision, precipitated by postural change or Valsalva; reflect transient hypoperfusion of the swollen optic nerve head (~68%).
- ▶ **Pulse-synchronous (pulsatile) tinnitus** (~52%) and **back pain** (~53%).
- ▶ **Diplopia** from **unilateral or bilateral sixth (abducens) nerve palsy** — a classic *false localizing sign* (the long intracranial course/Dorello's canal makes CN VI vulnerable to pressure).
- ▶ **Visual loss** — only ~32% report it at onset, but it is the *feared* outcome; vision is typically preserved until late, when chronic papilledema encroaches on the macula. Visual fields show an **enlarged blind spot**, then nasal/sector scotomas.
- ▶ **Papilledema** is the cardinal sign; the patient otherwise looks well with a normal neurological exam (except CN VI).

Diagnostic criteria (modified Dandy / Friedman 2013)

Criterion	Requirement for IIH
A. Papilledema	Present
B. Neurological exam	Normal except cranial nerve VI palsy
C. Neuroimaging	Normal brain parenchyma; venous sinus thrombosis excluded
D. CSF constituents	Normal (normal/low protein, normal glucose, no cells)
E. Opening pressure	Elevated LP pressure >250 mm CSF (>25 cm) in adults

- ▶ **IIH without papilledema (IIHWOP):** criteria B–E **plus** a unilateral/bilateral sixth-nerve palsy.
- ▶ Normal CSF opening pressure upper limit is ~180–200 mm H₂O; in IIH it usually exceeds 200 and may reach >500 mm. **Measure in the lateral decubitus position** with legs extended and neck straight — *sitting and prone (fluoroscopy) readings overestimate and are invalid.*

Investigations & differentiation

- ▶ **MRI brain with contrast + MR venography (MRV)** are *mandatory before LP* to exclude a mass, hydrocephalus, and **cerebral venous sinus thrombosis (CVST)** — the key IIH mimic. Supportive (non-specific) MRI signs: **empty sella, posterior scleral flattening, optic nerve sheath distension, vertical tortuosity of the optic nerve, optic nerve head enhancement, and transverse sinus stenosis.**
- ▶ **Lumbar puncture** with manometry confirms raised opening pressure and documents normal CSF; CSF removal transiently relieves headache and obscurations.
- ▶ **Papilledema vs papillitis:** in *papilledema* (raised ICP) acuity is preserved early and pupillary reactions are normal; in *papillitis* (optic neuritis) central vision is lost early with a relative afferent pupillary defect. Distinguish true papilledema from **pseudopapilledema** (optic disc drusen) — an ophthalmologist should confirm.
- ▶ **Formal perimetry (visual fields)** and serial funduscopy/OCT monitor the threat to vision.

Secondary “pseudotumor cerebri” — causes to exclude

- ▶ **Cerebral venous abnormalities:** venous sinus / bilateral jugular thrombosis or ligation, middle-ear/mastoid infection, raised right-heart pressure, SVC syndrome, AV fistula, hypercoagulable states.
- ▶ **Drugs/exposures:** tetracyclines (tetracycline, **minocycline, doxycycline**), nalidixic acid, sulfonamides/cotrimoxazole, nitrofurantoin; **vitamin A excess / retinoids (isotretinoin, all-trans retinoic acid)**; growth hormone, thyroxine (children), levonorgestrel, anabolic steroids; **withdrawal from chronic corticosteroids; lithium.**

- ▶ **Medical conditions:** Addison disease, hypoparathyroidism, hypothyroidism, hypercapnia, obstructive sleep apnea / **Pickwickian syndrome**, anemia, renal failure/uremia, Turner and Down syndromes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Fundus in papilledema (label):** hyperemic *elevated* optic disc, **blurred/obliterated disc margins**, filled-in physiologic cup, **engorged tortuous retinal veins**, **peripapillary flame-shaped hemorrhages**, **cotton-wool spots** (NFL infarcts), loss of spontaneous venous pulsations; chronic stage “*champagne-cork*” disc; end-stage secondary optic atrophy.
- ▶ **Pathophysiology loop (label):** transverse sinus stenosis → ↓venous outflow → cerebral venous hypertension → ↓CSF resorption → ↑ICP → external sinus compression (vicious cycle); annotate MRI signs — empty sella, posterior scleral flattening, optic nerve sheath distension, optic nerve tortuosity.

Management

- ▶ **Goal:** prevent permanent visual field loss; treat any identifiable secondary cause (stop offending drug, gradually re-taper steroids, correct endocrinopathy/anemia, treat OSA).
- ▶ **Weight loss** is disease-modifying — up to ~15% loss can induce remission; some authors regard it as important as drug therapy.
- ▶ **Acetazolamide** (carbonic anhydrase inhibitor; lowers CSF production): start **500 mg twice daily**, titrate as tolerated up to **4 g/day**; the IIHTT supported acetazolamide ≤4 g/day **with weight loss** for mild visual loss, improving papilledema, ICP and quality of life. Monitor for metabolic acidosis, paresthesias (~25%), hypokalemia.
- ▶ **Topiramate** — also a carbonic anhydrase inhibitor, with the bonus of weight loss; alternative when acetazolamide is not tolerated. **Furosemide** 20–40 mg/day as adjunct.
- ▶ **Corticosteroids** — reserved for **fulminant** disease with rapidly progressive visual loss; avoided for maintenance because of weight gain and relapse on withdrawal.
- ▶ **Serial therapeutic LPs** — temporizing measure only.
- ▶ **Bariatric surgery** — consider for BMI ≥35 (RCT showed reduction in ICP and weight at 2 years).
- ▶ **Surgical / interventional** (failed medical therapy or threatened vision): **optic nerve sheath fenestration** (best for vision-threatening papilledema with preserved headache control), **CSF diversion shunt** (ventriculoperitoneal preferred over lumboperitoneal for patency), and **venous sinus stenting** in selected patients with a documented pressure gradient across a transverse sinus stenosis (still considered investigational).
- ▶ **Fulminant IIH:** rare, urgent — high-dose steroids + acetazolamide + early surgical decompression; despite treatment ~50% may remain legally blind, underscoring that the condition is *not* benign.

Clinical / Diagnostic significance

- ▶ IIH must be actively sought in *every* young obese woman with chronic daily headache — fundoscopy for papilledema is the screening pivot.
- ▶ The diagnosis is by **exclusion**: imaging (MRI/MRV) precedes LP to rule out mass and CVST; a sixth-nerve palsy is a non-localizing sign of raised ICP.
- ▶ Vision, not headache, dictates urgency and the threshold for surgery; serial perimetry and OCT are essential.
- ▶ Headache may persist after ICP normalizes (coexistent migraine/medication-overuse headache in a large fraction of IIHTT patients) and is then treated by its phenotype.

High-yield exam pointers

- ▶ Triad concept: **raised ICP + papilledema + normal neuroimaging/CSF** = IIH; “benign” is a misnomer (blindness risk).
- ▶ **Demographic**: obese woman of reproductive age (IIHTT: mean age 29, 97.6% female, BMI 39.9).
- ▶ **Modified Dandy/Friedman criteria** — opening pressure >250 mm CSF, measured in lateral decubitus.
- ▶ CN VI palsy = **false localizing sign**; commonest symptom is headache, most feared is visual loss.
- ▶ MRI signs mnemonic: **empty sella, posterior scleral flattening, optic nerve sheath distension/tortuosity, transverse sinus stenosis**.
- ▶ Secondary causes: **tetracyclines, vitamin A/retinoids, steroid withdrawal, OSA, venous sinus thrombosis**.
- ▶ First-line therapy: **weight loss + acetazolamide (up to 4 g/day)**; topiramate as alternative; **optic nerve sheath fenestration / CSF shunt / venous sinus stenting** for refractory vision-threatening disease.
- ▶ Always **exclude CVST with MRV** before labelling as idiopathic.

SOURCE & COVERAGE

- ▶ **Bradley & Daroff's Neurology in Clinical Practice 8e** — “Brain Edema and Disorders of Cerebrospinal Fluid Circulation” (Idiopathic Intracranial Hypertension: clinical features, CSF criteria, treatment) and “Headache and Other Craniofacial Pain” (IIHTT data, IIH diagnostic criteria Table 102.1, secondary pseudotumor causes Table 102.2).
- ▶ **DeJong's The Neurologic Examination** — “The Optic Nerve” (stages of papilledema, papilledema vs pseudopapilledema, transient visual obscurations).
- ▶ **CMDT 2026** — “Nervous System Disorders” (Idiopathic Intracranial Hypertension: essentials of diagnosis, imaging, drug regimens, surgical options).

- **Harrison's Principles of Internal Medicine 22e** — neurologic history/disorders of the eye (vitamin A-associated pseudotumor cerebri; corroborating detail).

Coverage note: Harrison 22e covers IIH only sparsely and scattered (no dedicated section), as flagged in the spec; the substantive depth here is drawn from Bradley & Daroff, DeJong and CMDT 2026. A formal Frisén papilledema grading scale was not present in the searched corpus, so the four descriptive stages (early, fully developed, chronic, atrophic) from DeJong are used instead.



Cerebral venous sinus thrombosis

Asked in: Paper III May 2022 — RGUHS MD General Medicine

Definition / Introduction — Cerebral venous sinus thrombosis (CVST) is thrombotic occlusion of the dural venous sinuses and/or the cerebral veins, causing impaired venous drainage, raised intracranial pressure (ICP), venous congestion and frequently haemorrhagic venous infarction. It is an uncommon but eminently treatable cause of stroke (~0.5–1% of all strokes), distinguished from arterial stroke by its predilection for **young adults and women**, its **subacute, multi-symptom evolution**, and its excellent prognosis when anticoagulated early. Because lesions do not respect arterial territories and seizures and headache dominate the picture, a high index of suspicion is essential.

Applied anatomy of the cerebral venous system

- **Superficial (cortical) system:** cortical veins → **superior sagittal sinus (SSS)** along the falx; the *vein of Trolard* (superior anastomotic) and *vein of Labbé* (inferior anastomotic to transverse sinus) are key cortical channels.
- **Deep system:** internal cerebral veins + basal vein of *Rosenthal* → **great vein of Galen** → **straight sinus**.
- **Confluence and outflow:** SSS + straight sinus + inferior sagittal sinus meet at the **confluence of sinuses** (torcular Herophili) → paired **transverse (lateral) sinuses** → **sigmoid sinuses** → **internal jugular veins**.
- **Cavernous sinuses** flank the sella, transmitting the internal carotid artery and cranial nerves III, IV, VI and V1/V2; they drain via superior/inferior petrosal sinuses.
- **Commonest thrombosis sites:** superior sagittal sinus and transverse sinuses (often combined); deep venous and cavernous sinus thromboses are less common but distinctive.

Etiology and risk factors (Virchow's triad)

Multiple causes coexist in up to half of patients; an underlying prothrombotic state should always be sought.

Category	Examples
Hereditary thrombophilia	Factor V Leiden, prothrombin G20210A, protein C/S deficiency, antithrombin deficiency, hyperhomocysteinaemia
Acquired prothrombotic	Antiphospholipid syndrome, nephrotic syndrome, malignancy, paroxysmal nocturnal haemoglobinuria, myeloproliferative disease (JAK2 V617F)
Hormonal / obstetric	Pregnancy and puerperium , oral contraceptives, hormone replacement therapy
Infective (septic)	Otitis media / mastoiditis (transverse–sigmoid; “otitic hydrocephalus”), sinusitis, meningitis, facial/orbital sepsis (cavernous sinus thrombosis , classically <i>Staphylococcus aureus</i>)
Inflammatory / systemic	Behçet disease, SLE, inflammatory bowel disease, sarcoidosis, dehydration
Mechanical / iatrogenic	Head trauma, neurosurgery, jugular catheterisation, lumbar puncture
Drug / vaccine-related	Adenoviral-vector COVID-19 vaccines causing VITT (vaccine-induced immune thrombotic thrombocytopenia, anti-PF4 antibodies); COVID-19 infection itself

Pathophysiology

- ▶ **Two parallel mechanisms** produce symptoms: (1) sinus occlusion → impaired CSF absorption at arachnoid granulations → **raised ICP**; (2) cortical/deep vein occlusion → venous congestion → vasogenic and cytotoxic oedema → **venous (often haemorrhagic) infarction**.
- ▶ Venous infarcts characteristically **cross arterial boundaries**, are frequently bilateral/parasagittal (SSS) and have a **high propensity to haemorrhage** — a crucial point, since this haemorrhage does *not* contraindicate anticoagulation.
- ▶ **Deep venous (galenic/straight sinus) thrombosis** causes bilateral **thalamic and basal ganglia** oedema, presenting as encephalopathy or coma.

Clinical features — four classic presentations

Onset is usually **subacute** (days–weeks); **headache is the commonest and earliest symptom** (~90%), often diffuse, progressive and worse on recumbency or Valsalva; *thunderclap* onset can occur.

Syndrome	Key features
Isolated intracranial hypertension	Headache, papilloedema, visual obscurations, 6th-nerve palsy , pulsatile tinnitus (mimics idiopathic intracranial hypertension)
Focal syndrome	Focal deficits (hemiparesis, aphasia) and seizures — far commoner than in arterial stroke (~40%), often focal with secondary generalisation
Encephalopathy	Altered consciousness, multifocal signs, coma — typical of deep cerebral venous thrombosis (bilateral thalami)
Cavernous sinus syndrome	Painful ophthalmoplegia, proptosis , chemosis , ptosis , CN III/IV/VI palsies, V1–V2 sensory loss; frequently septic and may become bilateral

Investigations

- ▶ **D-dimer**: usually elevated and supportive, but a normal value does **not** exclude CVST (especially isolated headache or long-standing presentation).
- ▶ **Non-contrast CT**: often normal; may show a **hyperdense thrombosed sinus** (“dense triangle”/“cord sign”) and parenchymal venous infarct/haemorrhage not conforming to an arterial territory.
- ▶ **Contrast CT / CT venography**: the “**empty delta sign**” — enhancing dural walls surrounding a non-enhancing central thrombus in the SSS; CTV demonstrates the filling defect.
- ▶ **MRI + MR venography (MRV)**: investigation of **choice** — directly shows absent venous flow and the evolving thrombus signal, plus parenchymal oedema/haemorrhage; gradient-echo/SWI sequences highlight the clot.
- ▶ **Digital subtraction angiography (venous phase)**: reserved for equivocal cases or planned endovascular therapy.
- ▶ **Lumbar puncture**: raised opening pressure; may show elevated protein, red cells and pleocytosis — useful chiefly to relieve pressure and to exclude meningitis (defer if a large mass lesion risks herniation).
- ▶ **Etiological workup**: thrombophilia screen, antiphospholipid antibodies, autoimmune and malignancy screen; in suspected VITT — platelet count, anti-PF4 ELISA, fibrinogen.

Management

- ▶ **Anticoagulation is the cornerstone**, given even in the presence of haemorrhagic venous infarction:
 - **Acute**: therapeutic **low-molecular-weight heparin** (e.g., enoxaparin 1 mg/kg SC 12-hourly), preferred over dose-adjusted unfractionated heparin (UFH reserved when rapid reversal or renal failure is a concern).

- **Maintenance:** transition to **oral anticoagulation** — warfarin (target INR 2–3) or a DOAC (dabigatran 150 mg BD shown non-inferior in the RE-SPECT CVT trial).
- **Duration:** provoked/transient cause **3–6 months**; unprovoked **6–12 months**; recurrent VTE or strong thrombophilia → **indefinite**.
- ▶ **Endovascular thrombolysis/thrombectomy:** considered for clinical deterioration despite adequate anticoagulation (routine use not supported — TO-ACT trial neutral).
- ▶ **Raised ICP / mass effect:** head-end elevation, **acetazolamide**, therapeutic LP for refractory hypertension; **decompressive hemicraniectomy** is life-saving for impending herniation from a large venous infarct/haemorrhage.
- ▶ **Seizures:** antiseizure medication for clinical seizures (and considered prophylactically with a supratentorial parenchymal lesion).
- ▶ **Treat the cause:** antibiotics ± surgical drainage for septic CVST/cavernous sinus thrombosis; correct dehydration; manage malignancy/thrombophilia.
- ▶ **VITT-associated CVST:** use **non-heparin anticoagulants** (argatroban, fondaparinux, or a DOAC) plus IVIG; **avoid heparin and platelet transfusion**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Dural venous sinus map (superolateral/midsagittal view):** label *Superior sagittal sinus*, *Inferior sagittal sinus*, *Straight sinus*, *Great vein of Galen*, *Internal cerebral vein*, *Vein of Labbé*, *Vein of Trolard*, *Confluence of sinuses (torcular Herophili)*, *Transverse sinus*, *Sigmoid sinus*, *Internal jugular vein*, *Cavernous sinus*.
- ▶ **Diagram 2 — “Empty delta sign”:** triangular cross-section of the superior sagittal sinus with *enhancing dural wall* (outer rim) and *central non-enhancing thrombus*; label both.

Clinical / Diagnostic significance

- ▶ Consider CVST in any **young patient with new persistent headache, papilloedema, seizures, or a haemorrhagic infarct crossing arterial boundaries** — especially peripartum women or those on oral contraceptives.
- ▶ It is a key differential of **idiopathic intracranial hypertension** and of arterial stroke in the young; MRV/CTV is decisive.
- ▶ **Bilateral thalamic signal change** suggests deep venous thrombosis; **proptosis with ophthalmoplegia** suggests cavernous sinus thrombosis.
- ▶ **Prognosis is favourable** (~80% recover well; mortality ~5–10%). Poor predictors: coma/depressed consciousness, deep venous or posterior fossa involvement, intracranial haemorrhage, malignancy, CNS infection, male sex and older age.

High-yield exam pointers

- ▶ CVST = stroke of the young, women > men, classic triggers pregnancy/puerperium and OCPs.
- ▶ Headache is the commonest symptom; seizures are much commoner than in arterial stroke.
- ▶ Superior sagittal and transverse sinuses are the most frequent sites.
- ▶ Imaging signs: dense cord/triangle sign (NCCT), empty delta sign (CECT/CTV); MRV is the investigation of choice.
- ▶ Anticoagulate even when there is haemorrhagic venous infarction — the single most important management pearl.
- ▶ DOAC (dabigatran) is a validated alternative to warfarin (RE-SPECT CVT).
- ▶ Cavernous sinus thrombosis is usually septic (*S. aureus*) — proptosis, chemosis, CN III/IV/VI + V1–V2 involvement, may become bilateral.
- ▶ VITT-related CVST: non-heparin anticoagulation + IVIG; avoid heparin and platelets.
- ▶ Decompressive hemicraniectomy is the rescue for impending herniation.

SOURCE & COVERAGE

Harrison 22e — Ch 437 “Introduction to Cerebrovascular Diseases” (Smith & Hemphill).

Coverage note: The provided Ch 437 text covers arterial ischaemic stroke anatomy, hemorrhage and general cerebrovascular evaluation, but does **not** substantively cover cerebral venous sinus thrombosis — it mentions only DVT prophylaxis (Fig. 437-1) and cross-references raised intracranial pressure (Ch 439). Harrison’s primary CVST coverage lies in the Ischemic Stroke chapter (Ch 438), which was not supplied. Accordingly, this answer is grounded in **universally accepted standard internal-medicine** content; the disease framework, imaging signs (empty delta/cord sign), anticoagulation principle (including in haemorrhagic infarction), RE-SPECT CVT/TO-ACT trial data and VITT management are standard textbook/guideline material and were stated only where confidently accurate. No specifics were drawn unverified from Ch 437.



Clinical features and management of Alzheimer’s disease

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — Alzheimer’s disease (AD) is a chronic, progressive neurodegenerative disorder and the commonest cause of dementia, contributing an estimated **60–70%** of all dementia (≈55 million people worldwide). It is characterised pathologically by extracellular **neuritic plaques** of amyloid- β (A β) and intraneuronal **neurofibrillary tangles** (NFTs) of hyperphosphorylated tau, with cholinergic neuronal loss in the nucleus basalis of Meynert. Clinically it presents most often with insidious-onset, progressive loss of **episodic memory** that slowly engulfs other cognitive domains and, ultimately, function and independence. Typical symptomatic duration is **8–10 years** (range 1–25).

Epidemiology & risk factors

- ▶ **Age** is the dominant risk factor: ~10% of those >65 have AD — 3% at 65–74, 17% at 75–84, and 32% at ≥85 years.
- ▶ **Genetic / family history**: the **ApoE ε4** allele on chromosome 19 is the major susceptibility gene — one ε4 allele raises risk ~2–3-fold (more in women), two alleles **10–15-fold**; each ε4 allele lowers age of onset by ~10 years. Autosomal-dominant familial AD (1–2%) is caused by mutations in **APP (chr 21)**, **Presenilin-1 (PSEN-1, chr 14)** and **Presenilin-2 (PSEN-2, chr 1)**; PSEN-1 is the commonest cause of early-onset FAD. Adults with **trisomy 21 (Down syndrome)** invariably develop AD pathology after age 40.
- ▶ **Female sex** is an independent risk factor; **TREM2** and >40 GWAS variants (**CLU**, **PICALM**, **CR1**) add small effects.
- ▶ **Modifiable / vascular**: mid-life hypertension, diabetes (≈3-fold risk), obesity, dyslipidaemia, smoking, hearing loss, traumatic brain injury, physical inactivity, low education, depression and air pollution. SPRINT-MIND showed intensive BP control (SBP <120) reduced incident MCI.

Pathology & neurochemistry

- ▶ Earliest and most severe degeneration begins in the **medial temporal lobe** (entorhinal cortex, hippocampus) and **nucleus basalis of Meynert**, spreading to temporoparietal then frontal neocortex.
- ▶ **Aβ** (39–42 aa) is cleaved from **amyloid precursor protein (APP)** by **β- and γ-secretases**; soluble Aβ oligomers and Aβ42 are the toxic species, polymerising into plaques. Vascular Aβ deposition = **cerebral amyloid angiopathy (CAA)**.
- ▶ **NFTs** = paired helical filaments of hyperphosphorylated **tau**, which detaches from microtubules and spreads in a prion-like, stereotyped pattern (**Braak staging**).
- ▶ **Neurochemistry**: loss of cortical **acetylcholine** and choline acetyltransferase (basis of cholinesterase-inhibitor therapy), with noradrenergic (locus coeruleus) and serotonergic (dorsal raphe) depletion.

Clinical features

AD evolves through a recognised continuum — **preclinical** → **MCI/early symptomatic** → **dementia** (mild → moderate → severe).

- ▶ **Preclinical AD**: biomarker evidence of amyloid (± tau) pathology *without* symptoms; may precede symptoms by ≥20 years.
- ▶ **Mild cognitive impairment (MCI) / early symptomatic AD**: memory loss noticeable to patient and family and confirmed on testing, but daily function preserved. ~50% of MCI (≈12%/year) progress to dementia over 4 years.
- ▶ **Typical (amnestic) presentation**: insidious loss of **episodic memory** — repeating questions, forgetting recent conversations and appointments — reflecting hippocampal pathology.

Disorientation to time/place, getting lost on familiar routes, and impaired complex tasks (finances, work, driving) follow.

- ▶ **Mild dementia:** memory + word-finding difficulty (circumlocution), early visuospatial and executive decline; depression, anxiety, social withdrawal and apathy are common and may be a prodrome.
- ▶ **Moderate dementia:** unable to work, easily lost, needs daily supervision. Progressive **language** failure (naming → comprehension → fluency), **apraxia** (using utensils/appliances), **visuospatial deficits** (dressing, copying figures), and **acalculia/clock** difficulties. **Delusions** (theft, infidelity, misidentification), agitation, wandering, disinhibition and disrupted sleep–wake cycle appear.
- ▶ **Severe (late) dementia:** patient becomes rigid, mute, incontinent, bedridden and totally dependent; **myoclonus**, hyperreflexia, parkinsonian gait and **seizures** may occur. Death is usually from **aspiration**, infection, malnutrition or pulmonary embolism.
- ▶ **Atypical variants (~20%, often younger):** **posterior cortical atrophy** (progressive visual processing failure), **logopenic primary progressive aphasia** (impaired naming and repetition), **dysexecutive/behavioural (“frontal”) variant**, and a **corticobasal (akinetic-rigid-dystonic)** syndrome. Anosognosia (unawareness) may occur, but most retain insight early.

Diagnosis & investigations

- ▶ **Clinical diagnosis** rests on slowly progressive amnesic decline with normal systemic labs and posterior-predominant cortical + hippocampal atrophy; it is confirmed at autopsy in ~70–80%.
- ▶ **Cognitive screening:** MMSE (Folstein), **MoCA**, Mini-Cog — quick but insensitive to MCI; formal neuropsychometry for atypical cases.
- ▶ **Exclude reversible/secondary dementia (mandatory work-up):** serum **vitamin B12**, **TSH/free T4**, electrolytes, calcium, RPR/VDRL, HIV; LP where indicated. Treat the “treatable” differentials — B12 deficiency, hypothyroidism, normal-pressure hydrocephalus, neurosyphilis, depression (pseudodementia), chronic drug intoxication.
- ▶ **Structural MRI/CT:** medial temporal (hippocampal) and posterior-predominant cortical atrophy; chiefly excludes tumour, vascular disease, subdural haematoma and NPH.
- ▶ **Functional/molecular imaging:** **FDG-PET** shows temporoparietal hypometabolism (and distinguishes AD from FTD); **amyloid PET** ([18F]florbetapir/florbetaben/flutemetamol) confirms plaque burden; **tau PET** ([18F]flortaucipir) maps NFTs.
- ▶ **Fluid biomarkers:** CSF shows **low Aβ42**, reduced **Aβ42/Aβ40 ratio** and raised **phospho-tau (p-Tau181/p-Tau217)**. Plasma **p-Tau217** (and Aβ42/40) now offer scalable, blood-based confirmation.
- ▶ **Criteria:** evolution from NINCDS-ADRDA (1984) → NIA-AA (2011) clinical-biomarker criteria → 2018 ATN research framework (Amyloid, Tau, Neurodegeneration) and the 2024 Revised

Criteria defining AD *biologically* by “core 1” biomarkers (amyloid PET, CSF/plasma A β and p-Tau). ApoE genotyping is recommended *before* anti-amyloid therapy to assess ARIA risk.

Management

AD requires a **multidomain approach**: symptomatic neurotransmitter therapy, disease-modifying anti-amyloid antibodies, treatment of neuropsychiatric symptoms, and patient/caregiver support.

1. Neurotransmitter-based (symptomatic) therapy

Drug	Mechanism	Dosing	Approved stage
Donepezil	Cholinesterase inhibitor	Start 5 mg OD $\times$ 4 wk $\rightarrow$ 10 mg OD (23 mg for mod-severe)	Mild-severe
Rivastigmine	Cholinesterase inhibitor	1.5 mg BID, titrate to 3–6 mg BID; or 9.5 mg/24h patch	Mild-severe
Galantamine	Cholinesterase inhibitor	4 mg BID $\rightarrow$ 8–12 mg BID (24 mg/day ER)	Mild-severe
Memantine	NMDA-receptor antagonist	5 mg OD, $\uparrow$ 5 mg/wk $\rightarrow$ 10 mg BID	Moderate-severe

- Dose-escalate over **4–6 weeks**. Cholinesterase inhibitors modestly slow decline (MMSE maintained $\sim$ 1 year vs 2–3 point fall on placebo); main side effects are GI (**nausea, diarrhoea, cramps**), vivid dreams, bradycardia/syncope (obtain ECG in cardiac patients). A common strategy: start a cholinesterase inhibitor in mild AD and **add memantine** in moderate-severe disease. Memantine side effects: constipation, dizziness, headache, somnolence. Cholinesterase inhibitors are **avoided in frontotemporal dementia** (worsen behaviour).

2. Disease-modifying anti-amyloid monoclonal antibodies (first DMTs for AD)

- **Lecanemab** (anti-A β **protofibril**): 10 mg/kg IV every 2 weeks — **Clarity-AD** showed **27% slowing** of CDR-SB decline at 18 months.
- **Donanemab** (anti-pyroglutamate A β): 700 mg IV q4w $\times$ 3 then 1400 mg q4w — **TRAILBLAZER-ALZ2** showed 22% slowing on iADRS and 28% on CDR-SB; greatest benefit in low-medium tau-PET patients.
- **Aducanumab** received accelerated approval but was withdrawn (ambiguous efficacy).
- **Restricted to MCI or mild AD dementia with biomarker-confirmed amyloid (PET/CSF)**. Key toxicity = **ARIA** — ARIA-E (oedema/effusion on FLAIR) and ARIA-H (microbleeds/siderosis on GRE/SWI); $\sim$ 75% asymptomatic, but seizures, stroke-like episodes and rare death occur. Risk rises with each ϵ 4 allele (**box warning for ϵ 4 homozygotes**). Requires serial surveillance MRI; **contraindicated** with extensive CAA ($>$ 4 microbleeds/cortical siderosis), uncontrolled hypertension, anticoagulation, and concurrent **thrombolysis** for acute stroke.

3. Neuropsychiatric / behavioural symptoms

- ▶ **Depression/anxiety:** SSRIs with low anticholinergic burden (e.g., **escitalopram** 5–10 mg).
- ▶ **Agitation/psychosis:** non-pharmacological behavioural measures first; low-dose atypical antipsychotics (risperidone, quetiapine, olanzapine) carry an **FDA black-box warning** (increased mortality in elderly dementia). **Brexipiprazole** is the only agent FDA-approved for **agitation in AD**.
- ▶ **Seizures:** levetiracetam. **Avoid strong anticholinergics** (diphenhydramine, oxybutynin) which worsen cognition.

4. Non-pharmacological & caregiver support

- ▶ Memory aids (notebooks, posted reminders), home safety, eventual cessation of driving.
- ▶ Lifestyle: physical/cognitive/social activity, vascular risk-factor control, sleep hygiene, **Mediterranean/DASH diet**.
- ▶ Address **caregiver burnout** with respite care, adult day-care and support groups (Alzheimer's Association). (*Estrogen, statins, vitamin E and ginkgo have not shown benefit in RCTs.*)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **APP processing pathway:** membrane-spanning APP cleaved by β -secretase (BACE) then γ -secretase $\rightarrow$ toxic $A\beta_{42}$ (amyloidogenic) vs non-amyloidogenic α -secretase $\rightarrow A\beta_{40}/P3$.
Label: APP, $\alpha/\beta/\gamma$ -secretase, $A\beta_{42}$ (toxic plaque), $A\beta_{40}$, cell membrane.
- ▶ **Brain atrophy / pathology schematic:** coronal section showing **hippocampal + medial temporal lobe atrophy** with dilated temporal horns and posterior cortical atrophy; inset labelling **extracellular neuritic (amyloid) plaque** and **intraneuronal neurofibrillary tangle**, and the **nucleus basalis of Meynert** (cholinergic loss).

Clinical / Diagnostic significance

- ▶ **Episodic memory loss + medial temporal atrophy + temporoparietal hypometabolism** is the classic triad pointing to AD.
- ▶ Always **exclude reversible dementias** (B12, thyroid, NPH, neurosyphilis, depression, drugs) before labelling AD.
- ▶ **Distinguishing clues:** early gait disturbance with mild memory loss $\rightarrow$ vascular dementia/NPH; resting tremor, fluctuations and visual hallucinations $\rightarrow$ DLB; rapid decline with myoclonus $\rightarrow$ Creutzfeldt-Jakob disease; behavioural change with anterior atrophy $\rightarrow$ frontotemporal dementia.
- ▶ Biomarker confirmation is now **mandatory before disease-modifying therapy**, and **ApoE genotyping** stratifies ARIA risk.

High-yield exam pointers

- ▶ Commonest dementia (60–70%); hallmark = **amyloid plaques + tau NFTs**; cholinergic deficit (nucleus basalis of Meynert).
- ▶ **ApoE ε4** = major risk gene (2–3× heterozygote, 10–15× homozygote); FAD genes = **APP, PSEN-1, PSEN-2**; Down syndrome → early AD.
- ▶ Earliest clinical feature = **episodic (anterograde) memory loss**; atypical variants = posterior cortical atrophy, logopenic aphasia, frontal/dysexecutive.
- ▶ CSF: ↓Aβ42, ↓Aβ42/40 ratio, ↑p-Tau181/217; **plasma p-Tau217** emerging. FDG-PET = temporoparietal hypometabolism.
- ▶ Symptomatic drugs: **cholinesterase inhibitors** (donepezil, rivastigmine, galantamine) ± **memantine** (NMDA antagonist, moderate–severe).
- ▶ Disease-modifying: **lecanemab & donanemab** (anti-amyloid mAbs) for early AD; major risk = ARIA-E/ARIA-H; check ApoE before starting.
- ▶ **Brexpiprazole** = only drug FDA-approved for agitation in AD; antipsychotics carry a mortality **black-box warning**.
- ▶ Death usually from **aspiration pneumonia**, infection or malnutrition.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Alzheimer's Disease” (clinical manifestations, pathology, genetics, biomarkers, treatment including anti-amyloid antibodies, ARIA) and “Dementia.”
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Alzheimer Disease and Other Dementias” (MCI continuum, NINCDS-ADRDA/NIA-AA/2018 ATN diagnostic frameworks, structural/functional/amyloid–tau imaging).
- ▶ **CMDT 2026** — “Nervous System Disorders” (current drug dosing, anti-amyloid therapy regimens and cautions, diagnostic work-up).



Clinical features, pathophysiology and management of trigeminal neuralgia. Differentiate trigeminal neuralgia from trigeminal neuropathy

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Trigeminal neuralgia (tic douloureux)* is a chronic facial pain disorder characterised by recurrent paroxysms of excruciating, electric shock-like or stabbing pain confined to one or more divisions of the fifth cranial nerve, classically provoked by innocuous tactile stimuli to cutaneous **trigger zones** and, by definition, *without demonstrable sensory loss* on examination. It must be sharply distinguished from **trigeminal neuropathy**, in which structural disease of the nerve produces

objective sensory deficit and/or motor (masticatory) weakness. The estimated annual incidence is 4–8 per 100,000; it affects middle-aged and elderly persons, with ~60% of cases in women.

Pathophysiology

- ▶ **Ectopic impulse generation:** Pain arises from ectopic generation of action potentials in pain-sensitive afferent fibres of the trigeminal root *just before it enters the lateral surface of the pons* (the root entry zone).
- ▶ **Demyelination & ephaptic transmission:** Compression/pathology causes **focal demyelination of large myelinated (A β touch) fibres** that do not themselves carry pain. These become hyperexcitable and **electrically (ephaptically) coupled** to adjacent small unmyelinated/poorly myelinated nociceptive fibres — explaining why a light tactile stimulus, conveyed by large fibres, can ignite a paroxysm of pain.
- ▶ **Vulnerable myelin zone:** CN V is ensheathed by **oligodendrocyte-derived central myelin for up to 7 mm** after leaving the brainstem (vs a few mm for other nerves); demyelination occurs at this central–peripheral myelin **transition (Obersteiner–Redlich) zone**, accounting for the link with multiple sclerosis (a disorder of oligodendrocyte myelin).
- ▶ **Neurovascular compression (classic TN):** A tortuous artery — most often the **superior cerebellar artery**, occasionally the **anterior inferior cerebellar artery** or a vein — compresses/indents the root, causing axonal loss and demyelination. *Vascular contact alone is insufficient* (it is common in asymptomatic controls/cadavers); **morphological indentation/atrophy** of the root is required.
- ▶ **Ageing substrate:** Age-related brain sagging and increased vascular thickness/tortuosity explain the prevalence in later life.

Clinical features

- ▶ **Character:** Paroxysms of *excruciating*, superficial, stabbing/lancinating “electric-shock” pain; so intense the patient winces — hence *tic*.
- ▶ **Duration & periodicity:** Each jab lasts seconds to a minute or two; single jabs or clusters recur frequently **day and night for weeks–months**, then remit spontaneously. Remissions may be long but the disorder usually ultimately recurs.
- ▶ **Distribution:** Strictly **unilateral**, confined to trigeminal territory — most often **V2 (maxillary) and V3 (mandibular)**; the **ophthalmic (V1) division is involved in <5% of cases**.
- ▶ **Trigger zones / triggers:** Tactile stimulation of trigger points on the face, lips or tongue provokes attacks — *washing the face, brushing teeth, shaving, chewing, speaking, smiling, or a draught of cold air*. Patients hold the face still and avoid eating/talking.
- ▶ **Examination:** *No objective sensory loss and no motor weakness* — an **essential diagnostic feature**. (A dull background ache may persist between jabs in long-standing/”concomitant continuous pain” cases.)

Classification (ICHD-based) & differential diagnosis

Type	Mechanism	Clue
Classic TN	Neurovascular compression with morphological root change (SCA/AICA)	Older age, normal exam, vessel-nerve contact on MR angiography
Secondary (symptomatic) TN	MS plaque at root entry zone, cerebellopontine-angle tumour (acoustic schwannoma, meningioma), aneurysm, neurofibroma, chronic meningitis	Young/bilateral patient, subtle sensory loss → suspect MS or mass
Idiopathic TN	No cause found despite imaging	Diagnosis of exclusion

- ▶ **Differentiate from other facial pains:** Migraine/cluster pain is *deep, steady* (not superficial-stabbing); rarely cluster coexists (*cluster-tic*). SUNCT/SUNA and paroxysmal hemicrania are distinguished by attack frequency/duration and prominent cranial autonomic features (V1 territory). **Giant cell (temporal) arteritis** gives non-shocklike facial pain with myalgia and ↑ESR/CRP. Also exclude dental, jaw and sinus disease.
- ▶ **Red flags for a secondary cause:** onset <40 years, **bilateral** symptoms, V1 involvement, any objective sensory loss, or other cranial-nerve signs → mandates imaging.

Investigations

- ▶ **High-resolution contrast-enhanced brain MRI** in all: to exclude secondary causes (MS plaque, tumour, aneurysm) and demonstrate neurovascular compression. **MR angiography** delineates the nerve–vessel relationship and is used pre-operatively to plan decompression.
- ▶ ESR/CRP if temporal arteritis is suspected.
- ▶ Younger/atypical patients: evaluate for **MS** (a demyelinating plaque near the pontine root entry zone is the typical lesion).

Management

A. Medical therapy (first line):

- ▶ **Carbamazepine** — drug of choice, effective in ~50–75%. Start **100 mg once daily with food**, increase by 100 mg/day in divided doses every 1–2 days to >50% relief; usual maintenance **200 mg four times daily**; doses >1200 mg/day give no added benefit. Monitor for dizziness, ataxia, sedation, hyponatraemia and rare **agranulocytosis** (serial blood counts + LFTs). If effective, continue ~1 month then taper.
- ▶ **Oxcarbazepine 300–1200 mg bid** — equally efficacious, less marrow toxicity (preferred by many).

- Second-line / add-on: phenytoin 300–400 mg/day; lamotrigine 400 mg/day; baclofen 10–20 mg tid; topiramate 50 mg bid; gabapentin up to 3600 mg/day (useful in MS-related TN).

B. Surgical / interventional therapy (drug failure or intolerance): initial relief in $\geq 80\%$.

Procedure	Mechanism	Outcome / caveat
Microvascular decompression (MVD) — Jannetta	Suboccipital craniotomy; pad/separate offending vessel from root	>70% efficacy, ~75% long-term relief, low recurrence; <i>no sensory loss</i> ; best for classic lancinating pain; major surgery
Stereotactic (Gamma-knife) radiosurgery	Radiation lesion of root	Complete relief (often delayed) in $\sim 1/2$ (~45%); recurrence in $1/3$ over 2–3 yr; few serious complications
Radiofrequency thermal rhizotomy	Heat lesion of ganglion/nerve	>95% short-term, ~60% long-term; common facial numbness, masseter weakness, corneal denervation/keratitis (V1)
Percutaneous balloon compression	Mechanical ganglion injury (under GA)	~67% relief; ipsilateral facial numbness common

- MS-related TN: open surgical exploration is inappropriate; less-invasive ablative techniques may help. Glossopharyngeal neuralgia (a close mimic in the throat/ear) responds to the same drugs and MVD.

Trigeminal neuralgia vs trigeminal neuropathy

Feature	Trigeminal neuralgia	Trigeminal neuropathy
Nature of pain	Paroxysmal, brief (sec–min), shock-like/stabbing	Constant numbness/paraesthesia, burning, or no pain
Trigger zones	Present (tactile triggers)	Absent
Sensory loss	Absent (cardinal rule)	Present — objective facial numbness, ↓corneal reflex
Motor (masticatory) deficit	Absent	May be present — jaw deviates to the weak side (pterygoids)
Divisions	V2/V3 mainly; V1 <5%	Any; chin (mental) or cheek numbness may signal malignancy
Mechanism	Neurovascular compression / demyelination at root	Structural disease of nucleus, ganglion or nerve
Typical causes	Vascular loop; MS (secondary)	Sjögren's, SLE, scleroderma, MCTD; herpes zoster; leprosy; tumours (schwannoma, meningioma, nasopharyngeal Ca, perineural spread); GBS;

Feature	Trigeminal neuralgia	Trigeminal neuropathy
		sarcoidosis; trauma; drugs (stilbamidine, trichloroethylene); idiopathic
Examination dictum	Normal exam	“Diagnosed by the company they keep” — long-tract/other CN signs

- ▶ **Idiopathic trigeminal neuropathy:** numbness/paraesthesiae (sometimes bilateral) with sensory loss but *no jaw weakness*; gradual recovery is the rule.
- ▶ **Numb chin (mental neuropathy) or numb cheek syndrome:** isolated chin/cheek numbness may be the *sole presenting sign of systemic malignancy* (breast, lung, prostate, lymphoma) — never ignore.
- ▶ **Trigeminal trophic syndrome:** anaesthesia → self-induced ulceration of the **ala nasi** following ganglion damage/rhizotomy or central tract lesions.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Trigeminal nerve and its sensory territory on the face** — label: *Pons (root entry zone), Trigeminal (gasserian/semilunar) ganglion in Meckel’s cave, Ophthalmic V1, Maxillary V2, Mandibular V3*, and the corresponding facial dermatomal zones; mark the **trigger zone** on the cheek/lip.
- ▶ **Neurovascular compression schematic** — label: *Trigeminal root, Superior cerebellar artery (compressing vessel), Central (oligodendrocyte) myelin segment, Central–peripheral myelin transition (Obersteiner–Redlich) zone, focal demyelination with ephaptic coupling*.

Clinical / Diagnostic significance

- ▶ A strictly paroxysmal pain with trigger zones and a completely normal neurological examination is virtually diagnostic of TN; *any* sensory/motor deficit reclassifies the patient as trigeminal neuropathy and demands a search for structural disease.
- ▶ Bilateral TN, onset <40 years, or V1 involvement strongly suggests MS or a posterior-fossa mass — image early.
- ▶ MRI/MRA is both **diagnostic** (excludes secondary causes) and **therapeutic-planning** (defines the offending vessel before MVD).
- ▶ Carbamazepine response is itself **supportive of the diagnosis**; failure or need for escalating surgery should prompt re-imaging.

High-yield exam pointers

- ▶ *Tic douloureux* = paroxysmal, unilateral, shock-like V2/V3 pain with **trigger zones** and **NO sensory loss**.

- ▶ Incidence 4–8/100,000; ~60% women; middle-aged/elderly.
- ▶ Pathology = **demyelination + ephaptic coupling** at the root entry zone; **superior cerebellar artery** is the commonest compressing vessel.
- ▶ **V1 involved in <5%**; if young/bilateral/V1 → think MS (plaque at pontine root entry zone).
- ▶ **Carbamazepine** is first-line (50–75% response); oxcarbazepine an equal alternative; max CBZ benefit ≤1200 mg/day.
- ▶ Surgery of choice = **microvascular decompression (Jannetta)**, >70% **durable relief**, **no numbness**; ablative procedures cause facial numbness.
- ▶ **Neuropathy ≠ neuralgia**: neuropathy has **objective sensory loss ± jaw weakness** (deviation to weak side) and signals Sjögren's/zoster/leprosy/tumour/perineural spread.
- ▶ **Numb chin sign** = mental neuropathy = possible occult malignancy.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders” (clinical features, pathophysiology, drug doses, surgical options, Table of trigeminal nerve disorders).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Cranial Neuropathies” and “Cranial and Facial Pain” (classic vs symptomatic TN, neurovascular compression at central–peripheral myelin transition, SCA/AICA, <5% V1, numb-chin/cheek syndromes).
- ▶ **Brazis — Localization in Clinical Neurology** — “Cranial Nerve V: The Trigeminal Nerve” (trigeminal trophic syndrome, nuclear vs peripheral localization, “company they keep”).
- ▶ **CMDT 2026** — “Nervous System Disorders” (current diagnostic criteria, MRI rule for secondary causes <40 yr/bilateral, surgical success rates: MVD ~75%, RF rhizotomy 60%, balloon 67%, radiosurgery 45%).



Describe the physiological anatomy of neuromuscular junction and explain how diseases involving the neuromuscular junction cause muscle weakness

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — The **neuromuscular junction (NMJ)** is the specialised cholinergic synapse where a motor axon terminal makes functional contact with a skeletal muscle fibre, converting a nerve action potential into a muscle fibre action potential and hence contraction. It is uniquely vulnerable to disease because it lies *outside the blood–nerve barrier*, depends on a finely tuned excess of acetylcholine (ACh) release over demand (the **safety factor**), and is built from many distinct presynaptic and postsynaptic molecules, each of which can be targeted by autoantibodies, genetic mutation or toxins.

Failure of transmission at any of these sites produces the cardinal NMJ sign — **fatigable, fluctuating weakness without sensory loss**.

Physiological anatomy — three functional compartments

The NMJ is organised into a presynaptic motor nerve terminal, the synaptic cleft and the postsynaptic muscle end-plate.

Compartment	Key structures	Function
Presynaptic terminal	Synaptic vesicles each storing one <i>quantum</i> (~5000–10,000 ACh molecules); active zones (release sites) apposed to postsynaptic folds; voltage-gated (P/Q-type) Ca^{2+} channels ; voltage-gated Na^+/K^+ channels ; SNARE fusion proteins — <i>syntaxin-1</i> , <i>SNAP-25</i> , <i>synaptobrevin</i> , <i>synaptotagmin</i>	ACh is synthesised from acetate + choline by choline acetyltransferase (ChAT) , packaged into vesicles, and released by Ca^{2+} -triggered exocytosis
Synaptic cleft	~50 nm gap; synaptic basal lamina ; acetylcholinesterase (AChE) anchored to the basal lamina by its collagenic tail (COLQ); agrin	ACh diffuses across; rapidly hydrolysed by AChE, terminating signal
Postsynaptic membrane	Deeply infolded junctional (postsynaptic) folds ; acetylcholine receptors (AChRs) densely packed at the <i>crests</i> of folds; voltage-gated Na^+ channels in the depths of folds; clustering scaffold — MuSK , LRP4 , Dok-7 , rapsyn , dystroglycan	High-density AChR + Na^+ channels convert the chemical signal into a propagated muscle action potential

- ▶ The AChR is a pentamer of five subunits — **2 α , 1 β , 1 δ and 1 γ (fetal) or 1 ϵ (adult)** — arranged around a central cation pore; ACh binds the two α -subunits, opening the channel to Na^+ (and Ca^{2+}) influx.
- ▶ **End-plate maturation/maintenance pathway**: nerve-derived **agrin** → binds **LRP4** → activates **MuSK** → recruits **Dok-7** and **rapsyn** → clusters AChR at the fold crests. The same molecules implicated here are the antigens/genes of autoimmune and congenital NMJ disease.

Physiology of neuromuscular transmission — the sequence

- ▶ A nerve action potential invades the terminal and opens **voltage-gated (P/Q-type) Ca^{2+} channels**; Ca^{2+} influx triggers SNARE-mediated **vesicle docking and exocytosis at active zones**.
- ▶ A single impulse releases the contents of ~**150–200 vesicles** (Harrison); experimental estimates of quantal release vary (~50–300 quanta, mean ≈ 60 — Bradley). Quantal output $m = p \times n$,

where p is release probability (≈ 0.2 , proportional to Ca^{2+}) and n the immediately available vesicle pool.

- ▶ Each quantum acting on AChRs produces a **~ 1 mV** depolarisation — the **miniature end-plate potential (MEPP)** (spontaneous, sub-threshold).
- ▶ Summation of all quanta from one impulse produces the **end-plate potential (EPP)**, normally **~ 60 mV** — far larger than the threshold needed to open perijunctional Na^+ channels and fire a **muscle fibre action potential**.
- ▶ AChE hydrolyses ACh within milliseconds and diffusion clears the cleft, resetting the junction.

The “safety factor” — the key to understanding weakness

- ▶ Because the EPP (~ 60 mV) **greatly exceeds the threshold** needed to trigger a muscle action potential, every nerve impulse reliably excites its fibre. This excess is the **safety factor of neuromuscular transmission**.
- ▶ Its magnitude depends on: **quantal content** (ACh released), **AChR density/conductance**, **AChE activity** and the geometry of the junctional folds.
- ▶ **Presynaptic rundown**: ACh output normally declines over the first few impulses of a train. In health this is invisible because the EPP still clears threshold; remove the safety factor and the same rundown now causes intermittent transmission failure — i.e. **fatigable weakness**.
- ▶ *Any* disease that lowers the EPP toward threshold (fewer AChRs, less ACh release, blocked release, or excess cholinergic depolarisation) converts a guaranteed signal into a probabilistic one — successive impulses activate **fewer and fewer fibres**, manifesting as decremental weakness and clinical fatigue.

How NMJ diseases cause weakness — site-based mechanisms

Disorder	Site / target	Mechanism of reduced safety factor	Distinctive features
Myasthenia gravis (MG) — anti-AChR	Postsynaptic AChR	↓ available AChRs by (1) antibody cross-linking → accelerated endocytosis/turnover; (2) complement (MAC)-mediated lysis of folds; (3) direct blockade of ACh-binding site. Folds flatten/”simplify” → small EPPs fail to reach threshold	AChR-Ab in $\sim 85\%$ generalised, $\sim 50\%$ ocular; ptosis, diplopia, bulbar & proximal limb weakness; reflexes preserved
MG — anti-MuSK	Postsynaptic clustering	IgG4 antibody blocks MuSK-LRP4 interaction → loss of AChR clustering; does not fix complement	$\sim 40\%$ of AChR-negative generalised MG; prominent bulbar/neck/respiratory weakness + muscle atrophy; often <i>worsens</i> with anticholinesterases

Disorder	Site / target	Mechanism of reduced safety factor	Distinctive features
MG — anti-LRP4	Postsynaptic clustering	IgG1 → complement-mediated injury + interrupts agrin–MuSK signalling	1–3% of MG
Lambert-Eaton myasthenic syndrome (LEMS)	Presynaptic P/Q-type Ca^{2+} channel	Antibody against voltage-gated Ca^{2+} channels ↓ Ca^{2+} entry → ↓ quantal ACh release → low baseline EPP	Proximal leg weakness, <i>hyporeflexia</i> , autonomic features (dry mouth); post-exercise facilitation ; ~85% have P/Q-Ab; SCLC association
Botulism	Presynaptic SNAREs	<i>C. botulinum</i> toxin enzymatically cleaves SNARE proteins → blocks ACh exocytosis	Descending paralysis, bulbar onset, dilated pupils, autonomic failure; normal sensation
Congenital myasthenic syndromes (CMS)	Any component (pre-, synaptic, post-)	>30 gene mutations (e.g. ϵ-subunit AChR ~50%, <i>RAPSN</i> , <i>COLQ</i> , <i>DOK7</i> , <i>CHAT</i> , <i>agrin</i>) impair ACh synthesis, AChE anchoring, AChR kinetics or clustering	Non-immune; onset infancy/childhood; AChR & MuSK antibodies absent
Drug/toxin & metabolic	Variable	Aminoglycoside/quinolone/macrolide antibiotics, IV magnesium, procainamide, penicillamine (induces autoimmune MG), botulinum toxin — all impair release or block AChR	Exacerbate established MG; high doses weaken normal NMJ

- ▶ **Common final pathway:** every NMJ disease reduces the **EPP relative to threshold**. Presynaptic disorders (LEMS, botulism) do so by *reducing ACh release*; postsynaptic disorders (MG, most CMS) by *reducing the AChR response*. The result is identical — failure of a proportion of fibres to fire, i.e. **weakness that worsens with use**.

Electrodiagnostic correlation (proof of the physiology)

- ▶ **Slow repetitive nerve stimulation (2–3 Hz):** in MG the already-reduced safety factor lets the normal rundown drop successive EPPs below threshold → a **decremental CMAP response >10%** (postsynaptic pattern).
- ▶ **Rapid RNS (20–50 Hz) or 10-s exercise:** in LEMS the accumulating presynaptic Ca^{2+} raises ACh release → EPPs cross threshold → **incremental response (often >100–200%)** — the electrophysiological signature of a presynaptic defect.
- ▶ **Single-fibre EMG:** increased **jitter** (variability of inter-potential interval) and **blocking** are the most sensitive markers of impaired transmission, reflecting EPPs hovering near threshold.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Normal NMJ (longitudinal section).** Label: *motor axon terminal, mitochondria, synaptic vesicles (quanta), active zone, voltage-gated Ca^{2+} channel, SNARE proteins (syntaxin-1/SNAP-25/synaptobrevin/synaptotagmin), synaptic cleft + basal lamina, acetylcholinesterase (AChE), junctional (postsynaptic) folds, AChR clustered at fold crests, voltage-gated Na^+ channels in fold depths, clustering scaffold (agrin-LRP4-MuSK-Dok-7-rapsyn).*
- ▶ **Diagram 2 — Myasthenic vs normal end-plate.** Two panels side by side. Label: *normal — abundant AChRs, deep/normal folds, narrow cleft; MG — reduced AChR number, flattened/simplified folds, widened synaptic space, complement + AChR autoantibody on folds.* Optionally add an EPP-versus-threshold tracing showing the normal EPP above threshold and the myasthenic EPP failing threshold (the safety-factor concept).

Clinical / Diagnostic significance

- ▶ **Pattern recognition:** fatigable ptosis, diplopia, bulbar and proximal weakness with **preserved reflexes, normal sensation and normal pupils** localises to the NMJ; *hyporeflexia + autonomic features* point instead to LEMS.
- ▶ **Bedside tests:** **ice-pack test** (2 min over a ptotic lid; ≥ 2 mm lid rise = positive) exploits reduced AChE activity in the cold; the historical **edrophonium/anticholinesterase test** transiently improves strength.
- ▶ **Serology:** anti-AChR radioimmunoassay first; if negative, **anti-MuSK** then **anti-LRP4**. In LEMS test P/Q-type Ca^{2+} channel antibodies and screen for small-cell lung cancer.
- ▶ **Always image the chest (CT/MRI)** in MG — thymic hyperplasia (~65–70%) or thymoma (~10–15%) is common.
- ▶ **Management pearls (Harrison/CMDT 2026):** symptomatic pyridostigmine (30–180 mg, avg ~60 mg, four times daily) — but it may *worsen* anti-MuSK MG; **corticosteroids** (gradual uptitration to avoid early steroid dip) and steroid-sparing agents (**azathioprine 2–3 mg/kg/day, mycophenolate, rituximab** — rituximab especially effective in MuSK MG); **thymectomy** for thymoma and for generalised AChR-positive MG <65 yrs (MGTX trial); **rapid rescue with IVIg or plasmapheresis** for crisis/pre-op. Newer FDA-approved agents: **complement inhibitors** (eculizumab, ravulizumab, zilucoplan — require meningococcal vaccination) and **FcRn antagonists** (efgartigimod, rozanolixizumab). LEMS is treated with **3,4-diaminopyridine** (blocks K^+ channels $\rightarrow$ prolongs depolarisation $\rightarrow$ $\uparrow$ ACh release) $\pm$ pyridostigmine; botulism with **antitoxin** and ventilatory support.
- ▶ **Myasthenic crisis** = respiratory/bulbar failure needing ventilation; precipitated by infection, surgery, or offending drugs (aminoglycosides, magnesium) — a medical emergency.

High-yield exam pointers

- ▶ NMJ = cholinergic synapse outside the blood–nerve barrier → uniquely exposed to circulating antibodies.
- ▶ AChR = pentamer $2\alpha/\beta/\delta/\gamma$ -or- ϵ ; ACh binds the α -subunits.
- ▶ Quantum = 5000–10,000 ACh molecules → ~1 mV MEPP; one impulse → EPP ~60 mV >> threshold = safety factor.
- ▶ Agrin → LRP4 → MuSK → Dok-7/rapsyn → AChR clustering — the master end-plate pathway and the disease antigen map.
- ▶ MG = postsynaptic (3 antibody mechanisms; complement, turnover, blockade) → decrement on slow RNS.
- ▶ LEMS = presynaptic P/Q Ca^{2+} -channel antibody → low CMAP, increment after exercise/rapid RNS, hyporeflexia, SCLC.
- ▶ Botulism cleaves SNARE proteins; CMS = genetic, ϵ -subunit commonest (~50%).
- ▶ Final common pathway of all NMJ disease = EPP falls toward threshold → fibres fail intermittently → fatigable weakness.
- ▶ NMJ weakness spares sensation, reflexes (except LEMS) and pupils (except botulism).

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "*Myasthenia Gravis and Other Diseases of the Neuromuscular Junction*" (NMJ transmission physiology, AChR structure, antibody mechanisms, MG/LEMS/botulism/CMS, treatment).
- ▶ Bradley & Daroff's Neurology in Clinical Practice, 8e — "*Disorders of Neuromuscular Transmission*" (immunopathology, junctional-fold ultrastructure, MG subtypes) and "*Clinical Electromyography*" (quantal release $m = p \times n$, MEPP/EPP, safety factor, RNS decrement/increment, jitter).
- ▶ CMDT 2026 — "*Nervous System Disorders: Myasthenia Gravis & Lambert-Eaton Myasthenic Syndrome*" (diagnostic criteria, drug doses, thymectomy, FcRn/complement therapies).
- ▶ Coverage note: the corpus covers this topic richly. The per-impulse ACh figure differs slightly between sources (Harrison "150–200 vesicles" vs Bradley "~50–300 quanta, mean ~60"); both are quoted faithfully rather than reconciled.



Posterior (Vertebrobasilar) Circulation of the Brain: Anatomy and Clinical Relevance

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — The **posterior (vertebrobasilar) circulation** is the arterial system derived from the paired **vertebral arteries (VA)** and the **basilar artery**, terminating in the two **posterior cerebral arteries (PCA)**. It supplies the brainstem, cerebellum, labyrinth and cochlea, subthalamus, portions of the thalamus, and the inferomedial temporal and occipital lobes. Because dense, eloquent, life-sustaining structures are packed into a small volume, occlusion produces characteristic **crossed (alternating) brainstem syndromes** and visual deficits; “top-of-the-basilar” and basilar occlusion are neurological emergencies. About **87%** of strokes are ischaemic, and roughly one-fifth of ischaemic strokes are posterior-circulation events.

Arterial anatomy — origin, course and segments

- ▶ **Vertebral artery** arises from the **subclavian artery** and has four segments: **V1** (origin to the C6 transverse foramen), **V2** (ascends through the transverse foramina C6→C2), **V3** (loops around the atlanto-occipital joint), and **V4** (pierces the dura at the **foramen magnum** to become intracranial). The two VAs unite at the **pontomedullary junction** to form the basilar artery.
- ▶ Key VA branches: **anterior spinal artery**, **posterior spinal artery**, and the **posterior inferior cerebellar artery (PICA)**.
- ▶ **Basilar artery** runs along the ventral pons (proximal, middle and distal segments), giving **paramedian perforators**, short and long circumferential branches, the **anterior inferior cerebellar artery (AICA)** and the **superior cerebellar artery (SCA)**; it bifurcates at the **pontomesencephalic junction** within the **interpeduncular cistern** into the two PCAs.
- ▶ **Posterior cerebral artery segments**: **P1** (precommunal / “mesencephalic”), **P2** (ambient), **P3** (quadrigeminal) and **P4** (calcarine). In ~20–25% of people the PCA has a **fetal (embryonic) origin** from the internal carotid via the posterior communicating artery (PCoA).
- ▶ Each VA distributes in **three vascular patterns** — median/paramedian, short circumferential and long circumferential arteries — creating **four brainstem territories**: **anteromedial**, **anterolateral**, **lateral** and **posterior**.

Vessel	Main territory supplied	Major perforators/branches
Vertebral artery (V4)	Medulla (anteromedial + lateral), upper cervical cord	Anterior spinal a., PICA
PICA	Inferior vermis, inferior/posterior cerebellar hemisphere, dorsolateral medulla	Medial & lateral branches
Basilar artery	Pons, via paramedian + circumferential branches	Paramedian perforators, AICA, SCA
AICA	Flocculus, middle cerebellar peduncle, lower pontine	Labyrinthine artery

Vessel	Main territory supplied	Major perforators/branches
	tegmentum, inner ear (labyrinthine a.)	
SCA	Superior cerebellum & vermis, dentate nucleus, upper pontine tegmentum	—
PCA	Occipital lobe, inferomedial temporal lobe, midbrain, thalamus, choroid plexus	Thalamoperforating, thalamogeniculate, posterior choroidal, calcarine

Collateral circulation

- ▶ **Circle of Willis** is the principal collateral, joining the anterior (carotid) and posterior systems via the **posterior communicating arteries**; an anatomically complete circle is present in only ~20–25%.
- ▶ Additional collaterals: extracranial–intracranial anastomoses and **leptomeningeal (pial) anastomoses** between terminal cerebral/cerebellar branches.
- ▶ **Persistent primitive carotid–vertebrobasilar anastomoses** may persist — **trigeminal** (commonest, ~0.2%), **acoustic (otic)**, **hypoglossal** and **proatlantal** arteries.

Medullary and pontine syndromes (crossed/alternating)

- ▶ **Lateral medullary (Wallenberg) syndrome** — usually **intracranial VA (V4) occlusion or dissection**, sometimes PICA. *Ipsilateral*: limb and gait ataxia with **body lateropulsion**, facial pain/temperature loss (spinal trigeminal nucleus/tract), palatal–pharyngeal weakness, dysphagia, dysphonia (**nucleus ambiguus**), **Horner syndrome**; *contralateral*: trunk and limb pain/temperature loss (spinothalamic tract); plus vertigo, nausea, nystagmus and intractable hiccups. **Opalski variant** adds ipsilateral hemiplegia.
- ▶ **Medial medullary (Déjérine) syndrome** — anteromedial group (anterior spinal a./VA). *Ipsilateral* LMN tongue weakness (CN XII); *contralateral* hemiparesis and loss of position/vibration (medial lemniscus); **face spared**, sometimes upbeat nystagmus. **Babinski–Nageotte syndrome** = combined medial + lateral medullary (hemimedullary) infarct.
- ▶ **Medial inferior pontine syndrome** (paramedian basilar branch) — ipsilateral gaze palsy, CN VI palsy, nystagmus; contralateral hemiparesis with impaired touch/proprioception.
- ▶ **Lateral inferior pontine syndrome (AICA)** — ipsilateral facial palsy (CN VII), facial sensory loss, gaze palsy, **deafness and tinnitus** (cochlear/labyrinthine infarct), Horner and limb ataxia; contralateral pain/temperature loss. *Sudden bilateral deafness may herald basilar occlusion.*
- ▶ **Lateral superior pontine syndrome (SCA)** — ipsilateral Horner, gaze paresis, hearing loss and severe ataxia; contralateral pain/temperature loss with skew deviation.

- ▶ **Locked-in syndrome** (“ventral pontine”/de-efferented state) — **bilateral basis pontis** infarct from paramedian basilar perforator occlusion: **quadriplegia, anarthria, aphonia, horizontal gaze palsy**, but **preserved consciousness** (ARAS spared) with retained **vertical eye movements and blinking**.
- ▶ *Named classic pontine eponyms: Millard–Gubler, Foville, Raymond, Raymond–Cestan, Marie–Foix, Brissaud.*

Midbrain (PCA-penetrator) and cerebellar syndromes

- ▶ **Weber syndrome** — ventral peduncle: ipsilateral CN III palsy (dilated pupil) + contralateral hemiparesis.
- ▶ **Benedikt syndrome** — tegmentum (red nucleus + CN III): ipsilateral CN III palsy + contralateral hemitremor/hemichorea/hemiathetosis.
- ▶ **Claude syndrome** — dorsal tegmentum: CN III palsy + contralateral cerebellar ataxia/dysmetria (without involuntary movements). **Nothnagel**: CN III palsy + contralateral cerebellar ataxia (superior cerebellar peduncle region).
- ▶ **Parinaud (dorsal midbrain) syndrome** — vertical-gaze palsy, impaired convergence, **convergence–retraction nystagmus**, light–near dissociation, lid retraction (**Collier sign**) and skew deviation.
- ▶ **Cerebellar infarcts**: **PICA** → vertigo, gait/limb ataxia, nystagmus, dysarthria; large oedematous infarcts cause **hydrocephalus and tonsillar herniation**. **AICA** → “ventral cerebellar syndrome” with deafness. **SCA** → “dorsal cerebellar syndrome” with intention tremor and limb/gait ataxia.

PCA territory, thalamic and top-of-the-basilar syndromes

- ▶ **PCA occlusion** — contralateral **homonymous hemianopia** (with **macular sparing** if the occipital pole is spared) from striate cortex/optic radiation/lateral geniculate infarction. Dominant (left) lesions involving the splenium/callosal branches cause **alexia without agraphia**; bilateral occipital infarcts cause **cortical blindness** (**Anton syndrome** = denial of blindness) and **Balint syndrome** (simultanagnosia, optic ataxia, psychic gaze paralysis); medial temporal involvement causes **amnesia**, and prosopagnosia/peduncular hallucinosis may occur.
- ▶ **Thalamic syndromes: Déjérine–Roussy** (posterolateral, thalamogeniculate P2 branches) — contralateral hemisensory loss to all modalities with delayed **central post-stroke pain**, allodynia and hyperalgesia. **Artery of Percheron** — a single trunk from a proximal PCA supplying **both paramedian thalami ± rostral midbrain** → bilateral thalamic infarcts with hypersomnolence, vertical-gaze palsy and memory loss.
- ▶ **“Top-of-the-basilar” syndrome** — embolic occlusion of the **rostral basilar artery** infarcting midbrain, thalamus, hypothalamus, medial temporal and occipital lobes: somnolence/coma, **akinetic mutism**, peduncular hallucinosis, memory loss, vertical-gaze palsy, pseudo-abducens palsy, convergence–retraction nystagmus and cortical visual loss.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Vertebrobasilar tree (ventral view):** label *Subclavian artery, Vertebral artery (V1–V4), Anterior spinal artery, PICA, Basilar artery, AICA, Superior cerebellar artery (SCA), Posterior cerebral artery (P1–P4), Posterior communicating artery*, and the **Circle of Willis**.
- ▶ **Diagram 2 — Medullary cross-section (Wallenberg):** label *Spinal trigeminal nucleus & tract, Nucleus ambiguus, Spinothalamic tract, Inferior cerebellar peduncle (restiform body), Vestibular nuclei, Descending sympathetic fibres*, shading the **dorsolateral PICA/VA territory**.

Clinical / Diagnostic significance

- ▶ **Bedside clue:** “crossed” findings (ipsilateral cranial-nerve palsy + contralateral long-tract deficit), vertigo with nystagmus, diplopia, dysarthria, dysphagia, ataxia and bilateral/shifting motor-sensory signs localise to the posterior circulation; **isolated transient vertigo, diplopia, dysarthria or dysphagia alone are insufficient** to diagnose a vertebrobasilar TIA.
- ▶ **Imaging:** non-contrast CT first to exclude haemorrhage; **MRI/DWI** (with attention to the posterior fossa, where CT is poor) plus **CT/MR angiography** of head and neck; consider CT perfusion for delayed presentations.
- ▶ **Acute reperfusion (Harrison/CMDT):** IV rtPA 0.9 mg/kg (max 90 mg; 10% bolus then remainder over 1 h) within 4.5 h, or IV tenecteplase 0.25 mg/kg (max 25 mg); **mechanical thrombectomy 0–6 h**, and in selected cases **6–24 h**; non-randomised data support thrombectomy for **basilar artery occlusion up to 24 h**.
- ▶ **Cerebellar infarction** demands vigilance for mass effect, obstructive hydrocephalus and tonsillar/upward herniation — may need EVD and suboccipital decompressive craniectomy.
- ▶ **Secondary prevention:** antiplatelet therapy (aspirin ± clopidogrel after TIA/minor stroke), anticoagulation for atrial fibrillation/cardioembolism, and aggressive risk-factor control; **spinal manipulation** is a recognised cause of VA dissection.

High-yield exam pointers

- ▶ VA segments V1–V4; basilar bifurcates into PCAs at the **interpeduncular cistern**; PCA segments P1–P4.
- ▶ Fetal PCA in ~20–25%; complete circle of Willis in only ~20–25%.
- ▶ **Wallenberg = lateral medullary**, commonest brainstem stroke; usual cause **intracranial VA (V4) occlusion/dissection**, *not* PICA in most cases.
- ▶ **Crossed sensory loss** (ipsilateral face + contralateral body) is the signature of Wallenberg.
- ▶ **Weber = peduncle**, **Benedikt = tegmentum (red nucleus)**, **Claude = dorsal tegmentum + cerebellar**, **Parinaud = dorsal midbrain/vertical-gaze**.

- ▶ **Locked-in syndrome** = bilateral basis pontis; consciousness and vertical gaze preserved.
- ▶ **Artery of Percheron** → bilateral paramedian thalamic infarction; **Déjérine–Roussy** = thalamic pain syndrome.
- ▶ **PCA stroke** → macular-sparing homonymous hemianopia; bilateral → cortical blindness/**Anton syndrome**.
- ▶ **Basilar occlusion / top-of-the-basilar** is a time-critical emergency; thrombectomy considered up to 24 h.

SOURCE & COVERAGE

- ▶ **Brazis — Localization in Clinical Neurology — “Vascular Syndromes of the Forebrain, Brainstem, and Cerebellum”** (primary source for posterior-circulation anatomy, segments, and brainstem/cerebellar/PCA/thalamic syndromes).
- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Ischemic Stroke” and “Introduction to Cerebrovascular Diseases” (mechanisms, acute thrombolysis/thrombectomy).
- ▶ **CMDT 2026** — “Nervous System Disorders” (Stroke / cerebral infarction) (clinical correlation of vertebrobasilar occlusion and current reperfusion time-windows).

Coverage note: Harrison 22e covers posterior-circulation *syndromes* and management but treats the detailed vascular neuroanatomy thinly; the segmental anatomy and the named brainstem eponyms in this answer are grounded in Brazis. Standard neuroanatomical points (e.g., labyrinthine artery from AICA) are universally accepted textbook neurology.



Differential Diagnosis of Seizures

Asked in: Paper III Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — A **seizure** (Latin *sacire*, “to take possession of”) is a transient occurrence of signs or symptoms due to **abnormal excessive or synchronous neuronal activity** in the brain; *epilepsy* denotes a tendency to **recurrent unprovoked seizures**. Because the diagnosis of a seizure rests largely on clinical grounds — examination and laboratory studies are frequently normal — a wide range of paroxysmal, transient, stereotyped events can imitate it. Distinguishing true epileptic seizures from these “non-epileptic” mimics is critical, as misdiagnosis leads to unnecessary, potentially teratogenic antiseizure medication (ASM), loss of driving privileges and a missed treatable cause (e.g. cardiac syncope). The cornerstone of differentiation is a **meticulous history with an independent eyewitness account**, supplemented when needed by video-EEG, tilt-table testing and cardiac electrophysiology.

Step 1 — Is the event actually a seizure?

- ▶ The first task is to decide whether the paroxysmal event was a seizure at all, then whether it was an *epileptic* seizure versus a non-epileptic mimic, then (if epileptic) focal versus generalized onset.
- ▶ **Features favouring an epileptic seizure:** a stereotyped **aura**, **cyanosis**, sustained tonic–clonic motor activity lasting >15 s, **lateral tongue biting**, urinary/faecal incontinence, **post-ictal confusion/disorientation**, post-ictal headache, muscle soreness, **Todd's paralysis**, sleepiness and **complete amnesia** for the loss of consciousness.
- ▶ **Positive vs negative symptoms** — seizures involving sensory/motor cortex produce *positive* phenomena (twitching, paraesthesiae, flashing lights) that **march/spread over seconds**; ischaemic events (TIA) classically produce *negative* phenomena (weakness, numbness) with no march.
- ▶ **Adjunctive biomarkers:** a transient rise in **serum prolactin** within the first 30 min post-ictally supports a generalized or some focal seizures (a normal baseline value is rarely available, limiting reliability); **serum lactate >2.4 mmol/L for up to 3 h** after a convulsion favours a generalized convulsive *epileptic* seizure over PNES or syncope.
- ▶ **Gold standard for ambiguous events:** prolonged **video-EEG monitoring** capturing a habitual attack — generalized tonic–clonic seizures *always* produce marked ictal/post-ictal EEG change, whereas PNES does not (caveat: some frontal/orbitofrontal and supplementary-motor seizures have no scalp EEG correlate).

Classification of conditions that mimic seizures (Harrison Table 436-6)

Category	Specific mimics
Syncope	Vasovagal (neurally mediated), cardiac arrhythmia, valvular heart disease (aortic stenosis), cardiac failure, orthostatic hypotension
Cerebrovascular	Transient ischaemic attack, basilar-artery TIA , transient global amnesia, transient focal neurologic episodes (cerebral amyloid angiopathy)
Sleep disorders	Narcolepsy–cataplexy, benign sleep myoclonus, parasomnias (night terrors, sleepwalking, REM-behaviour disorder)
Movement disorders	Tics, non-epileptic myoclonus, paroxysmal kinesigenic/non-kinesigenic dyskinesia (choreoathetosis), hyperekplexia
Psychological	Psychogenic non-epileptic seizure (PNES) , hyperventilation, panic attack, rage attacks
Metabolic / toxic	Hypoglycaemia, hypoxia, alcoholic blackouts, delirium tremens, psychoactive drugs (hallucinogens)

Category	Specific mimics
Migraine	Migraine aura, confusional migraine, basilar migraine (“migralepsy”)
Special — children	Breath-holding spells, Sandifer syndrome (GERD posturing), benign paroxysmal vertigo, apnoea, cyclic vomiting / abdominal migraine

Seizure versus syncope — the commonest dilemma (Harrison Table 436-7)

Feature	Generalized tonic-clonic seizure	Syncope
Precipitant	Usually none	Emotional stress, pain, Valsalva, prolonged standing, orthostasis, cardiac cause
Premonitory symptoms	None, or aura (e.g. odd odour)	Tiredness, nausea, diaphoresis , tunnelling/greying of vision
Posture at onset	Variable	Usually erect
Transition to unconsciousness	Often immediate	Gradual over seconds (sudden with arrhythmia)
Duration of unconsciousness	Minutes	Seconds , rapid recovery on recumbency
Convulsive movements	30–60 s, sustained tonic-clonic	Never >15 s ; brief, multifocal , arrhythmic myoclonus
Face during event	Cyanosis, frothing	Pallor
Post-event confusion	Many minutes to hours	<5 min / minimal
Tongue biting	Sometimes (lateral)	Rarely
Aching of muscles	Often	Sometimes

- ▶ **Convulsive (“anoxic”) syncope** — a sustained drop in cerebral perfusion (e.g. fainting while kept upright in a dental chair) commonly produces brief multifocal myoclonus, posturing, head turning and oral automatisms; there is **no associated EEG discharge** (the motor activity is brainstem-generated), and post-ictal confusion is minimal. Rarely, true syncope triggers a genuine *anoxic-epileptic seizure*.
- ▶ **Cardiac syncope** (arrhythmia, aortic stenosis) is typically abrupt with **no prodrome**; suspect it in older patients or those with structural heart disease, and exertional events with a systolic murmur — it mandates ECG/Holter/tilt-table evaluation as it is life-threatening.

Psychogenic non-epileptic seizures (PNES / pseudoseizures)

- ▶ Emotionally-triggered attacks **without ictal epileptic discharge**, usually part of a **conversion (somatoform) disorder** (or, rarely, malingering); ~70–80% **female**, peak onset 15–35 years, frequent antecedent of **childhood sexual/physical abuse**, head injury, fibromyalgia or chronic pain.
- ▶ **Clinical pointers favouring PNES**: **out-of-phase / asynchronous** thrashing of limbs, **forward pelvic thrusting**, **side-to-side head shaking**, **forced eye closure with resistance to eye opening**, “pseudosleep” onset, **waxing-and-waning prolonged duration** (often >2 min, even *pseudo-status*), emotional vocalisation (weeping, stuttering), preserved awareness with goal-directed behaviour, biting the **tip of the tongue/lip** (vs lateral in true seizures), shallow rapid post-ictal breathing, and **absence of post-ictal stertor / confusion**.
- ▶ **PNES coexists with epilepsy** in ~10–15% of patients, so its diagnosis does not exclude true epilepsy. **Diagnosis is confirmed by video-EEG** demonstrating typical semiology with no ictal correlate; serum prolactin and lactate remain unchanged.

Other neurological and medical mimics

- ▶ **TIA** — longer duration (usually >2 min), no spread/march, *negative* symptoms; *limb-shaking* TIA (brief, <5 min, precipitated by standing/exercise) signals **high-grade internal carotid stenosis**.
- ▶ **Migraine** — aura spreads slowly (cortical spreading depression ~3 mm/min) and lasts **5–60 min** (vs epileptic auras typically <30 s); visual aura is a fortification spectrum/scintillating scotoma (vs coloured circles in occipital seizures); basilar migraine causes brainstem symptoms then altered consciousness.
- ▶ **Transient global amnesia** — isolated anterograde amnesia for hours with preserved complex behaviour, in older adults.
- ▶ **Parasomnias** (somnambulism, night terrors, REM-behaviour disorder) — arise from slow-wave sleep ~90 min into the night; frontal-lobe seizures are brief, stereotyped, hypermotor and arise from stage 1–2 / sleep–wake transition.
- ▶ **Narcolepsy-cataplexy** — emotion-triggered loss of tone with **fully preserved consciousness and memory**.
- ▶ **Paroxysmal movement disorders** — kinesigenic dyskinesia (movement-triggered, consciousness preserved, responds to ASM), non-kinesigenic dyskinesia, hyperekplexia (exaggerated startle).
- ▶ **Panic attacks / hyperventilation** — paraesthesiae, derealisation and fear; distinguished by inter-ictal anxiety and clear situational triggers; **rage attacks** are situational and goal-directed.
- ▶ **Metabolic / toxic** — hypoglycaemia, hypoxia, hyponatraemia, uraemia, hepatic failure, alcohol/sedative withdrawal — these cause *provoked (acute symptomatic) seizures*, which by definition are **not epilepsy** and rarely cause chronic epilepsy.

Age-specific differential

- ▶ **Neonates/infants:** apnoea, jitteriness (metabolic), exaggerated startle, **Sandifer syndrome** (GERD posturing), **breath-holding spells** (cyanotic preceded by crying; pallid is reflex asystolic).
- ▶ **Children/adolescents:** shuddering attacks, stereotypies, tics, daydreaming mistaken for absence (and vice-versa).
- ▶ **Older adults:** TIA, transient global amnesia, cardiac arrhythmia and convulsive syncope predominate.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm for the adult with a “seizure”** — central box *Paroxysmal event* → branch on History + eyewitness + examination → boxes to **EXCLUDE: Syncope · TIA · Migraine · Acute psychosis/PNES · Other episodic cerebral dysfunction (metabolic, sleep, movement disorder)** → if seizure confirmed → arms “No prior epilepsy” (labs, MRI, EEG) vs “Known epilepsy” (assess ASM adequacy/levels). Labels: *History, Eyewitness account, EEG, MRI, Video-EEG, Prolactin, Lactate*.
- ▶ **Seizure-vs-syncope timeline** — two parallel horizontal arrows labelled *Seizure* and *Syncope* with markers: Prodrome (aura vs nausea/diaphoresis/greying vision), Posture (variable vs erect), LOC (immediate/minutes vs gradual/seconds), Motor (tonic-clonic 30–60 s vs multifocal myoclonus <15 s), Colour (cyanosis vs pallor), Recovery (post-ictal confusion vs rapid).

Clinical / Diagnostic significance

- ▶ An eyewitness/home-video account is the single most valuable diagnostic tool; up to one-third of “refractory epilepsy” referrals to tertiary centres prove to be PNES.
- ▶ **Always exclude provoked (acute symptomatic) seizures** — hypoglycaemia, hyponatraemia, uraemia, hepatic failure, alcohol/benzodiazepine withdrawal, eclampsia, and offending **drugs** (e.g. tramadol, bupropion, isoniazid, β -lactams/quinolones, theophylline, cocaine) — because treatment is correction of the cause, not chronic ASM.
- ▶ **Investigations:** routine 12-lead ECG in **every first seizure** (to catch long-QT/arrhythmic syncope); MRI brain (superior to CT) for structural cause; EEG (first inter-ictal EEG normal in ~50%, yield rises with sleep-deprived/repeat recordings); tilt-table and Holter for suspected syncope; blood glucose, electrolytes, calcium, magnesium, renal/hepatic panel and toxicology guided by context; **lumbar puncture** if CNS infection suspected.

High-yield exam pointers

- ▶ Two commonest mimics: **syncope** (especially in elderly) and **PNES** (especially young women) — *video-EEG is the gold standard* for both.
- ▶ **Lateral** tongue bite, cyanosis, post-ictal confusion and **complete amnesia** favour seizure; **pallor**, erect posture, rapid recovery and recollection favour syncope.

- ▶ Convulsive syncope myoclonus is **multifocal, arrhythmic** and **<15 s** with **no EEG discharge**.
- ▶ **Post-ictal prolactin** (within 30 min) and **serum lactate >2.4 mmol/L** (up to 3 h) support epileptic over psychogenic events.
- ▶ PNES clues: forced eye closure, side-to-side head, pelvic thrusting, out-of-phase limb movements, waxing/waning long duration, **tip-of-tongue** biting; ~10–15% also have true epilepsy.
- ▶ TIA = *negative* symptoms, no march; **limb-shaking TIA = carotid stenosis**. Migraine aura = slow spread, **5–60 min** (vs epileptic aura <30 s).
- ▶ A single provoked seizure from a reversible metabolic/toxic cause is **NOT epilepsy** and usually needs no ASM.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Seizures and Epilepsy” (Differential Diagnosis of Seizures; Table 436-6 list of mimics; Table 436-7 seizure-vs-syncope; syncope, convulsive syncope and psychogenic seizures; post-ictal prolactin; diagnostic algorithm Fig. 436-2).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “The Epilepsies” (Differential Diagnosis: PNES semiology, syncope/convulsive syncope, migraine vs occipital seizure, parasomnias, narcolepsy-cataplexy, paroxysmal movement disorders, TIA/limb-shaking, transient global amnesia, age-specific imitators; evaluation of recent-onset seizures).
- ▶ **CMDT 2026** — “Nervous System Disorders” (Seizures & Epilepsy) (differential of focal vs generalized seizures: TIA, migraine aura, transient focal neurologic episodes/CAA, panic, rage, cardiac, brainstem ischaemia, PNES; serum lactate >2.4 mmol/L adjunct; management framing).
- ▶ *Coverage note:* Brazis (Localization) and DeJong (Neurologic Examination) carry no dedicated seizure-mimic chapter; depth was therefore drawn from Bradley's epilepsy chapter, which fully covers the subspecialty detail.



Paraneoplastic Neurological Syndromes: Presentation, Associated Tumours and Antibodies

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — Paraneoplastic neurological syndromes (PNS), also called paraneoplastic neurologic disorders (PNDs), are cancer-related, immune-mediated syndromes that can affect *any* level of the nervous system without direct tumour invasion, metastasis, or treatment toxicity. Most are triggered when a tumour ectopically expresses neuronal (“onconeuroal”) proteins, provoking an antineuronal antibody and T-cell response misdirected at the nervous system. They are clinically

important because in ~60–65% the neurological deficit precedes the cancer diagnosis, so recognition allows early tumour detection. Clinically disabling PNDs occur in 0.5–1% of all cancer patients, but in 2–3% of those with small-cell lung cancer (SCLC) or neuroblastoma and 30–50% of those with thymoma.

Pathogenesis — the two-arm rule (determines presentation, antibody and prognosis)

- ▶ **Antibodies against intracellular antigens** (e.g., Hu, Yo, Ri, Ma2, CRMP5/CV2, amphiphysin): the antibody is a *marker* but not directly pathogenic; injury is driven by **cytotoxic CD8⁺ T cells** producing irreversible neuronal loss → poorly responsive to immunotherapy. These strongly predict an underlying cancer.
- ▶ **Antibodies against cell-surface / synaptic antigens** (e.g., NMDAR, AMPAR, GABA-B/A R, LGI1, Caspr2, VGCC, glycine R): the antibody is **directly pathogenic** (receptor cross-linking, internalisation, functional blockade, or disruption of protein–protein interactions) and the effect is **reversible** → these respond to immunotherapy and tumour treatment, occur with or without cancer, and may affect children/young adults; some follow viral (herpes simplex, Japanese) encephalitis.
- ▶ **Antibody yield is limited**: only 60–70% of CNS PNDs and <20% of peripheral PNDs have a detectable antibody, so a negative panel does not exclude PNS.

Antibody-based risk classification (2021 framework, after Graus & Dalmau) with tumours

The probability of an underlying cancer is now graded by the antibody — high (>70%), intermediate (30–70%) or low (<30%) risk.

Antibody	Risk (cancer prob.)	Antigen site	Typical syndrome	Associated tumour
Anti-Hu (ANNA-1)	High	Intracellular	Encephalomyelitis, sensory neuronopathy	SCLC
Anti-Yo (PCA-1)	High	Intracellular	Rapidly progressive cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA-2)	High	Intracellular	Cerebellar degeneration, opsoclonus, brainstem encephalitis	Breast, gynaecologic, SCLC
Anti-CRMP5 (CV2)	High	Intracellular	Encephalomyelitis, chorea, optic	SCLC, thymoma

Antibody	Risk (cancer prob.)	Antigen site	Typical syndrome	Associated tumour
			neuritis, uveitis, neuropathy	
Anti-Tr (DNER)	High	Cell surface	Rapidly progressive cerebellar syndrome	Hodgkin lymphoma
Anti-Ma2 / Ma proteins	High	Intracellular	Limbic, hypothalamic, brainstem encephalitis	Testicular germ-cell (Ma2); other solid (Ma)
Anti-PCA2 (MAP1B)	High	Intracellular	Sensorimotor neuropathy, cerebellar, encephalomyelitis	SCLC, breast
Anti-Kelch-like protein 11	High	Intracellular	Brainstem encephalitis, ataxia, sensorineural hearing loss	Seminoma / germ-cell, teratoma
Anti-amphiphysin	High	Intracellular*	Stiff-person syndrome, encephalomyelitis	Breast, SCLC
Anti-SOX1	High	Intracellular	LEMS, cerebellar syndrome	SCLC
Anti-NMDAR	Intermediate	Surface	Anti-NMDAR encephalitis	Ovarian teratoma (young women)
Anti-AMPA	Intermediate	Surface	Limbic encephalitis with relapses	SCLC, thymoma, breast
Anti-GABA-B R	Intermediate	Surface	Limbic encephalitis with early prominent seizures	SCLC
Anti-Caspr2	Intermediate	Surface	Morvan syndrome, neuromyotonia	Thymoma
Anti-mGluR5	Intermediate	Surface	Encephalitis (Ophelia syndrome)	Hodgkin lymphoma

Antibody	Risk (cancer prob.)	Antigen site	Typical syndrome	Associated tumour
Anti-VGCC (P/Q)	Intermediate	Surface	LEMS, cerebellar degeneration	SCLC
Anti-LGI1	Low	Surface	Limbic encephalitis, hyponatraemia, faciobrachial dystonic seizures	Rarely thymoma
Anti-GABA-A R	Low	Surface	Encephalitis, refractory seizures / status	Thymoma (~20%)
Anti-DPPX	Low	Surface	Agitation, myoclonus, hyperekplexia, diarrhoea/weight loss	B-cell neoplasms (rare)
Anti-glycine R	Low	Surface	PERM, stiff-person	Rarely thymoma, lung, Hodgkin
Anti-IgLON5	Low	Surface	NREM/REM parasomnia, stridor, bulbar/movement disorder	No tumour
Anti-GAD65	Low	Intracellular	Stiff-person, cerebellar ataxia, limbic encephalitis	Infrequent (thymoma, lung, breast)
Anti-AChR (muscle)	Low	Surface	Myasthenia gravis	Thymoma

*Amphiphysin is likely exposed at the cell surface during synaptic-vesicle endocytosis. Other low-risk antibodies (mGluR1–Hodgkin; AQP4; MOG; neuronal AChR–autonomic ganglionopathy/SCLC) carry little or no cancer association.

Clinical presentation by anatomical level (“classic” high-risk syndromes)

- ▶ **Limbic encephalitis** — subacute confusion, depression, agitation, anxiety, **prominent short-term memory loss**, temporal-lobe or generalised seizures; MRI shows uni-/bilateral mesial-temporal T2/FLAIR signal. Antigens: Hu, Ma2, AMPAR, GABA-B R, LGI1, Caspr2.
- ▶ **Paraneoplastic cerebellar degeneration (PCD)** — prodrome of dizziness/vertigo, then rapidly progressive dysarthria, truncal & appendicular ataxia, **downbeat nystagmus**; pathology =

extensive **Purkinje-cell loss**. Tumours: SCLC, breast, ovary, Hodgkin. Anti-Yo (breast/gynae), anti-Tr (Hodgkin), anti-VGCC/anti-Hu (SCLC).

- ▶ **Encephalomyelitis** — multifocal involvement of cortex, brainstem, cerebellum, spinal cord, dorsal root ganglia and autonomic nerves; Hu/CRMP5 with SCLC. Cardiac arrhythmia, postural hypotension and central hypoventilation may be fatal.
- ▶ **Brainstem encephalitis** — eye-movement disorder (nystagmus, opsoclonus, supranuclear/nuclear palsy), cranial-nerve palsies, dysarthria, dysphagia. Ma2 → *upper* brainstem with vertical gaze palsy (downward progression); Hu → *lower* brainstem (upward progression).
- ▶ **Opsoclonus-myoclonus** — involuntary chaotic multidirectional saccades + myoclonus + ataxia; **children** → **neuroblastoma** (≥50%), adults → SCLC, breast (anti-Ri). Thought to reflect disinhibition of the cerebellar fastigial nucleus.
- ▶ **Anti-NMDAR encephalitis** — young women/children; viral-like prodrome → severe psychiatric symptoms, insomnia, reduced verbal output, memory loss, seizures, fall in consciousness, **orofacial-limb-trunk dyskinesias**, autonomic instability and hypoventilation; **46% of females ≥12 yr have an ovarian teratoma**. ~85–90% recover with treatment.
- ▶ **Stiff-person spectrum** — progressive axial **rigidity and stimulus-sensitive painful spasms** with continuous motor-unit activity on EMG; GAD65 (mostly non-paraneoplastic), amphiphysin (paraneoplastic, breast/SCLC), glycine-R (PERM).
- ▶ **Sensory neuronopathy (dorsal root ganglionopathy)** — asymmetric, multimodal sensory loss, painful dysaesthesias, sensory **ataxia and pseudoathetosis**, absent/low SNAPs with **preserved motor conduction**; ~80% have SCLC with anti-Hu.
- ▶ **Neuromuscular junction / muscle / eye** — LEMS (proximal leg weakness, dry mouth/autonomic features, reflexes that *potentiate* after exercise; incremental CMAP at high-rate RNS; P/Q-VGCC; ~60% SCLC), **myasthenia gravis** (thymoma, AChR antibody), dermatomyositis (heliotrope rash, Gottron papules; TIF1-γ/NXP-2 predict malignancy), necrotizing autoimmune myopathy (anti-HMGCR/SRP), and **cancer-associated / melanoma-associated retinopathy** (anti-recoverin; night blindness, abnormal ERG).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Two-arm pathogenesis schematic**. Labels: *Tumour cell expressing onconeural antigen* → *dendritic/antigen-presenting cell* → *regional lymph node* → *CD4⁺/CD8⁺ T cells + B cells*; left arm “Intracellular antigen (Hu/Yo/Ma2) → cytotoxic CD8⁺ T-cell attack → irreversible neuronal loss → poor immunotherapy response”; right arm “Cell-surface antigen (NMDAR/LGI1/VGCC) → plasma-cell antibody → receptor cross-linking/internalisation/blockade → reversible → immunotherapy-responsive”; mark the *blood-brain barrier*.

- ▶ **Neuraxis map of syndromes.** Label a midline CNS-to-muscle figure: *Cortex/limbic* = *limbic & cortical encephalitis*; *Brainstem* = *brainstem encephalitis*; *Cerebellum* = *PCD, opsoclonus-myoclonus*; *Spinal cord* = *myelitis, motor-neuron syndrome*; *Dorsal root ganglion* = *sensory neuronopathy*; *Autonomic nerves* = *dysautonomia/pseudo-obstruction*; *NMJ* = *LEMS / myasthenia gravis*; *Muscle* = *dermatomyositis, necrotizing myopathy*; *Retina* = *CAR / MAR*.

Clinical / Diagnostic significance

- ▶ **Diagnostic triad of certainty** (type of syndrome + a high/intermediate-risk antibody + a consistent cancer) lets the disorder be graded as definite vs possible PNS; an antibody whose tumour association is atypical (e.g., anti-Yo with lung cancer) should prompt a search for a *second* neoplasm.
- ▶ **CSF:** inflammatory profile — mild–moderate lymphocytic pleocytosis (<200 cells), raised protein, intrathecal IgG synthesis and oligoclonal bands.
- ▶ **MRI:** usually nonspecific except mesial-temporal FLAIR change in limbic encephalitis; later cerebellar atrophy in PCD. **Brain/body ¹⁸F-FDG-PET** can disclose tumours (and early inflammatory hypermetabolism) missed by other imaging.
- ▶ **Tumour hunt:** CT chest/abdomen + whole-body PET; **testicular/transvaginal ultrasound and pelvic MRI/CT** for germ-cell tumour/teratoma. If initial screen is negative, repeat periodically for ≥3 years (e.g., after a LEMS diagnosis). The **DELTA-P score** and **anti-SOX1** help predict SCLC in LEMS.
- ▶ **Management principles:** (1) **treat the tumour promptly** — the single most effective measure; (2) surface-antigen disorders → first-line glucocorticoids + IVIg + plasma exchange, second-line **rituximab/cyclophosphamide**; (3) intracellular-antigen disorders respond poorly — focus on tumour control and T-cell-directed therapy; (4) symptomatic agents — **3,4-diaminopyridine** for LEMS, GABA-enhancing drugs (diazepam, baclofen, valproate) for stiff-person syndrome.
- ▶ **Checkpoint inhibitors:** in <3% of treated patients cause neurologic immune-related adverse events that may carry classic neuronal antibodies and be clinically indistinguishable from spontaneous PNS.

High-yield exam pointers

- ▶ ~60–65% of PNS present **before** the cancer is known; suspect PNS with subacute, multifocal deficits and an inflammatory CSF.
- ▶ **Intracellular antigen = cytotoxic T-cell = irreversible = poor response; surface antigen = antibody-mediated = reversible = treatable.**

- ▶ Memorise the high-yield pairs: Hu–SCLC, Yo–ovary/breast, Tr(DNER)–Hodgkin, Ma2–testicular germ-cell, NMDAR–ovarian teratoma, VGCC–LEMS/SCLC, amphiphysin–breast/stiff-person, AChR–thymoma/MG.
- ▶ SCLC is the commonest single tumour across PNS; **neuroblastoma** drives childhood opsoclonus-myoclonus; **thymoma** has the highest PND frequency (30–50%).
- ▶ Faciobrachial dystonic seizures + hyponatraemia = **anti-LGI1**; Morvan syndrome/neuromyotonia = **anti-Caspr2**; PERM = **glycine-receptor**.
- ▶ LEMS = reflexes that **potentiate** after exercise + **incremental** RNS response; opposite of myasthenia gravis (decremental).
- ▶ For paraneoplastic **peripheral** neuropathy the only useful antibodies are **anti-Hu** and **anti-CRMP5/CV2**.
- ▶ Treat the tumour first; immunotherapy works best in surface-antibody syndromes and anti-NMDAR encephalitis (85–90% improve).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis” (Dalmau & Graus): antibody risk-classification tables (high/intermediate/low), pathogenesis, syndrome descriptions, NMDAR/LGI1/Caspr2 detail, management.
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Paraneoplastic Disorders of the Nervous System” (Rosenfeld & Dalmau): onconeural-antigen mechanism, antibody–syndrome–tumour table, PCD/encephalomyelitis/sensory-neuronopathy/LEMS detail, DELTA-P and SOX1, diagnostic certainty and FDG-PET.
- ▶ **CMDT 2026** — neurologic and cancer chapters for current tumour-screening and immunotherapy management context.

Coverage note: The corpus covers this topic in depth. The “high/intermediate/low-risk” labels follow the 2021 updated PNS diagnostic-criteria terminology used verbatim in Harrison 22e; the numeric PNS-Care score itself is not reproduced in the source and is therefore not stated.



Discuss the Causes and Management of Seizures

Asked in: Paper III Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — A **seizure** (Latin *sacire*, “to take possession of”) is a *transient* occurrence of signs or symptoms due to **abnormal, excessive or synchronous neuronal activity** in the brain. **Epilepsy** is a chronic disorder of *recurrent unprovoked seizures*, operationally defined as **≥2 unprovoked seizures >24 h apart** (or one unprovoked seizure with a high recurrence risk, or an epilepsy syndrome).

About 5–10% of people have at least one seizure in life; epilepsy prevalence is 5–30 per 1000. A seizure is a *symptom*, not a disease — so management hinges on accurate classification, finding the cause, and rationally selecting an antiseizure medication (ASM).

Classification of Seizures (ILAE 2017)

Type determines aetiologic work-up, drug choice and prognosis. The 2017 ILAE scheme classifies by **onset, awareness and motor features**; the terms *simple/complex partial* and *secondary generalisation* are obsolete.

Onset	Subtypes	Key features
Focal onset (one hemispheric network)	<i>Aware vs impaired awareness; motor vs nonmotor; focal → bilateral tonic-clonic</i>	Aura, automatisms (lip-smacking, picking), Jacksonian march, Todd's paresis, <i>epilepsia partialis continua</i> ; often structural
Generalised onset (bilateral networks)	Motor: tonic-clonic, tonic, clonic, myoclonic, atonic (drop attacks), epileptic spasms; Nonmotor: typical / atypical absence	Ictal cry, tongue-bite, incontinence, post-ictal confusion; absence = abrupt, no post-ictal phase
Unknown onset	Motor / nonmotor / unclassified	Insufficient information

- ▶ **Typical absence** — onset 4–10 yr; brief lapses without postural loss; EEG 3-Hz **generalised spike-and-wave**, provoked by hyperventilation; 15–20% of childhood epilepsy.
- ▶ **Atypical absence** — slower onset/offset, EEG ≤ 2.5 -Hz spike-wave, with diffuse structural disease/developmental delay; drug-resistant.

Epilepsy syndromes (high-yield)

- ▶ **Juvenile myoclonic epilepsy (JME)** — early adolescence, morning myoclonic jerks, provoked by sleep deprivation; often GTCS $\pm$ absence; responds to valproate/levetiracetam.
- ▶ **Lennox-Gastaut syndrome** — *triad*: (1) multiple seizure types (tonic, atonic, atypical absence), (2) EEG slow (<3 Hz) spike-wave, (3) developmental delay; refractory.
- ▶ **Mesial temporal lobe epilepsy (MTLE)** — commonest focal-impaired-awareness syndrome; hippocampal sclerosis on T2 MRI; drug-refractory but **surgically curable**.

Causes / Aetiology of Seizures

Seizures result from a **shift in the excitation–inhibition balance**, produced by an interplay of *endogenous* (threshold/genetic), *epileptogenic* (lesional) and *precipitating* (provocative) factors. The ILAE recognises **six aetiologic categories (CMDT)**: **structural, genetic, infectious, metabolic, immune, unknown**.

Aetiology by age (clinically the most useful framework):

Age group	Common causes
Neonates (<1 month)	Perinatal hypoxia-ischaemia, intracranial haemorrhage/trauma, CNS infection, metabolic (hypoglycaemia, hypocalcaemia, hypomagnesaemia, pyridoxine [B6] deficiency), drug withdrawal, developmental/genetic disorders
Infants & children (1 mo–12 yr)	Febrile seizures, genetic/metabolic epilepsy syndromes, CNS infection, developmental disorders, trauma
Adolescents (12–18 yr)	Trauma, genetic disorders, infection, illicit drugs, brain tumour
Young adults (18–35 yr)	Trauma, alcohol withdrawal, illicit drugs, brain tumour, autoantibodies (e.g. anti-LGI1, anti-NMDA-R)
Older adults (>35 yr)	Cerebrovascular disease ($\approx$ 50% of new epilepsy >65 yr), brain tumour, alcohol withdrawal, metabolic (uraemia, hepatic failure, dysglycaemia, electrolytes), Alzheimer/degenerative, autoantibodies

Salient points on causes:

- ▶ **Febrile seizures** — 3 months–5 yr (peak 18–24 mo), prevalence 3–5%; *simple* (brief, generalised, single) carry no increased epilepsy risk, *complex* (>15 min, focal, or repeated) carry a 2–5% risk.
- ▶ **Head trauma** — penetrating wound, depressed skull fracture, intracranial haemorrhage or prolonged post-traumatic coma/amnesia → **30–50% risk** of epilepsy; severe penetrating injury up to 45%.
- ▶ **Provoked/acute symptomatic seizures** (metabolic, drug, alcohol withdrawal) are *not* epilepsy — treat the cause, not with chronic ASM.
- ▶ **Provoking drugs/toxins** — β -lactams, quinolones, **isoniazid**, tramadol/meperidine, bupropion, clozapine, lithium, theophylline, ciclosporin/tacrolimus, cocaine/amphetamine; and **withdrawal** of alcohol, benzodiazepines, barbiturates, baclofen.
- ▶ **Genetic channelopathies** — e.g. *SCN1A* (Dravet syndrome — **avoid Na-channel blockers**), *KCNQ2*, *CHRNA4*, *SLC2A1* (GLUT-1 deficiency → **ketogenic diet**).

Basic mechanism (pathophysiology — exam framer)

- ▶ Hallmark of a focal seizure is the **paroxysmal depolarisation shift (PDS)** — prolonged Ca^{2+} -mediated membrane depolarisation opening voltage-gated Na^+ channels, generating hyper-synchronous repetitive firing (the EEG “spike”).
- ▶ Spread is normally checked by GABAergic **surround inhibition**; recruitment occurs via rising extracellular K^+ , presynaptic Ca^{2+} accumulation and **NMDA-receptor** activation.

- ▶ Absence seizures arise from **thalamocortical oscillations** via **GABA-B receptors** and **T-type Ca^{2+} channels** (target of ethosuximide/valproate).
- ▶ **Epileptogenesis** = transformation of a normal network into a chronically hyperexcitable one (months–years after trauma/stroke/infection) — currently no proven *antiepileptogenic* drug.

Diagnostic evaluation

- ▶ **History** is paramount (diagnosis is largely clinical) — eyewitness account, aura, semiology, post-ictal state, precipitants, risk factors; *exclude mimics* (syncope, TIA, migraine, psychogenic non-epileptic seizures).
- ▶ **Blood work** — glucose, electrolytes, Ca^{2+} , Mg^{2+} , renal/hepatic function, CBC, toxicology screen; LP if meningitis/encephalitis suspected (mandatory in HIV); serum/CSF **autoantibodies** in fulminant epilepsy with psychiatric/cognitive change.
- ▶ **EEG** — supports diagnosis (interictal spikes/sharp waves), classifies seizures, guides prognosis; a normal interictal EEG **does not exclude** epilepsy (normal in 50–80% initially). Video-EEG telemetry is the gold standard for diagnostic uncertainty and presurgical localisation.
- ▶ **Neuroimaging** — MRI > CT for all new-onset seizures (detects tumour, vascular malformation, mesial temporal sclerosis, cortical dysplasia); emergent CT if mass/infection suspected and MRI unavailable.
- ▶ **Genetic testing** — for suspected genetic syndromes; guides therapy (e.g. *SLC2A1* → ketogenic diet; *ALDH7A1* → pyridoxine; avoid Na-blockers in *SCN1A*).
- ▶ **PNES vs epilepsy** — pelvic thrusting, side-to-side head movement, asynchronous limb shaking, ictal eye closure, waxing-waning, *no* post-ictal prolactin rise favour PNES; confirm with video-EEG.

Management — Antiseizure Drug (ASM) Therapy

ASMs act by **Na^{+} -channel block** (phenytoin, carbamazepine, lamotrigine, lacosamide, oxcarbazepine), **Ca^{2+} -channel block** (gabapentin, pregabalin; T-type — ethosuximide, valproate), **GABA potentiation** (benzodiazepines, barbiturates, valproate, tiagabine), **glutamate attenuation** (perampanel, topiramate, lamotrigine) and **SV2A modulation** (levetiracetam, brivaracetam).

General principles: treat reversible causes/avoid precipitants (esp. **sleep deprivation**) first; start ASM after a first seizure *only* with high recurrence risk (prior brain insult, epileptiform EEG, abnormal imaging, or nocturnal seizure); aim for **monotherapy at lowest effective dose**, titrate slowly; clinical seizure control, not serum level, is the endpoint.

Seizure type	First-line	Alternatives
Focal ($\pm$ bilateral TC)	Lamotrigine, Levetiracetam, Carbamazepine, Oxcarbazepine, Phenytoin	Zonisamide, Brivaracetam, Topiramate, Lacosamide,

Seizure type	First-line	Alternatives
		Valproate, Cenobamate, Perampanel
Generalised tonic-clonic	Valproate, Lamotrigine, Levetiracetam	Topiramate, Zonisamide, Perampanel (avoid CBZ/OXC/PHT — may worsen)
Typical absence	Ethosuximide, Valproate, Lamotrigine	Levetiracetam, Clonazepam
Myoclonic / atonic / atypical absence	Valproate, Lamotrigine, Topiramate	Clonazepam, Clobazam, Rufinamide, Fenfluramine

- ▶ **Key drug pearls:** Lamotrigine → rash/SJS (slow titration; even slower with valproate which doubles its half-life). Phenytoin → **non-linear kinetics**, gum hypertrophy, hirsutism, osteomalacia. Valproate → **teratogenic (neural tube defects), hepatotoxicity, thrombocytopenia** — *avoid in women of child-bearing age*. Carbamazepine → SIADH/hyponatraemia, marrow suppression; test *HLA-B1502 (Asians) for SJS risk before CBZ/PHT/OXC/LTG. Levetiracetam → **behavioural/mood effects but no significant interactions****.
- ▶ **Refractory epilepsy** (~30%, defined as failure of ≥2 appropriate ASMs): rational polytherapy with differing mechanisms → consider **surgery** (anteromedial temporal lobectomy/amygdalohippocampectomy makes ~70% of well-selected MTLE patients seizure-free; lesionectomy, corpus callosotomy, hemispherectomy), **laser thermal ablation**, **neurostimulation** (VNS, responsive neurostimulation, thalamic DBS), or **ketogenic diet**.

Status Epilepticus (SE) — the emergency

SE = continuous seizures or repetitive seizures without inter-ictal recovery of consciousness; operationally ≥5 min of generalised convulsive activity warrants treatment. Mortality up to 20%; commonest cause is ASM non-adherence/withdrawal. Stepwise protocol:

Stage	Therapy
0–5 min (stabilise)	ABC, O ₂ , IV access, check glucose → IV 50% dextrose 25–50 mL (+ thiamine), correct metabolic derangements
5–20 min (1st line — benzodiazepine)	IV lorazepam 0.1 mg/kg (4 mg, repeat once) or IM midazolam 10 mg or rectal diazepam 0.2 mg/kg
20–40 min (2nd line — IV ASM load)	Fosphenytoin 18–20 mg PE/kg @150 mg PE/min (or phenytoin 18–20 mg/kg @50 mg/min, ECG monitor) or Valproate 20–40 mg/kg or Levetiracetam 60 mg/kg (ESETT trial: all three equivalent)

Stage	Therapy
>40 min (refractory SE)	Add phenobarbital; continuous IV anaesthesia — midazolam infusion (0.2 mg/kg → 0.05–0.6 mg/kg/h), propofol (2 mg/kg → 2–10 mg/kg/h) or pentobarbital/thiopental , with intubation + continuous EEG

Non-convulsive SE is diagnosed on EEG and treated by the same ladder (IV anaesthesia often not required).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **ILAE 2017 seizure classification tree** — top box “Seizure” branching to **Focal onset** (→ *aware / impaired awareness; motor / nonmotor; focal-to-bilateral tonic-clonic*), **Generalised onset** (→ *motor: tonic-clonic, myoclonic, atonic, spasms / nonmotor: typical & atypical absence*), and **Unknown onset**.
- ▶ **Stepwise status-epilepticus management ladder** — vertical timeline boxes: *0–5 min stabilise + IV glucose/thiamine → 5–20 min IV lorazepam / IM midazolam → 20–40 min fosphenytoin OR valproate OR levetiracetam → >40 min refractory: midazolam/propofol/pentobarbital infusion + continuous EEG.*

Clinical / Diagnostic significance

- ▶ **Classification drives therapy** — carbamazepine, oxcarbazepine and phenytoin can *aggravate* absence, myoclonic and atonic seizures; valproate/levetiracetam/lamotrigine are safe broad-spectrum choices.
- ▶ **First seizure ≠ epilepsy** — only ~30–50% recur; treat after one seizure only with defined high-risk features.
- ▶ **Time-critical SE** — outcome depends on the interval between onset and effective treatment; benzodiazepine + IV ASM load must not be delayed.
- ▶ **Women & epilepsy** — counsel on valproate teratogenicity, **folate 1–4 mg/d** pre-conception, enzyme-inducer effect on oral contraceptives, and vitamin K in the last weeks of pregnancy; prefer levetiracetam/lamotrigine.
- ▶ **SUDEP** — sudden unexpected death in epilepsy; risk rises with frequent nocturnal GTCS; mortality in epilepsy is 2–3× the general population.
- ▶ **Driving, occupation and lifestyle** counselling (avoid heights, unsupervised swimming/bathing) are integral to management.

High-yield exam pointers

- ▶ Epilepsy = ≥2 unprovoked seizures (or one + high recurrence risk).
- ▶ ILAE 2017: **Focal / Generalised / Unknown onset**; “partial” is obsolete.

- ▶ **Absence** = 3-Hz spike-wave, **ethosuximide** drug of choice (no benefit in GTCS).
- ▶ **Valproate** = broadest spectrum but **teratogenic** — avoid in women of child-bearing potential.
- ▶ **Lamotrigine** → SJS; **HLA-B1502* + carbamazepine → SJS in Asians**.
- ▶ **Lennox-Gastaut triad**: multiple seizure types + slow spike-wave + developmental delay.
- ▶ **Status epilepticus** treated at 5 min: lorazepam → fosphenytoin/valproate/levetiracetam (ESETT) → anaesthesia.
- ▶ **MTLE with hippocampal sclerosis** = drug-resistant but **surgically curable** (~70% seizure-free).
- ▶ Commonest cause of new-onset epilepsy in the **elderly** = **stroke**; in **young adults** = **trauma/alcohol withdrawal**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Seizures and Epilepsy” (classification, aetiology by age, mechanisms, ASM selection & doses, status epilepticus, surgery, women/SUDEP).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “The Epilepsies” (semiology, syndrome classification, PNES).
- ▶ **CMDT 2026** — “Nervous System Disorders: Seizures & Epilepsy” (ILAE six aetiologic categories; status epilepticus dosing — lorazepam, fosphenytoin, valproate/levetiracetam ESETT equivalence, refractory anaesthesia).



Acute Ischemic Stroke Involving the Right Internal Capsule

Asked in: Paper III Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Ischemic stroke* is the acute onset of a focal neurological deficit due to occlusion of a cerebral vessel producing infarction of brain tissue. The **internal capsule** is a compact band of ascending and descending white-matter fibres between the caudate/thalamus medially and the lentiform nucleus laterally; it carries the *corticospinal*, *corticobulbar* and *thalamocortical tracts*. Infarction here is most often a **small-vessel (lacunar) stroke** from occlusion of a single deep penetrator. A lesion of the **right** internal capsule produces a **contralateral (left-sided) deficit**, classically a *pure motor hemiparesis*, characteristically without cortical signs.

Functional anatomy & blood supply (basis of localization)

- ▶ The capsule has three parts: **anterior limb** (frontopontine, anterior thalamic radiation), **genu** (corticobulbar fibres) and **posterior limb** (corticospinal tract, superior thalamic/sensory radiations, and posteriorly the optic and auditory radiations).

- ▶ **Somatotopy of the corticospinal tract** in the posterior limb: face/arm fibres lie ventromedially (near the genu) and leg fibres dorsolaterally — so a small capsular lesion can affect *face, arm and leg together* (proportionate weakness), unlike cortical strokes which are patchy.
- ▶ **Arterial supply** (all are end-arteries with poor collaterals → infarcts are small but dense):
 - **Lenticulostriate branches** of the MCA (M1) → superior portions of anterior and posterior limbs, putamen, globus pallidus, caudate body, corona radiata.
 - **Anterior choroidal artery (AChA)** — arises from the internal carotid distal to the posterior communicating artery → **posterior limb of the internal capsule**, optic tract, lateral geniculate body, medial temporal lobe, midbrain.
 - **Recurrent artery of Heubner** (medial lenticulostriate from ACA A1/A2) → anterior limb and head of caudate.

Etiopathogenesis

- ▶ **Small-vessel / lacunar disease (commonest mechanism here; ~20–25% of all ischemic strokes):** chronic **hypertension** and **diabetes** cause *lipohyalinosis* (medial hypertrophy and fibrinoid deposition) or *microatheroma* at the origin of a 30–300 µm penetrating artery → in-situ thrombotic occlusion → a small infarct (lacune, 3 mm–2 cm; “lake” of fluid at autopsy). **Hypertension and age are the principal risk factors**; diabetes is also well recognised.
- ▶ **Tempo as a clue to mechanism:** slowly-paced (stuttering) deficits suggest haemodynamic failure of a tightly stenosed penetrator; rapid onset suggests in-situ thrombosis. A *crescendo* of stereotyped TIAs preceding a capsular lacune is the **capsular warning syndrome**.
- ▶ **Other mechanisms** producing capsular/striatocapsular infarction: artery-to-artery embolism from carotid plaque, cardioembolism (atrial fibrillation, valve disease, LV thrombus), large MCA-stem thrombosis with lenticulostriate involvement, and AChA-territory occlusion.
- ▶ **Ischemic cascade:** energy failure → loss of ionic gradients → glutamate excitotoxicity, Ca^{2+} influx, free-radical and arachidonic-acid generation, inflammation → infarct *core* surrounded by a salvageable, perfusion-dependent **penumbra** (the target of reperfusion therapy).

Mechanism	Typical source	Capsular relevance
Small-vessel (lacunar)	Lipohyalinosis / microatheroma of penetrator; HTN, DM	Most common — pure motor / sensorimotor lacune
Artery-to-artery embolism	Carotid bifurcation / arch plaque	Striatocapsular infarct
Cardioembolism	AF, valve disease, LV thrombus	Larger deep infarct
Large-vessel thrombosis	MCA-stem / ICA atherosclerosis	Lenticulostriate territory

Clinical features (lesion of the **RIGHT** internal capsule → **LEFT-sided deficit**)

- ▶ **Pure motor hemiparesis (the commonest lacunar syndrome):** a unilateral (left) motor deficit affecting face, arm and leg almost equally, often with mild dysarthria at onset, an extensor (Babinski) plantar response, and — crucially — **no aphasia, no apraxia, no agnosia, no sensory, visual or higher-cortical loss**. Because the lesion spares the cortex, *higher functions are intact*; and as the right hemisphere is non-dominant in most patients, language is preserved regardless.
- ▶ **Sensorimotor stroke:** lacune of the posterior limb plus adjacent posteroventral thalamus → combined left face–arm–leg motor and sensory deficit.
- ▶ **Ataxic hemiparesis:** posterior-limb lacune → left lower-limb-predominant weakness with disproportionate ipsilateral limb incoordination and an extensor plantar.
- ▶ **Dysarthria–clumsy hand syndrome:** lacune of the genu / anterior limb → dysarthria, dysphagia, supranuclear facial weakness, tongue deviation and loss of fine motor control of the left hand.
- ▶ **Anterior choroidal artery syndrome (Foix, 1925):** the classic triad of **contralateral hemiparesis (posterior-limb corticospinal fibres) + hemianesthesia (superior thalamic radiation) + homonymous hemianopia (optic tract/LGB/radiation)**. With a right AChA infarct expect additional non-dominant signs — *left visuospatial neglect, anosognosia, constructional apraxia* and a relative afferent pupillary defect.
- ▶ General features favouring ischemia over haemorrhage: deficit maximal at onset (or remitting), normal/only modestly raised BP, preserved consciousness. Recovery from small-vessel strokes is usually rapid and fairly complete (partial/complete resolution over 4–6 weeks), though early stuttering worsening can occur.

Lacunar syndrome	Usual capsular site	Left-sided manifestation (right capsule)
Pure motor hemiparesis	Posterior limb / corona radiata	Face + arm + leg weakness, ± dysarthria
Pure sensory stroke	VPL thalamus (± capsule)	Numbness/paraesthesia, cheiro-oral pattern
Ataxic hemiparesis	Posterior limb	Leg-predominant weakness + limb ataxia
Dysarthria–clumsy hand	Genu / anterior limb	Dysarthria + clumsy hand
Sensorimotor stroke	Posterolateral thalamus + posterior limb	Combined hemimotor + hemisensory loss

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Axial section of the internal capsule:** label *anterior limb, genu, posterior limb, head of caudate, thalamus, putamen, globus pallidus (lentiform nucleus)*; arrow the corticospinal somatotopy (**face/arm ventromedial, leg dorsolateral**) and the *optic/auditory radiations* in the retrolenticular part.

Lacunar syndrome	Usual capsular site	Left-sided manifestation (right capsule)
▶ Arterial supply schematic: show <i>MCA lenticulostriate branches, anterior choroidal artery (posterior limb), recurrent artery of Heubner (anterior limb)</i> feeding the capsule.		

Clinical / Diagnostic significance

- ▶ **Emergency non-contrast CT head first** — to *exclude haemorrhage*; it is insensitive to acute infarction (often normal in the first 6–24 h) but mandatory before thrombolysis.
- ▶ **Diffusion-weighted MRI is the gold standard** — confirms and localises the small capsular lacune.
- ▶ **Vascular & cardioembolic work-up:** CTA/MRA (great-vessel and intracranial stenosis), CT-perfusion to define core vs penumbra (selects late thrombectomy), carotid duplex, ECG and prolonged ambulatory monitoring for AF, transthoracic/transoesophageal echo, blood glucose, lipid profile, CBC; hypercoagulable screen in young/cryptogenic cases.
- ▶ **NIHSS** quantifies severity and guides reperfusion eligibility; “time last seen normal” defines the therapeutic window.

Management

A. Acute / hyperacute (penumbra rescue):

- ▶ **ABC**, finger-stick glucose (correct hypo-/hyperglycaemia), continuous monitoring; treat fever with antipyretics/cooling; keep glucose ~3.3–10.0 mmol/L (60–180 mg/dL).
- ▶ **Permissive hypertension:** lower BP only if **>220/120 mmHg**, or malignant hypertension / concurrent myocardial ischaemia, or **>185/110 mmHg if thrombolysis is planned** — collateral flow is pressure-dependent, so over-aggressive lowering worsens outcome.
- ▶ **IV thrombolysis (≤ 4.5 h of onset):** alteplase (rtPA) **0.9 mg/kg (max 90 mg)**, 10% as bolus then the remainder over 60 min; or **tenecteplase 0.25 mg/kg (max 25 mg) single IV bolus**. CT must show no haemorrhage and no oedema $> \frac{1}{3}$ MCA territory; observe contraindications (recent surgery/bleed, bleeding diathesis, uncontrolled BP). No other antithrombotic for 24 h.
- ▶ **Endovascular mechanical thrombectomy** for large-vessel occlusion (ICA, M1/M2, basilar): standard window **0–6 h**, and **6–24 h** in selected patients chosen by perfusion (core/penumbra mismatch) imaging — most relevant when the capsular infarct results from a proximal large-vessel clot rather than a pure lacune.
- ▶ **Supportive:** DVT prophylaxis with pneumatic compression stockings $\pm$ subcutaneous heparin; aspiration/pneumonia precautions. For large hemispheric infarcts with malignant oedema (peaks day 2–3): mannitol/hypertonic saline and **decompressive hemicraniectomy** (halves mortality); suboccipital decompression for space-occupying cerebellar infarction.

- ▶ Anticoagulation is NOT used routinely for acute atherothrombotic stroke (no benefit, more bleeding).

B. Secondary prevention (the mainstay for lacunar stroke):

- ▶ **Antiplatelets:** aspirin (after a 325 mg load, then 81 mg/d). For minor stroke / TIA (NIHSS <5) give **short-term dual antiplatelet therapy** — aspirin + clopidogrel (300–600 mg load then 75 mg/d) for ~21 days then single-agent — as in CHANCE/POINT; long-term DAPT (SPS3) is *avoided* in small-vessel stroke (more bleeding, no benefit).
- ▶ **Blood-pressure control is the single most effective measure** — target <130/80 mmHg long-term (thiazides and ACE inhibitors well supported); SPRINT supports lower targets.
- ▶ **High-intensity statin** (atorvastatin 80 mg / rosuvastatin 40 mg; SPARCL) to LDL <70 mg/dL; tight diabetic control; smoking cessation.
- ▶ **For cardioembolic source (AF):** oral anticoagulation — a DOAC (e.g., apixaban 5 mg BD) preferred over warfarin (INR 2–3); risk-stratify by CHA₂DS₂-VASc.
- ▶ **Carotid revascularisation** (endarterectomy) for significant ipsilateral symptomatic stenosis.

C. Rehabilitation: early multidisciplinary stroke-unit care with physiotherapy, occupational and speech therapy; constraint-induced movement therapy for hemiparesis; prevention of contractures, pressure sores and post-stroke depression — improves outcome and reduces mortality.

High-yield exam pointers

- ▶ Right internal-capsule lacune → **left pure motor hemiparesis of face, arm AND leg, with NO cortical signs and preserved language.**
- ▶ Posterior limb = corticospinal tract; **leg fibres dorsolateral, face/arm ventromedial.**
- ▶ **Anterior choroidal artery triad = hemiplegia + hemianaesthesia + hemianopia.**
- ▶ **Lipohyalinosis of penetrators from chronic hypertension** is the core pathology; HTN + age + diabetes are the key risk factors.
- ▶ **DWI-MRI** is the gold-standard investigation; **non-contrast CT** is done first only to exclude haemorrhage.
- ▶ **Alteplase 0.9 mg/kg ≤4.5 h** or **tenecteplase 0.25 mg/kg**; thrombectomy 0–6 h (up to 24 h by perfusion mismatch).
- ▶ Acute BP: treat only if >185/110 (if lysing) or >220/120 otherwise — *permissive hypertension*.
- ▶ Secondary prevention: antiplatelet + BP <130/80 + high-intensity statin; **DAPT for 21 days only** in minor stroke/TIA.
- ▶ **Capsular warning syndrome** = crescendo capsular TIAs that herald a completed lacune.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Ischemic Stroke” (pathophysiology of small-vessel/lacunar stroke, ischemic cascade, acute treatment, thrombolysis/thrombectomy, secondary prevention) and “Introduction to Cerebrovascular Diseases”.
- ▶ **Brazis – Localization in Clinical Neurology** — “Vascular Syndromes of the Forebrain, Brainstem and Cerebellum” (internal-capsule blood supply, lacunar syndromes and table, anterior choroidal artery [Foix] syndrome, corticospinal somatotopy).
- ▶ **CMDT 2026** — “Nervous System Disorders: Lacunar Infarction” and stroke-subtype management table (time windows, antiplatelet, risk-factor control).



Discuss the indications and options for reperfusion therapy in acute stroke

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — *Reperfusion therapy* is the emergency restoration of blood flow to an acutely occluded cerebral artery, aiming to salvage the **ischaemic penumbra** (ischaemic but still viable tissue surrounding the infarct core) before it progresses to irreversible infarction. “**Time is brain**” — outcome is directly proportional to the speed of recanalisation. Two proven modalities exist: (1) **intravenous (IV) thrombolysis** with a plasminogen activator (alteplase or tenecteplase), and (2) **endovascular mechanical thrombectomy** for large-vessel occlusion (LVO). They are complementary, not mutually exclusive — eligible patients receive thrombolysis first (“bridging”) and then thrombectomy.

Rationale — the penumbra and the therapeutic window

- ▶ A cerebral blood flow of **0 mL/100 g/min** kills neurons within **4–10 min**; values **<16–18 mL/100 g/min** infarct within an hour; **<20 mL/100 g/min** causes reversible ischaemia (the penumbra) unless prolonged.
- ▶ Restoring flow re-supplies oxygen and glucose, reverses tissue acidosis, clears excitotoxic **glutamate** and reactive oxygen species, and halts cortical spreading depression — preventing the penumbra from infarcting.
- ▶ The penumbra (and thus the *individual* therapeutic window) is imaged as a **core–perfusion mismatch** on CT perfusion (CTP) or MR diffusion–perfusion (DWI/PWI) — this is what extends eligibility beyond the rigid clock-based windows.

Mandatory pre-reperfusion assessment (“Code Stroke”)

- ▶ Secure ABCs; finger-stick glucose (treat hypo-/hyperglycaemia — mimics).

- ▶ Establish **time last seen normal** (wake-up stroke = time patient went to bed) and quantify deficit with the NIHSS.
- ▶ **Emergency non-contrast CT (NCCT)** to exclude haemorrhage — the *only* mandatory imaging before IV thrombolysis (with glucose). No edema/hypodensity $> \frac{1}{3}$ of the MCA territory.
- ▶ For possible thrombectomy: **CT angiography (CTA)** (atria → vertex) to confirm LVO; add **CTP/MR perfusion** for late-window selection (6–24 h).
- ▶ Other labs (CBC, coagulation, ECG, electrolytes) must **not delay** thrombolysis in an otherwise-eligible patient.

Option 1 — Intravenous thrombolysis

Evidence: *NINDS rt-PA Study* established benefit of IV alteplase within 3 h (absolute 12% increase in minimal-disability outcome; symptomatic ICH 6.4% vs 0.6%). *ECASS III* extended efficacy to the 3–4.5 h window (good outcome 52.4% vs 45.2%, OR 1.34; sICH 2.4% vs 0.2%). Tenecteplase is **non-inferior** to alteplase and increasingly preferred as a single bolus.

Agent	Dose	Window	Notes
Alteplase (rt-PA)	0.9 mg/kg (max 90 mg); 10% as bolus, remainder over 60 min	0–4.5 h	US label 0–3 h; off-label/EU to 4.5 h. Asian dose often 0.6 mg/kg (less ICH)
Tenecteplase (TNK)	0.25 mg/kg IV push (max 25 mg) over ~5 s	0–4.5 h	Single bolus — no infusion; eases inter-hospital transfer for thrombectomy. Off-label

Indications (must satisfy ALL): clinical ischaemic stroke with disabling deficit; onset-to-needle ≤ 4.5 h; age ≥ 18 y; NCCT shows no haemorrhage and no large established infarct.

Key contraindications (Table 438-1 + NINDS exclusions):

Absolute	Relative / caution
Sustained BP $> 185/110$ mmHg despite treatment	Recent MI
Active bleeding / bleeding diathesis	GI or GU bleeding (within 21 days)
Recent head injury or intracerebral haemorrhage	Major surgery within preceding 14 days
Hypodensity $> \frac{1}{3}$ MCA territory / large infarct on CT	Rapidly improving or minor non-disabling deficit (NIHSS 0–5)
Platelets $< 100,000$; INR > 1.7 / PT > 15 s; heparin in 48 h	Seizure at onset (only if deficit is post-ictal)
Glucose < 50 mg/dL (2.8 mmol/L)	Arterial puncture at non-compressible site (7 days)

- ▶ **Extended/unknown-onset window:** MRI-based DWI–FLAIR mismatch (WAKE-UP) or perfusion mismatch (EXTEND) selects benefit up to ~9 h or on awakening — penumbra-guided, not clock-guided.
- ▶ **Peri-thrombolysis care:** lower BP to <185/110 (IV labetalol/nicardipine) before bolus; keep <180/105 for 24 h; **no antithrombotics for 24 h**; repeat CT for deterioration; for bleeding, stop infusion + give cryoprecipitate.

Option 2 — Endovascular mechanical thrombectomy (EVT)

LVO (MCA-M1, intracranial ICA, basilar) carries a large clot burden that often **fails to recanalise with IV thrombolysis alone** — these need EVT. Six 2015 RCTs (*MR CLEAN*, *ESCAPE*, *EXTEND-IA*, *SWIFT PRIME*, *REVASCAT*) proved benefit with **stent retrievers**: pooled OR 2.49; mRS 0–2 in 46% vs 26.5%, with a mortality benefit. Outcome is time-critical — odds of good outcome >3 if groin puncture <2 h, falling to ~2 by 8 h.

Indications — 2018 AHA/ASA Class I criteria:

- ▶ Pre-stroke mRS 0–1
- ▶ Causative occlusion of ICA or proximal MCA (M1)
- ▶ Age ≥18 y
- ▶ NIHSS ≥6
- ▶ ASPECTS ≥6 (limited established core on NCCT)
- ▶ Groin puncture within 6 h of onset
- ▶ Receipt of IV alteplase within 4.5 h **if eligible** (do not withhold/delay thrombolysis to do EVT)

Late window (6–24 h) — perfusion-selected (Class I/IIa):

- ▶ ****DAWN trial:** LVO, last-seen-well 6–24 h, clinical–core mismatch (RAPID software) → **good outcome** 47% vs 13%**.
- ▶ ****DEFUSE-3 trial:** perfusion mismatch, 6–16 h → **mRS 0–2 in 45% vs 17%****.
- ▶ Basilar occlusion: non-randomised data support thrombectomy up to **24 h**.
- ▶ **Stent retrievers are preferred** to older devices (e.g., MERCI coil retriever); aspiration catheters are an alternative. Bridging tenecteplase before transfer is increasingly favoured.

Integrated time-window algorithm

Time from onset	Reperfusion option
0–4.5 h	IV thrombolysis (alteplase/TNK) if eligible + EVT if anterior LVO
4.5–6 h	EVT for LVO (thrombolysis window closed)
6–24 h	EVT only if penumbra/mismatch on CTP/MR perfusion (DAWN/DEFUSE-3)

Time from onset	Reperfusion option
Wake-up / unknown, ≤ 9 h	IV thrombolysis if DWI-FLAIR or perfusion mismatch

Adjuncts and therapies that do NOT replace reperfusion

- ▶ **Antiplatelets:** Aspirin (160–325 mg) within 48 h gives a small net benefit (IST, CAST) — start after 24 h if thrombolysed. Short-term **dual antiplatelet** (aspirin + clopidogrel/ticagrelor) for 21 days in **minor stroke/TIA** (NIHSS $\leq 3-5$).
- ▶ **Anticoagulation:** No role in acute atherothrombotic stroke (no benefit, $\uparrow$ bleeding); reserved for dural sinus thrombosis.
- ▶ **Neuroprotection** (glutamate antagonists, hypothermia, magnesium, free-radical scavengers): **no agent proven** in humans despite >120 trials.
- ▶ **Decompressive hemicraniectomy** for malignant MCA infarction (within ~ 48 h) reduces mortality $\sim 50\%$ and improves survivor outcome; **suboccipital decompression** for space-occupying cerebellar infarct.
- ▶ **Supportive:** permissive hypertension (only treat if $>220/120$), euglycaemia, normothermia, stroke-unit care and early rehabilitation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Penumbra schematic:** concentric zones — central black “core” (irreversible infarct) surrounded by a stippled “penumbra” (salvageable), with arrows labelled *Reperfusion* $\rightarrow$ *penumbra saved*; axis showing CBF thresholds (0 mL/100 g/min $\rightarrow$ death in 4–10 min, <20 $\rightarrow$ reversible ischaemia).
- ▶ **Acute-stroke reperfusion algorithm flowchart:** boxes — *Suspected stroke* $\rightarrow$ *Code Stroke / NCCT* $\rightarrow$ branch **No haemorrhage**; *Onset <4.5 h* $\rightarrow$ *IV thrombolysis (alteplase/TNK)* and *CTA* $\rightarrow$ *anterior LVO?* $\rightarrow$ *Thrombectomy (<6 h)*; *Onset 6–24 h* $\rightarrow$ *CTP/MR perfusion* $\rightarrow$ *favourable mismatch* $\rightarrow$ *Thrombectomy*. Label time windows on each arm.

Clinical / Diagnostic significance

- ▶ IV rt-PA raises the chance of recovery without significant disability from $\sim 26\%$ to $\sim 39\%$ when given <3 h; EVT makes functional independence $\geq 30\%$ more likely in LVO.
- ▶ **Door-to-needle ≤ 60 min** and **door-to-groin** times are key quality metrics; pre-hospital “stroke code” activation and tele-stroke speed delivery.
- ▶ **Systems of care:** primary stroke centres deliver thrombolysis and transfer (“drip-and-ship”) to **comprehensive/thrombectomy-capable centres**; the bolus-only tenecteplase simplifies transfer.

- ▶ After reperfusion: 24-h follow-up CT before starting antithrombotics; then establish aetiology (AF → anticoagulation; carotid stenosis >50% → endarterectomy; high-intensity statin, LDL <70 mg/dL) for secondary prevention.

High-yield exam pointers

- ▶ Two reperfusion options: **IV thrombolysis** (alteplase **0.9 mg/kg**, max 90 mg, 10% bolus + 60-min infusion; tenecteplase **0.25 mg/kg** bolus) and **mechanical thrombectomy** (stent retriever).
- ▶ IV thrombolysis window **≤4.5 h** (NINDS 0–3 h; ECASS III 3–4.5 h); thrombectomy **≤6 h**, extended to **24 h** with perfusion mismatch (**DAWN 6–24 h**, **DEFUSE-3 6–16 h**).
- ▶ **BP must be <185/110 mmHg** before thrombolysis; treat acute BP only if **>220/120 mmHg** otherwise.
- ▶ Only **NCCT + glucose** are mandatory before IV thrombolysis — don't wait for other labs.
- ▶ Thrombectomy Class I: **ICA/M1 occlusion**, **NIHSS ≥6**, **ASPECTS ≥6**, **pre-stroke mRS 0–1**, **age ≥18**, **groin <6 h**.
- ▶ Symptomatic ICH is the major thrombolysis complication (~6% NINDS) — reverse with **cryoprecipitate**.
- ▶ **No neuroprotective drug** is proven; aspirin only modest; anticoagulation not for acute atherothrombotic stroke.
- ▶ Bridging thrombolysis-then-thrombectomy is standard for eligible LVO; do **not** delay thrombolysis to perform EVT.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Ischemic Stroke” (Table 438-1, NINDS/ECASS III, DAWN/DEFUSE-3, endovascular revascularisation; penumbra pathophysiology).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Ischemic Cerebrovascular Disease” (alteplase inclusion/exclusion criteria, 2018 AHA/ASA Box 65.8 thrombectomy criteria, MR CLEAN/ESCAPE/EXTEND-IA/SWIFT PRIME/REVASCAT, NNT/benefit data).
- ▶ **CMDT 2026** — “Nervous System Disorders / Stroke” (current dosing, tenecteplase non-inferiority, 0–4.5 h thrombolysis and 0–6/6–24 h embolectomy windows, extended-window perfusion selection, peri-thrombolysis BP control).



Endovascular revascularization for acute ischemic stroke

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — *Endovascular revascularization* (endovascular mechanical **thrombectomy**) is the catheter-based removal of an occluding thrombus from a large intracranial artery to restore cerebral blood flow and salvage the ischemic **penumbra**. It is one of the six categories of acute ischemic stroke treatment in Harrison (medical support, IV thrombolysis, **endovascular revascularization**, antithrombotic treatment, neuroprotection, and stroke centers/rehabilitation). It is the definitive reperfusion therapy for **large-vessel occlusion (LVO)** strokes, which often fail to open with IV thrombolysis alone, and is used as an *alternative or adjunct* to IV thrombolysis.

Rationale and target lesions

- ▶ Ischemic stroke from **large-vessel intracranial occlusion** carries high rates of mortality and morbidity.
- ▶ These occlusions involve a **large clot burden** and often **fail to recanalize with IV thrombolysis alone**, providing the rationale for direct mechanical clot retrieval.
- ▶ **Eligible target vessels** (proven on CT angiography):
 - **Intracranial internal carotid artery (ICA)**
 - **Middle cerebral artery** — first division (M1) and second division (M2)
 - **Basilar artery (BA)** (posterior circulation)
- ▶ Thrombectomy is offered to patients who are **ineligible for or have contraindications to thrombolytics**, or who **failed to recanalize after IV thrombolysis**.
- ▶ Reperfusion aims to rescue the penumbra — clinical outcome is critically **time-dependent**.

Patient selection and time windows

- ▶ **Disabling deficit**: patients with NIHSS >5 (National Institutes of Health Stroke Scale) are candidates for thrombolytic and/or endovascular therapy.
- ▶ **Imaging gateway**: noncontrast head CT to exclude hemorrhage, then **CT angiography (CTA)** to confirm the LVO; for late windows, **CT perfusion / MR perfusion** to assess salvageable tissue.
- ▶ **Early window (<6 h from onset)**: thrombectomy for **ICA / M1–M2 / basilar** occlusion confirmed on CTA, **with or without** IV thrombolysis pretreatment.
- ▶ **Extended/late window (6–24 h, including wake-up and unwitnessed-onset strokes)**: effective **only if perfusion imaging shows good collaterals / a favorable mismatch** (small core, large penumbra). Selection rests on perfusion imaging rather than thrombolysis eligibility.
- ▶ **Posterior circulation**: for basilar artery occlusion, nonrandomized data show thrombectomy is **safe up to 24 h** from onset and is associated with lower 3-month Rankin scores.
- ▶ **Time is brain — procedural timing data**:
 - Odds of a good outcome **exceed 3** if **groin puncture occurs within 2 h** of symptom onset, but fall to ~2 if 8 h elapse.

- >80% of patients with vessel opening within 1 h of ED arrival had a good outcome, versus only one-third if 6 h elapsed.

Evidence base (key trials)

Trial group / window	Patients selected	Outcome (mRS 0–2 unless stated)
Six 2015 RCTs (combined meta-analysis); <6 h	ICA & MCA occlusion on CTA, ± IV tPA	Large benefit: OR 2.49 (95% CI 1.76–3.53, $p < .001$); 46% vs 26.5% (endovascular vs medical)
DAWN (Trevo stent retriever); up to 24 h	Wake-up / late-presenting, clinical–imaging mismatch	Good outcome 47% vs 13% ($p < .0001$)
DEFUSE-3; up to 16 h	Perfusion mismatch on CT/MR perfusion	Good outcome 45% vs 17% ($p < .001$)
Basilar occlusion (nonrandomized); up to 24 h	Posterior circulation LVO	Safe; lower 3-month Rankin scores

- ▶ mRS 0–2 = “normal or symptomatic but independent.”
- ▶ A more recent meta-analysis additionally demonstrated a **mortality benefit** with thrombectomy.
- ▶ One trial concluded patients were **home nearly 2 months earlier** when treated with endovascular therapy.

Procedure, adjuncts and bridging therapy

- ▶ **Technique:** catheter-based clot removal (stent retriever, e.g., *Trevo*, and/or aspiration) via femoral/groin access, with restoration of antegrade flow confirmed on catheter angiography.
- ▶ **Bridging with IV thrombolysis:** outcomes are **likely improved by giving IV rtPA before thrombectomy** when the patient is rtPA-eligible and it is safe to administer.
 - IV rtPA (alteplase): 0.9 mg/kg (max 90 mg), 10% as bolus then remainder over 60 min, within 4.5 h.
 - IV tenecteplase (TNK): 0.25 mg/kg IV bolus (max 25 mg) over 5 s. Recent data support **replacing rtPA with tenecteplase** before thrombectomy — its single-bolus administration (no 1-h infusion) **simplifies inter-hospital transfer** to an endovascular center and obviates critical-care transport. Several trials of TNK before endovascular therapy found it safe.
- ▶ **Adjunctive imaging workflow** (Fig. 438-3): noncontrast CT → CTA (confirm LVO; *hyperdense MCA sign* is highly specific but seen in only ~20%) → CT perfusion (core vs penumbra/mismatch) → catheter angiography with clot removal → follow-up diffusion-weighted MRI; advanced imaging can yield a **better-than-predicted** outcome.

Systems of care

- ▶ Now that thrombectomy is proven effective, **comprehensive stroke centers** that rapidly identify and treat LVO are an international priority.
- ▶ **Regional systems of care:** patients are first evaluated at **acute stroke-ready hospitals / primary stroke centers** (can give IV rtPA or tenecteplase), then **transferred to thrombectomy-capable or comprehensive stroke centers**, or **directly triaged** to such centers based on prehospital field assessment.
- ▶ **Telemedicine / telestroke** services extend evaluation for thrombolysis and endovascular treatment.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Acute stroke management pathway** (Fig. 438-2) — flowchart with labels: *Suspected acute stroke* → *Prehospital call ahead* → *Code stroke activation*; branch **Onset <6 h**: *CT no hemorrhage* → *IV PA if eligible (<4.5 h)* → *Perform CTA* → *ICA/M1-2 or BA occlusion?* → *Yes* → *Thrombectomy*; branch **Onset 6–24 h**: *CT no hemorrhage* → *CTA/CTP* → *Favorable perfusion?* → *Yes* → *Thrombectomy*; *No* → *Inpatient management*.
- ▶ **LVO imaging-to-reperfusion sequence** (Fig. 438-3) — panels labelled: *Noncontrast CT (hyperdense MCA sign, arrow)*; *CTA (MCA branch occlusion)*; *CT perfusion (core = no pink signal; penumbra = green, mismatch volume, mismatch ratio, Tmax >6.0 s, CBF <30%)*; *Catheter angiogram (occlusion → restored flow after clot removal)*; *Follow-up DWI (small residual infarct)*.

Clinical / Diagnostic significance

- ▶ Identifies the subgroup — **large-vessel occlusion** — that derives the greatest reperfusion benefit and that IV thrombolysis alone usually cannot recanalize.
- ▶ **CTA is the decision-maker** for early-window thrombectomy; **perfusion imaging** (CTP/MR perfusion) opens the 6–24 h window for wake-up and late-presenting strokes.
- ▶ Drives **prehospital triage and hospital networks**: “call ahead,” stroke-code activation, and direct routing to thrombectomy-capable centers shorten door-to-groin times.
- ▶ **Door/onset-to-reperfusion time is the strongest modifiable outcome determinant** — every minute of delay reduces the odds of independence.
- ▶ Reinforces post-reperfusion secondary prevention from the same chapter: high-intensity statin (atorvastatin 80 mg / rosuvastatin 40 mg, LDL <70 mg/dL), apixaban for atrial fibrillation, dual antiplatelet for minor stroke/intracranial atherosclerosis, and carotid endarterectomy for significant ICA stenosis.

High-yield exam pointers

- ▶ Endovascular thrombectomy = definitive therapy for **LVO** (intracranial ICA, MCA M1–M2, basilar artery).

- ▶ Use as **alternative or adjunct** to IV thrombolysis — for the ineligible, contraindicated, or failed-recanalization patient.
- ▶ **Early window <6 h** on CTA; **extended window up to 24 h** requires favorable perfusion mismatch/collaterals.
- ▶ Landmark numbers: **OR 2.49 (CI 1.76–3.53)**; mRS 0–2 **46% vs 26.5%**; **DAWN 47% vs 13%** (≤ 24 h); **DEFUSE-3 45% vs 17%** (≤ 16 h).
- ▶ **Time targets**: good-outcome odds >3 if **groin puncture <2 h**; **$>80\%$ good outcome if vessel opened within 1 h** of ED arrival.
- ▶ **Bridging**: give IV rtPA (**0.9 mg/kg**) or tenecteplase (**0.25 mg/kg bolus**) first if eligible; TNK simplifies transfer.
- ▶ **Hyperdense MCA sign** is highly specific but only $\sim 20\%$ sensitive for MCA occlusion.
- ▶ Requires **comprehensive/thrombectomy-capable stroke centers** and organized regional systems of care.

SOURCE & COVERAGE

Harrison 22e — Ch 438 “Ischemic Stroke” (TREATMENT: Endovascular Revascularization; Intravenous Thrombolysis; Stroke Centers; Figs. 438-2 and 438-3; Table 438-1).

Coverage note: Harrison names only the DAWN and DEFUSE-3 trials and the Trevo stent retriever; the six 2015 RCTs are described collectively (as a combined meta-analysis) and not individually named — the commonly examined names (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, REVASCAT) are standard but are NOT in this chapter. Procedural grading/selection metrics frequently quoted in exams — **mTICI 2b–3 reperfusion grade**, **ASPECTS ≥ 6** , and aspiration-vs-stent-retriever device choice — are universally accepted standard practice but are also NOT explicitly stated in the provided Harrison text and should be cited as general knowledge, not from this chapter.



Reversible Causes of Dementia and Differentiation of Alzheimer’s Disease from Frontotemporal Dementia

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — **Dementia** is an *acquired*, usually progressive deterioration in two or more cognitive domains (episodic memory, language, visuospatial function, praxis, executive function, behaviour) of sufficient severity to impair the successful performance of activities of daily living, occurring in clear consciousness (distinguishing it from delirium). Although most cases are due to irreversible neurodegeneration (Alzheimer’s disease [AD] accounts for 60–70%), a clinically vital subset is **potentially reversible or treatable** — in a study of 1000 consecutive memory-clinic patients, $\sim 19\%$

had a potentially reversible *cause* and a further ~23% had a reversible *contributing condition*. Because no single treatable aetiology is common, a structured screen is mandatory in every patient so that a treatable cause is never missed.

Reversible / potentially treatable causes of dementia

The three commonest potentially reversible diagnoses are **depression (pseudodementia)**, **normal-pressure hydrocephalus (NPH)**, and **alcohol dependence**; *medication side-effects* should be sought in every patient. A useful working classification (Harrison Table 31-1, “potentially reversible” entries):

Category	Specific reversible causes
Drugs & toxins	Sedative–hypnotics, benzodiazepines, opioids/analgesics, anticholinergics, antiepileptics (chronic intoxication); alcohol dependence ; heavy-metal poisoning (lead, mercury, arsenic, manganese); organic toxins
Metabolic / endocrine / organ failure	Hypothyroidism ; adrenal insufficiency and Cushing’s syndrome; hypo- and hyperparathyroidism; chronic renal failure (uraemic encephalopathy); hepatic failure ; pulmonary failure (hypoxia / CO ₂ narcosis)
Nutritional deficiencies	Thiamine (B1) — Wernicke encephalopathy; vitamin B12 — subacute combined degeneration; niacin — pellagra; elevated homocysteine / folate deficiency
Infections	HIV (HIV-associated neurocognitive disorder); neurosyphilis ; progressive multifocal leukoencephalopathy (JC virus); tuberculous, fungal and protozoal CNS infection; Whipple’s disease
Structural / neurosurgical	Normal-pressure hydrocephalus ; chronic subdural haematoma ; primary or metastatic brain tumour
Autoimmune / inflammatory	Paraneoplastic and autoimmune limbic encephalitis (anti-LGI1, NMDA-R, Caspr2, AMPA-R); CNS vasculitis ; neurosarcoidosis ; corticosteroid-responsive (Hashimoto) encephalopathy
Psychiatric	Depression (pseudodementia) ; schizophrenia; conversion disorder
Miscellaneous	Recurrent non-convulsive seizures ; acute intermittent porphyria

- A simple bedside aide-mémoire is “**DEMENTIAS**”: **D**rugs, **E**motional/depression, **M**etabolic-endocrine, **E**yes & ears (sensory deprivation) / **N**utritional, **T**umour/trauma (SDH, NPH), **I**nfection, **A**utoimmune, **S**eizures/structural — all map onto the categories above.

Approach to detect a reversible cause (investigations)

- ▶ **Routine (AAN-recommended) screen** in all: complete blood count; electrolytes, glucose, renal and liver function; **thyroid function (TSH)**; serum vitamin B12; and **structural neuroimaging (MRI or non-contrast CT)** to exclude tumour, subdural haematoma, infarcts, white-matter disease and NPH.
- ▶ **Selective / focused tests** driven by clues: serum RPR/VDRL and **HIV serology**; lumbar puncture (cells, protein, oligoclonal bands, autoimmune-encephalitis antibodies, AD biomarkers) when infection/inflammation or rapidly progressive dementia is suspected; urine toxin / heavy-metal screen; ESR, CRP, ANA; anti-thyroperoxidase/thyroglobulin antibodies; 24-h urine copper (Wilson); EEG (non-convulsive seizures, CJD periodic complexes).
- ▶ NPH is suggested by the triad of **gait apraxia** (“magnetic” gait), **urinary incontinence** and **dementia** with ventriculomegaly disproportionate to sulcal atrophy; objective gait improvement after high-volume (30–50 mL) CSF removal (tap test) predicts response to ventriculoperitoneal shunting (gait improves most; cognition least).
- ▶ **Treatment of the reversible component**: thyroxine for hypothyroidism; thiamine/B12 replacement and folate for elevated homocysteine; antiretrovirals for HIV and antimicrobials for opportunistic infection; CSF shunting for NPH; surgery/radiotherapy/chemotherapy for neoplasm; immunotherapy (steroids/IVIG/plasma exchange) for autoimmune encephalitis; and **withdrawal of cognition-impairing drugs**.

Differentiating Alzheimer’s disease from frontotemporal dementia

Both are cortical neurodegenerative dementias and below age 65 FTD rivals AD as the commonest cause, so distinction is a frequent clinical problem. The two are separated on **age, presenting symptom, neuropsychological profile, behaviour, neurological signs, imaging, molecular pathology, genetics** and drug response:

Feature	Alzheimer’s disease (AD)	Frontotemporal dementia (FTD)
Typical onset age	Most common >65 yr; rises with each decade (insidious)	Younger — 5th–7th decade; ~30% present >65
First / presenting symptom	Episodic memory loss (recent memory) in ~75%	Personality / behaviour change (bvFTD) or progressive language failure (PPA); memory relatively spared
Cognitive (neuropsych) profile	Amnesic — impaired learning/delayed recall, then language, executive, visuospatial deficits	Executive dysfunction and/or language ; <i>relative sparing of episodic memory and visuospatial/drawing skills</i>

Feature	Alzheimer's disease (AD)	Frontotemporal dementia (FTD)
Behaviour / neuropsychiatry	Early irritability, anxiety, depression; social graces preserved until late	Early disinhibition, apathy, loss of empathy, compulsivity, hyperorality/overeating, loss of insight
Core clinical syndromes	Typical amnesic AD; atypical — posterior cortical atrophy, logopenic aphasia, frontal/dysexecutive, corticobasal	bvFTD (commonest), semantic-variant PPA, non-fluent/agrammatic PPA; ± FTD-MND, CBS, PSP-RS
Motor / neurological signs	Normal early; myoclonus, rigidity, parkinsonism only late	Early axial rigidity, vertical supranuclear gaze palsy, dystonia, alien limb, or motor-neuron disease
Structural MRI	Entorhinal + hippocampal (medial temporal) atrophy; posterior-predominant cortical atrophy	Frontal, insular and/or anterior temporal atrophy; <i>posterior parietal lobe spared</i>
FDG-PET	Temporo-parietal hypometabolism; posterior cingulate / precuneus involvement	Frontal and anterior temporal hypometabolism
Molecular pathology	A β neuritic plaques + neurofibrillary tangles of hyperphosphorylated tau; amyloid/tau PET positive	FTLD-tau (e.g. Pick bodies) or FTLD-TDP-43 (~90% combined); FTLD-FET ~10%; AD-tau PET ligands not reliably positive
Neurotransmitter deficit	Cholinergic loss (nucleus basalis of Meynert)	Cholinergic system relatively spared; serotonergic loss
Genetics	APP (chr 21), PSEN-1 (chr 14), PSEN-2 (chr 1) in <2%; ApoE ϵ 4 (chr 19) susceptibility (1 allele $\approx$ 2–3 $\times$, 2 alleles $\approx$ 10–15 $\times$ risk)	Autosomal dominant in 10–20%: C9orf72 (chr 9), GRN (chr 17), MAPT (chr 17)
Biofluid biomarkers	CSF/plasma: $\downarrow$ A β 42 (low A β 42/A β 40), $\uparrow$ p-Tau181/217	No specific positive AD biomarker; AD biomarkers <i>negative</i> support FTLD
Drug response	Cholinesterase inhibitors + memantine give modest symptomatic benefit; anti-A β antibodies (lecanemab, donanemab) in early AD	No disease-modifying or symptomatic cognitive drug; cholinesterase inhibitors may worsen behaviour, memantine ineffective; SSRIs for behavioural symptoms

Feature	Alzheimer's disease (AD)	Frontotemporal dementia (FTD)
Course / survival	Symptomatic duration typically 8–10 yr (range 1–25)	Median survival ~6 yr; FTD-MND ~3 yr

- **Practical discriminators for the exam:** an elderly patient who first *gets lost and forgets recent events*, with hippocampal atrophy and a positive amyloid scan → **AD**; a younger patient brought by family for *socially inappropriate behaviour, apathy, overeating and loss of empathy with preserved memory* and frontal atrophy → **FTD**. International consensus (Rascovsky) criteria for **bvFTD** require ≥3 of: early disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviour, hyperorality/dietary change, and a dysexecutive neuropsychological profile that *sparing memory and visuospatial function*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Two coronal-brain silhouettes side by side.** Label the *AD brain*: “Medial temporal / hippocampal + entorhinal atrophy”, “Posterior-predominant (temporo-parietal) cortical atrophy”, “Nucleus basalis of Meynert – cholinergic loss”. Label the *FTD brain*: “Frontal + anterior temporal + insular atrophy”, “Anterior cingulate / orbitofrontal involvement (salience network)”, “Posterior parietal lobe SPARED”.
- **A simple two-circle/branch chart of reversible causes** with the eight category headings as labels: Drugs/Toxins; Metabolic-Endocrine; Nutritional (B1/B12/Niacin); Infection (HIV, neurosyphilis, PML, Whipple); Structural (NPH, SDH, tumour); Autoimmune (limbic encephalitis, vasculitis, Hashimoto); Psychiatric (depression); Seizures/Porphyria — each annotated with its specific treatment.

Clinical / Diagnostic significance

- The whole point of enumerating reversible causes is **therapeutic**: even a screening test with a 1–2% yield is justified because the alternative is missing a curable dementia (e.g. B12 deficiency, hypothyroidism, NPH, neurosyphilis, autoimmune encephalitis).
- **Rapidly progressive dementia** (decline to dementia in <1 year) widens the differential to prion disease (CJD — cortical ribboning on DWI, periodic EEG complexes, RT-QuIC), autoimmune/paraneoplastic encephalitis and toxic-metabolic states — many of which are treatable, so it warrants aggressive CSF and antibody work-up.
- **Depression** must be actively screened for and treated (SSRI/SNRI) before labelling a patient as having irreversible dementia; conversely a true dementia may coexist with low mood.
- **Misclassifying FTD as AD matters**: cholinesterase inhibitors can aggravate FTD behaviour, anti-amyloid antibodies are inappropriate, the prognosis and genetic counselling (C9orf72, GRN, MAPT; possible MND) differ, and behavioural/psychosocial caregiver support is the mainstay.

High-yield exam pointers

- ▶ Dementia = acquired, progressive cognitive decline impairing ADLs in clear consciousness (vs delirium); AD = 60–70%, the commonest cause overall.
- ▶ ~19% of memory-clinic patients have a potentially reversible cause; commonest reversible trio = depression, NPH, alcohol + drug side-effects.
- ▶ Routine reversible-cause screen: TSH, B12, CBC, metabolic panel, MRI/CT ($\pm$ RPR/VDRL, HIV, LP).
- ▶ NPH triad = magnetic gait + urinary incontinence + dementia; CSF tap test predicts shunt response (gait improves most).
- ▶ AD = memory-first, hippocampal/posterior atrophy, amyloid + tau pathology, cholinergic loss, ApoE ϵ 4; FTD = behaviour/language-first, frontotemporal atrophy, tau or TDP-43 pathology, cholinergic sparing, C9orf72/GRN/MAPT.
- ▶ FTD spares episodic memory and visuospatial skills early; AD spares motor and behaviour/social graces early.
- ▶ Cholinesterase inhibitors + memantine help AD; they are ineffective or harmful in FTD (no cognition-modifying drug).
- ▶ FTD presents younger (5th–7th decade) and below 65 rivals AD in frequency.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Dementia" (differential diagnosis / Table 31-1 reversible causes, evaluation, treatment), "Alzheimer's Disease" (clinical features, pathology, genetics, biomarkers, therapy), "Frontotemporal Dementia" (clinical syndromes, FTLT pathology, genetics).
- ▶ Bradley & Daroff's Neurology in Clinical Practice, 8e — "Alzheimer Disease and Other Dementias" (bvFTD/PPA clinical variants, Rascovsky International Consensus Criteria for bvFTD, FTD subtype anatomy and pathology, reversible memory-clinic data).
- ▶ CMDT 2026 — "Nervous System Disorders" (dementia evaluation, normal-pressure hydrocephalus, rapidly progressive dementia work-up, cholinesterase-inhibitor and memantine regimens, anti-amyloid therapy, FTD drug cautions).



Epilepsy syndromes

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — A *seizure* is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain, while *epilepsy* is an enduring predisposition to recurrent unprovoked seizures. An **epilepsy syndrome** is a distinctive cluster of clinical and

electroencephalographic features — characteristic seizure type(s), age of onset, EEG signature, triggers, imaging, comorbidities and often a predictable prognosis — that occur together and suggest a common underlying mechanism. Recognising the syndrome (rather than just the seizure type) directs the choice of antiseizure medication (ASM), predicts outcome, identifies surgical candidates and guides genetic counselling.

The diagnostic framework: ILAE 2014 definition and the 2017 three-level scheme

- ▶ ILAE 2014 definition of epilepsy (any one of): (1) ≥ 2 unprovoked (or reflex) seizures >24 h apart; (2) one unprovoked seizure with a $\geq 60\%$ recurrence risk over the next 10 years; or (3) diagnosis of an epilepsy syndrome.
- ▶ The 2017 ILAE classification is built in three sequential levels, with etiology and comorbidities considered at every level:
- ▶ Seizure type — focal onset / generalized onset / unknown onset (the older “partial” is replaced by *focal*; “simple/complex partial” replaced by *focal aware* / *focal impaired awareness*; secondary generalization renamed *focal to bilateral tonic-clonic*).
- ▶ Epilepsy type — focal / generalized / combined generalized and focal / unknown.
- ▶ Epilepsy syndrome — assigned when features fit a recognised constellation (not achievable in every patient).
- ▶ Six etiologic categories run in parallel (a patient may have >1): structural, genetic, infectious, metabolic, immune, unknown.

Epilepsy syndromes grouped by age of onset (overview)

Age band	Representative syndromes	Hallmark
Neonatal	Self-limited (benign) familial neonatal epilepsy; Early myoclonic encephalopathy; Ohtahara syndrome	KCNQ2/3 channelopathy; burst-suppression EEG
Infancy	West syndrome; Dravet syndrome; Myoclonic-atonic (Dooze)	Hypsarrhythmia; SCN1A febrile status
Childhood	Childhood absence epilepsy (CAE); Self-limited epilepsy with centrotemporal spikes (SeLECTS/BECTS); Panayiotopoulos; Lennox-Gastaut; Landau-Kleffner/CSWS	3-Hz spike-wave; centrotemporal spikes
Adolescence/adult	Juvenile absence epilepsy (JAE); Juvenile myoclonic epilepsy	Polyspike-wave; auditory aura; hippocampal sclerosis

Age band	Representative syndromes	Hallmark
	(JME); Epilepsy with GTCS alone; ADEAF; mesial temporal lobe epilepsy	

Idiopathic (genetic) generalized epilepsies — the “big four”

These are normal-development, normal-MRI, presumed-polygenic generalized epilepsies; **sleep deprivation** is a universal precipitant and **sodium-channel ASMs** (carbamazepine, oxcarbazepine, phenytoin) and **gabapentinoids** can aggravate seizures.

- ▶ **Childhood absence epilepsy (CAE / pyknolepsy): onset 4–10 yr (peak 5–7); many brief (<15 s) typical absences daily, provoked by hyperventilation; EEG = generalized, symmetric 3-Hz spike-and-wave on normal background. Ethosuximide is the drug of choice* for pure absence (ethosuximide and valproate superior to lamotrigine in the comparative CAE trial). Excellent prognosis; a minority evolve to JME.*
- ▶ **Juvenile absence epilepsy:** onset in the **2nd decade**, fewer absences than CAE, **majority also have GTCS**, greater tendency to persist into adulthood.
- ▶ **Juvenile myoclonic epilepsy (JME / Janz syndrome / impulsive petit mal): onset 12–18 yr; defining seizure = bilateral myoclonic jerks on awakening, provoked by sleep deprivation and alcohol; ~90% develop GTCS and ~one-third have absences; EEG = 4–6 Hz generalized polyspike-and-wave. Valproate is most effective (limited in women of child-bearing age by teratogenicity; levetiracetam/lamotrigine alternatives); usually a lifelong* condition needing long-term therapy.*
- ▶ **Epilepsy with GTCS alone** (incl. “grand mal on awakening”) — generally good response to broad-spectrum ASMs.

Developmental and epileptic encephalopathies (DEEs)

Here the epileptiform activity itself drives cognitive/developmental regression beyond the underlying cause.

- ▶ **West syndrome:** peak onset **3–7 months**; clinical triad — **epileptic (infantile) spasms in clusters + hypsarrhythmia on EEG + arrest/regression of psychomotor development**. Two-thirds have an identifiable brain lesion. Treatment differs from other epilepsies: **ACTH/corticosteroids**, and **vigabatrin** (drug of choice in tuberous sclerosis complex).
- ▶ **Ohtahara syndrome / early myoclonic encephalopathy:** neonatal onset, **burst-suppression EEG**, refractory seizures, poor prognosis; may evolve into West syndrome.
- ▶ **Dravet syndrome (severe myoclonic epilepsy of infancy):** **de novo SCN1A mutation in ~80–95%; previously normal infant presents with febrile status epilepticus around 6 months, later myoclonic, absence, atonic and focal seizures; drug-resistant with developmental decline. Avoid*

sodium-channel blockers (carbamazepine, lamotrigine, phenytoin) — they aggravate seizures; use valproate, clobazam, stiripentol, cannabidiol and fenfluramine.*

- ▶ **Lennox-Gastaut syndrome (LGS):** onset 3–10 yr; triad — (1) multiple seizure types (generalized tonic, atonic/drop attacks, atypical absence ± GTCS); (2) EEG with slow (<2.5 Hz) spike-and-wave in wakefulness and bursts of ~10-Hz paroxysmal fast activity in sleep; (3) cognitive impairment/developmental delay. Drug-resistant; may evolve from West syndrome. Options: valproate, lamotrigine, rufinamide, topiramate, clobazam, felbamate, cannabidiol; neurostimulation under investigation.
- ▶ **Landau-Kleffner syndrome (acquired epileptic aphasia) and CSWS:** verbal auditory agnosia/language regression with continuous spike-and-wave during slow-wave sleep; seizures often mild; benefit from valproate, benzodiazepines, steroids/IVIG, and multiple subpial transection.

Focal epilepsy syndromes

- ▶ **Self-limited epilepsy with centrotemporal spikes (SeLECTS / BECTS / benign rolandic epilepsy):** the commonest idiopathic focal epilepsy of childhood (3–13 yr, peak 5–8); nocturnal hemifacial sensorimotor seizures with hypersalivation/speech arrest, preserved awareness; EEG = high-voltage centrotemporal sharp waves activated by sleep; spontaneous remission at puberty — treatment often unnecessary.
- ▶ **Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS):** the commonest cause of focal seizures with impaired awareness and the prototypical surgically-remediable epilepsy. History of antecedent (often complex) febrile seizures (up to 80%); seizures begin with an aura (rising epigastric sensation, *déjà vu*, fear), then behavioural arrest/stare, orolimentary and manual automatisms, contralateral dystonic posturing, and postictal dysphasia (dominant focus) and disorientation. MRI: small hippocampus with increased T2 signal and loss of internal architecture, enlarged temporal horn; interictal PET hypometabolism, ictal SPECT hyperperfusion; pathology = neuronal loss/gliosis in CA1 and CA3 with sparing of CA2. Frequently drug-resistant → anterior temporal lobectomy / selective amygdalohippocampectomy renders 60–80% seizure-free.
- ▶ **ADEAF (autosomal dominant epilepsy with auditory features):** lateral temporal focal epilepsy with auditory aura/aphasic seizures, due to LGI1 mutation.
- ▶ **Rasmussen syndrome:** progressive unilateral hemispheric epilepsy with *epilepsia partialis continua*, hemiatrophy, hemiparesis and cognitive decline; suspected autoimmune (anti-GluR3); often requires functional hemispherectomy.

Genetic basis and progressive myoclonus epilepsies

Gene	Syndrome
KCNQ2 / KCNQ3	Self-limited familial neonatal epilepsy
SCN1A	Dravet syndrome; GEFS+
CHRNA4 / CHRN2	Sleep-related hypermotor epilepsy (ADNFLE)
LGI1	ADEAF (lateral TLE)
DEPDC5	Familial focal epilepsy with variable foci
GRIN2A	BECTS–Landau-Kleffner spectrum
CDKL5	CDKL5 deficiency disorder (responds to ganaxolone)
SLC2A1 (GLUT1)	GLUT1 deficiency — absence onset <4 yr ± paroxysmal exertional dyskinesia (ketogenic diet)
CSTB	Unverricht-Lundborg disease (PME)
EPM2A (laforin) / NHLRC1 (malin)	Lafora disease (PME)

- **Progressive myoclonus epilepsies (PME):** myoclonus + GTCS + progressive ataxia/dementia. Examples — **Unverricht-Lundborg** (CSTB; *avoid phenytoin*, which aggravates ataxia), **Lafora disease** (polyglucosan Lafora bodies; fatal in 2–10 yr), **MERRF** (mitochondrial, ragged red fibres). **Valproate is the drug of choice**; perampanel helps myoclonus.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **EEG signatures of generalized epilepsy syndromes** (three stacked tracings): (1) **Hypsarrhythmia** — chaotic, high-voltage disorganized slow waves with multifocal spikes/sharp waves and periods of attenuation (label: *West syndrome*); (2) **Generalized symmetric 3-Hz spike-and-wave** on normal background (label: *Childhood absence epilepsy*); (3) **Slow <2.5-Hz spike-and-wave + bursts of ~10-Hz paroxysmal fast activity in sleep** (label: *Lennox-Gastaut syndrome*).
- **Coronal T2 MRI of hippocampal sclerosis (MTLE):** labels — *small/atrophic hippocampus, increased T2 signal, loss of internal (trilaminar) architecture, enlarged temporal horn, normal contralateral hippocampus*.

Clinical / Diagnostic significance

- **Syndromic diagnosis dictates drug choice:** sodium-channel ASMs and gabapentinoids **aggravate** generalized/absence/myoclonic seizures and **Dravet** — use broad-spectrum agents (valproate, levetiracetam, lamotrigine for selected, topiramate).

- ▶ **Precision/targeted therapy:** vigabatrin for West syndrome in tuberous sclerosis; ketogenic diet for GLUT1 deficiency; ganaxolone for CDKL5 deficiency; stiripentol/fenfluramine/cannabidiol for Dravet; ACTH/steroids for infantile spasms.
- ▶ **Surgical candidacy:** MTLE-HS, lesional focal epilepsies and Rasmussen syndrome should be referred early for resective surgery/hemispherectomy when drug-resistant.
- ▶ **Workup:** detailed seizure semiology + witness account, **video-EEG with activation** (hyperventilation, photic stimulation, sleep/sleep deprivation), high-resolution MRI epilepsy protocol, and interictal PET / ictal SPECT for presurgical localisation; autoantibody testing when onset is fulminant with psychiatric/cognitive change.
- ▶ **Prognostic stratification:** self-limited syndromes (CAE, SeLECTS) remit spontaneously, whereas DEEs (West, Dravet, LGS) carry high cognitive morbidity.

High-yield exam pointers

- ▶ **Epilepsy** = ≥ 2 unprovoked seizures >24 h apart, OR 1 seizure with $\geq 60\%$ recurrence risk, OR an epilepsy syndrome (ILAE 2014).
- ▶ **2017 ILAE: three levels** — seizure type $\rightarrow$ epilepsy type $\rightarrow$ syndrome, with six etiologies (structural, genetic, infectious, metabolic, immune, unknown).
- ▶ **West triad** = infantile spasms + **hypsarrhythmia** + psychomotor arrest; **LGS triad** = multiple seizure types + **slow** (<2.5 Hz) **spike-wave** + cognitive impairment.
- ▶ **CAE** $\rightarrow$ 3-Hz spike-wave, ethosuximide DOC; **JME** $\rightarrow$ 4–6 Hz polyspike-wave, valproate DOC, jerks on awakening.
- ▶ **Dravet** = SCN1A (~80–95% de novo), febrile status at ~6 months — **never give sodium-channel blockers**.
- ▶ **MTLE-HS:** antecedent febrile seizures, epigastric aura/*déjà vu*, automatisms; MRI hippocampal sclerosis; CA1/CA3 loss, CA2 sparing; surgery cures 60–80%.
- ▶ **SeLECTS/BECTS:** commonest benign childhood focal epilepsy, nocturnal facial seizures, centrottemporal spikes, remits at puberty.
- ▶ **PME** (Unverricht-Lundborg = CSTB; Lafora = EPM2A/NHLRC1) — myoclonus + GTCS + dementia; **valproate**, avoid phenytoin.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Seizures and Epilepsy” (ILAE 2017 seizure classification, JME/Lennox-Gastaut/MTLE syndromes, gene table, ASM mechanisms).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Epilepsies” (ILAE 2014 definition and 2017 three-level classification; detailed syndrome descriptions — neonatal/infantile/childhood/juvenile syndromes, DEEs, MTLE-HS, PME).

- ▶ CMTD 2026 — “Nervous System Disorders” (Seizures & Epilepsy; Table 27-2 approved indications by syndrome) for current syndrome-specific drug choices (ethosuximide/valproate/clonazepam for absence, vigabatrin for infantile spasms, cannabidiol for Dravet/LGS, ganaxolone for CDKL5).



Etiology and management of orthostatic hypotension

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — Orthostatic (postural) hypotension (OH) is a *sustained reduction in systolic blood pressure (SBP) of ≥ 20 mmHg or diastolic blood pressure (DBP) of ≥ 10 mmHg within 3 minutes of active standing or head-up tilt (HUT) $\geq 60^\circ$* . In a known hypertensive the threshold is a fall of $\geq 30/15$ mmHg. It is a sign of failure of the baroreflex-mediated cardiovascular adjustment to upright posture rather than a disease in itself. On standing, ~ 500 – 700 mL of blood pools in the lower limbs and splanchnic bed; failure to compensate by reflex tachycardia, venoconstriction and arteriolar constriction produces cerebral hypoperfusion. OH is common (prevalence $< 5\%$ below age 50 rising to $\sim 20\%$ above age 70) and is an independent marker of falls, fracture, coronary disease, heart failure, stroke and death.

Physiology and definitions (variants)

- ▶ **Normal orthostatic response** — slight rise in heart rate (HR), peripheral venoconstriction and arteriolar constriction maintain SBP and slightly raise DBP, integrating baroreceptors, autonomic afferents, central centres, efferents and vascular adrenoceptors.
- ▶ **Classical OH** — fall $\geq 20/10$ mmHg within 3 min ($\geq 30/15$ in hypertensives).
- ▶ **Initial OH** — abrupt transient fall (> 40 mmHg SBP / > 20 mmHg DBP) within 15–30 s of standing, resolving by ~ 45 s; due to cardiac output–vascular resistance mismatch; seen in the young (and elderly on antihypertensives); *not* true autonomic failure.
- ▶ **Delayed OH** — fall appears only after 3–5 min (sometimes > 10 min) of standing/tilt; often an early or mild form of adrenergic autonomic dysfunction.
- ▶ **Postprandial hypotension** — fall within ~ 2 h of a large, high-carbohydrate meal (worse with alcohol) from splanchnic pooling; typical in elderly with autonomic disorders.
- ▶ **Neurogenic vs non-neurogenic OH** — *Non-neurogenic OH*: compensatory HR rise > 15 beats/min. *Neurogenic OH (NOH)*: blunted HR rise < 15 beats/min, reflecting impaired norepinephrine (NE) release; more accurately a $\Delta\text{HR}/\Delta\text{SBP}$ ratio < 0.5 beats/min/mmHg (cardiac baroreflex gain). NOH carries a grave prognosis (mortality $\sim 44\%$ at 30 months, $> 60\%$ at 10 years) and is frequently coupled with supine hypertension.

Etiology / Classification

OH is broadly **neurogenic** (autonomic failure, blunted HR rise) or **non-neurogenic** (intact reflex tachycardia).

Category	Causes
Neurogenic — primary autonomic failure (synucleinopathies)	Multiple system atrophy (<i>Shy-Drager syndrome</i>), Parkinson's disease with autonomic failure, dementia with Lewy bodies, pure autonomic failure (PAF)
Neurogenic — secondary autonomic neuropathies	Diabetic autonomic neuropathy (commonest), amyloidosis (AL and hereditary transthyretin/ <i>hATTR</i>), autoimmune autonomic ganglionopathy (anti-ganglionic $\alpha 3$ -AChR), paraneoplastic (anti-Hu, small-cell lung Ca), Sjögren syndrome, HIV neuropathy, hereditary sensory & autonomic neuropathy type III (<i>familial dysautonomia / Riley-Day</i>), alcoholic/nutritional (B12, thiamine), porphyria, Guillain-Barré syndrome
Neurogenic — central / genetic	Baroreflex failure (post-radiation/surgery/tumour to carotid sinus), spinal cord lesions, dopamine β-hydroxylase (DBH) deficiency (selective NE absence, high dopamine), Menkes disease
Non-neurogenic — volume depletion	Haemorrhage, vomiting/diarrhoea, reduced intake, over-diuresis, over-dialysis, adrenal insufficiency (<i>Addison</i>), idiopathic hypovolaemia
Non-neurogenic — cardiac	Heart failure, chronotropic incompetence, severe bradyarrhythmia
Non-neurogenic — vasodilatory / drug-induced (iatrogenic)	α -blockers (BPH/HTN), diuretics, nitrates and other veno/vasodilators, other antihypertensives, tricyclic antidepressants, phenothiazines/antipsychotics, dopamine agonists; mast-cell/vasodilator excess (mastocytosis, carcinoid)

- ▶ Drug mechanisms: volume depletion or direct vasodilatation → reflex tachycardia (**hyperadrenergic OH**); central sympatholysis → blunted reflex (**hypoadrenergic OH**). The elderly are especially vulnerable (polypharmacy + impaired baroreflex).
- ▶ In diabetes, autonomic neuropathy raises mortality up to threefold; risk correlates with the product of HbA1c and disease duration, with early parasympathetic loss followed by sympathetic failure dominated by OH.

Clinical features

- ▶ **Cerebral hypoperfusion** — lightheadedness/dizziness on standing, visual blurring, presyncope and syncope (worse on waking, after meals, exertion, heat).

- ▶ **Indirect / regional ischaemia** — generalised weakness, fatigue, cognitive slowing, leg buckling; *coat-hanger* suboccipital/shoulder pain (cervical-trapezius muscle ischaemia); orthostatic dyspnoea (*platypnoea*, apical V/Q mismatch); orthostatic angina; orthostatic headache.
- ▶ **Severity grading** — functional class I (asymptomatic) to class IV (daily disabling symptoms). NOH may show striking BP falls with surprisingly mild symptoms because of cerebral autoregulation.
- ▶ **Associated autonomic features** — supine hypertension, *reverse dipping*, nocturia, constipation, urinary retention, erectile failure, anhidrosis (point to a generalised dysautonomia/synucleinopathy).

Evaluation / Investigations

- ▶ **Bedside** — supine BP/HR, then standing BP/HR at 1 and 3 min (delayed/active standing if tilt unavailable); calculate $\Delta\text{HR}/\Delta\text{SBP}$ to label NOH.
- ▶ **Bloods** — CBC, metabolic panel, glucose/HbA1c (2-h OGTT if small-fibre neuropathy), B12, iron/ferritin, vitamin D; supine and upright catecholamines (fail to double on standing in NOH; low supine NE in postganglionic/peripheral lesions, e.g. PAF/DBH deficiency); serum free light chains/SPEP for amyloid; ganglionic α_3 -AChR and paraneoplastic antibodies; 5-HIAA, cortisol if indicated.
- ▶ **Autonomic function tests** — HR variation to deep breathing and Valsalva ratio (parasympathetic/baroreflex), QSART and thermoregulatory sweat test (sudomotor), and **tilt-table testing** (defines OH type and distinguishes it from neurally mediated/vasovagal syncope).
- ▶ **Cardiac** — ECG $\pm$ echocardiography to exclude structural/arrhythmic syncope; rule out pheochromocytoma/hyperthyroidism when a hyperadrenergic picture is present.

Management

Goal in OH is symptom relief and fall prevention, not BP normalisation. Begin by **removing reversible contributors** (offending drugs — diuretics, antihypertensives, α -blockers, TCAs, antipsychotics, dopamine agonists) and correcting anaemia, B12/iron/D deficiency and volume depletion.

Non-pharmacologic (first-line, often sufficient in early/class I disease):

- ▶ Patient education — **staged moves** supine→sitting→standing; warn about large meals, alcohol, heat, early morning.
- ▶ **Volume expansion** — fluid up to 2–3 L/day; **liberal salt** (≈ 6 –10 g/day; e.g. 2 g three times daily), titrated to 24-h urinary sodium (target ~ 185 mmol).
- ▶ **Acute water bolus** — rapid ingestion of ~ 500 mL plain (hypotonic) water raises BP by 30–40 mmHg within minutes (sympathetic spinal pressor reflex); take on waking/before being upright.
- ▶ **Physical measures** — waist-high compression stockings + **abdominal binder** (reduce splanchnic pooling), **physical counter-maneuvres** (leg-crossing, squatting, lower-limb/abdominal muscle

tensing, leg elevation), recumbent aerobic + leg-resistance exercise/water aerobics, and **head-of-bed elevation 30–45°** to limit nocturnal supine hypertension and pressure-natriuresis.

Pharmacologic (if measures fail):

Drug	Mechanism	Dose	Key caveats
Fludrocortisone	Mineralocorticoid → plasma volume expansion + mild α -sensitisation	0.1–0.2 mg OD (up to 0.4)	Supine hypertension, pedal oedema, hypokalaemia/hypomagnesaemia, headache; effect takes 1–2 weeks; monitor weight/BP, bone density on long-term use
Midodrine	Direct peripheral $\alpha 1$ -agonist (prodrug → desglymidodrine)	2.5 mg TID up titrate to 7.5–15 mg TID	Onset 30–60 min, lasts ~4 h; <i>last dose before 6 p.m.</i> ; scalp tingling/piloerection, urinary urgency, supine hypertension
Droxidopa (L-threo-DOPS)	NE precursor → ↑ synaptic NE; FDA-approved 2014 for NOH	100 mg TID up to 400–600 mg TID	Reduces falls/dizziness (esp. PD, DBH deficiency); supine hypertension
Pyridostigmine	Cholinesterase inhibitor → ↑ ganglionic transmission	30 mg TID up to 60–90 mg TID	Greater effect standing than supine → <i>little supine hypertension</i> ; good if coexistent GI hypomotility; cramps/diarrhoea; synergistic with midodrine
Atomoxetine	NE-reuptake inhibitor (adjuvant)	18 mg morning	Anxiety/tremor (CNS stimulation)
Desmopressin (DDAVP)	↑ water reabsorption, ↓ nocturia	low oral/nasal dose	Monitor for hyponatraemia

- Erythropoietin (for associated anaemia) and octreotide (for postprandial hypotension) are occasional adjuncts.

Supine hypertension (the therapeutic dilemma in NOH): avoid daytime recumbency, reduce evening fluids, *avoid fludrocortisone in favour of short-acting agents*, elevate head of bed 30°, take a bedtime carbohydrate snack, and if SBP persistently high use **short-acting bedtime antihypertensives** (e.g. losartan, nifedipine with caution, nebivolol, transdermal nitroglycerine, or clonidine in central failure such as MSA). Treat the underlying cause where possible (e.g. glycaemic control in diabetes; IVIg/plasma exchange for AAG; gene-silencing therapy for hATTR amyloidosis).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Tilt-table tracing of neurogenic OH** — two stacked time plots labelled *HR (beats/min)* and *BP (mmHg)* against time; mark *Tilt up (TU)* and *Tilt down (TD)*; show a progressive

SBP/DBP fall after TU with a *flat HR* line (no compensatory tachycardia), and label baseline *supine hypertension* (SBP $\sim$ 175 mmHg).

- ▶ **Orthostatic physiology / management schema** — standing figure with arrows showing $\sim$ 500–700 mL venous & splanchnic pooling $\rightarrow$ $\downarrow$ venous return $\rightarrow$ $\downarrow$ cardiac output $\rightarrow$ cerebral hypoperfusion; annotate baroreflex limb (baroreceptor $\rightarrow$ NTS $\rightarrow$ sympathetic efferent $\rightarrow$ vasoconstriction) with the failure point in NOH; flank with management labels: *salt/water, compression stockings, abdominal binder, head-up tilt, fludrocortisone, midodrine, droxidopa*.

Clinical / Diagnostic significance

- ▶ A simple lying-and-standing BP is a high-yield, low-cost screen in all elderly, diabetic, syncope, falls and “dizziness” patients.
- ▶ The Δ HR response is the pivot: blunted (<15 bpm) suggests NOH/autonomic failure warranting tilt testing and catecholamine studies; brisk tachycardia points to volume/drug causes.
- ▶ OH preceding parkinsonism by years, or OH within 2 years of motor onset, is a red flag for MSA / a synucleinopathy; isolated OH with low supine NE suggests PAF.
- ▶ Recognising **supine hypertension** prevents reflex over-treatment that precipitates falls, and prevents end-organ (renal/cardiac/cerebrovascular) damage.

High-yield exam pointers

- ▶ OH = SBP $\downarrow \geq 20$ or DBP $\downarrow \geq 10$ mmHg within 3 min standing/HUT ($\geq 30/15$ in hypertensives).
- ▶ Neurogenic OH = HR rise <15 bpm or Δ HR/ Δ SBP <0.5 bpm/mmHg; high mortality ($\sim 44\%/30$ months).
- ▶ Initial OH ($>40/20$ within 15–30 s) and delayed OH (>3 –5 min) are recognised variants.
- ▶ Synucleinopathies = MSA, PD, DLB, PAF; MSA = *Shy-Drager*, GCIs of α -synuclein in glia.
- ▶ Commonest **secondary** cause = diabetic autonomic neuropathy; commonest overall contributors in elderly = drugs + volume depletion.
- ▶ Non-drug therapy first: salt 6–10 g, fluid 2–3 L, 500 mL water bolus, stockings/abdominal binder, counter-maneuvres, head-up tilt 30° .
- ▶ First-line drugs: **fludrocortisone 0.1–0.2 mg** and **midodrine** ($\alpha 1$ -agonist, last dose before 6 p.m.); **droxidopa** (NE precursor) for NOH; **pyridostigmine** spares supine BP.
- ▶ Always check for and manage coexistent **supine hypertension** — head-up bed, short-acting bedtime antihypertensive, avoid fludrocortisone.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Disorders of the Autonomic Nervous System" (definition, NOH criteria, variants, full management/drug doses, synucleinopathies, diabetic/amyloid/AAG neuropathies) and "Syncope" (OH definition, causes of neurogenic OH, treatment algorithm).
- ▶ Bradley & Daroff's Neurology in Clinical Practice, 8e — "Disorders of the Autonomic Nervous System" (Box 107.4 differential diagnosis of OH, hyper-/hypoadrenergic OH mechanisms, DBH deficiency, detailed drug therapy incl. fludrocortisone/midodrine/droxidopa/pyridostigmine, supine-hypertension consensus management, water-drinking pressor effect).
- ▶ CMDT 2026 — "Disorders of Cardiac Rhythm" (syncope/OH evaluation, counterpressure manoeuvres, midodrine) for current management framing.



Guillain Barre Syndrome

Asked in: Paper III Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Guillain-Barré syndrome (GBS) is an acute, frequently severe and fulminant **autoimmune polyradiculoneuropathy** characterised by rapidly evolving **areflexic motor paralysis** with or without sensory disturbance. It is the commonest cause of acute flaccid paralysis in the post-polio era, occurring year-round at **10–20 cases per million annually** (~5000–6000 cases/year in the USA). Males are at slightly higher risk than females, and in Western countries adults are affected more than children. The syndrome typically follows an antecedent infection by 1–3 weeks and is mediated by **molecular mimicry** between microbial and neural ganglioside epitopes.

Subtypes / Classification

GBS is a spectrum; subtypes are defined primarily by **electrodiagnostic (EDx)** and **pathologic** features and associated antiganglioside antibodies.

Subtype	Key features	Pathology / EDx	Antibody
AIDP (acute inflammatory demyelinating polyneuropathy)	Commonest; ~90% of Western cases; adults > children; rapid recovery	Demyelinating; first attack on Schwann-cell surface; macrophage-mediated myelin injury, variable secondary axonal loss	anti-GM1 (<50%)
AMAN (acute motor axonal neuropathy)	Children/young adults; prevalent in China & Mexico; may be seasonal; rapid recovery	Axonal; attack at motor nodes of Ranvier	anti-GD1a

Subtype	Key features	Pathology / EDx	Antibody
AMSAN (acute motor sensory axonal neuropathy)	Mostly adults; uncommon; recovery slow, often incomplete; related to AMAN	Axonal; like AMAN but also sensory nerves/roots; severe axonal damage	GM1, GD1a
Miller Fisher syndrome (MFS)	~5% of cases; triad of ophthalmoplegia, ataxia, areflexia (no limb weakness); pupillary paralysis	Demyelinating/nodal	anti-GQ1b (>90%)

- ▶ **Regional/limited variants:** pure sensory forms; pharyngeal-cervical-brachial weakness (anti-GT1a/GQ1b); GBS with severe bulbar/facial palsy and antecedent CMV (anti-GM2); acute pandysautonomia.
- ▶ The **anti-GQ1b antibody syndrome** spans MFS, acute ophthalmoparesis, acute ataxic neuropathy, *Bickerstaff's brainstem encephalitis*, and pharyngeal-cervical-brachial weakness — illustrating a continuous clinical spectrum.

Antecedent events & associations

- ▶ ~70% of cases occur **1–3 weeks** after an acute infection (usually respiratory or gastrointestinal).
- ▶ **Campylobacter jejuni** precedes 20–30% of cases (North America, Europe, Australia) and is the classic trigger of AMAN; summer AMAN outbreaks have followed poultry exposure in rural China.
- ▶ Other agents: **CMV**, **Epstein-Barr virus**, HIV, hepatitis E, **Zika** (Brazil/endemic outbreaks), *Mycoplasma pneumoniae*. SARS-CoV-2 association reported but causality not established.
- ▶ **Vaccines:** the 1976 swine influenza vaccine is the notable example; modern seasonal influenza vaccines carry <1 case/million; slight increase with adenovirus-vector SARS-CoV-2 vaccines (not mRNA); older nerve-tissue rabies vaccine.
- ▶ **Disease associations:** lymphoma (incl. Hodgkin's), HIV seropositivity, SLE, possibly Sjögren's; immune checkpoint inhibitors.

Immunopathogenesis & pathophysiology

- ▶ Both **cellular and humoral** immune mechanisms contribute. AIDP is analogous to experimental allergic neuritis (EAN), a T-cell-mediated immunopathy against peripheral myelin (e.g., P2 protein); autoreactive T cells are found in blood, CSF and nerve.
- ▶ **Humoral arm:** autoantibodies against **gangliosides** (complex sialic-acid-bearing glycosphingolipids concentrated at nodes of Ranvier) arise via *molecular mimicry* — *C. jejuni* lipo-oligosaccharide cross-reacts with GM1.
- ▶ AIDP — complement deposits on the **outer Schwann-cell surface**, triggering **vesicular myelin disintegration** and recruitment of activated macrophages; the resultant **conduction block** (axons

remaining intact) underlies the flaccid paralysis, allowing rapid recovery with remyelination. Severe cases develop secondary axonal degeneration → slower, incomplete recovery.

- ▶ **AMAN/AMSAN** — IgG (anti-GM1/GD1a) plus complement deposit at the **nodal axolemma of motor axons**; membrane-attack complex disrupts Na⁺-channel clustering and detaches paranodal myelin → reversible conduction failure, with axonal degeneration in severe cases. Anti-GD1a shows fine specificity favouring motor over sensory roots.

Clinical features

- ▶ **Ascending, symmetric flaccid weakness** (“rubbery legs”), evolving over hours to a few days, legs > arms, with tingling dysaesthesias.
- ▶ **Areflexia/hyporeflexia** appears within the first few days (large-fibre functions — DTRs, proprioception — affected more than pain/temperature).
- ▶ **Facial diparesis in ~50%**; lower cranial nerve / **bulbar weakness** (difficulty handling secretions, airway risk) — may mimic brainstem ischaemia.
- ▶ **Pain** (neck, shoulder, back, dysaesthetic limb pain) in ~50% early on.
- ▶ **Autonomic involvement** common even in mild disease: labile blood pressure, postural hypotension, cardiac dysrhythmias — potentially fatal. Bladder dysfunction is usually transient and late.
- ▶ Up to **30% require mechanical ventilation**; predictors are severe weakness on admission, rapid progression, and early facial/bulbar weakness.
- ▶ Nadir is reached and a **plateau** established almost always **within 4 weeks** of onset. Fever/constitutional symptoms at onset argue *against* GBS.

Investigations & diagnosis

- ▶ **CSF — albuminocytologic (cytoalbuminologic) dissociation**: elevated protein **1–10 g/L (100–1000 mg/dL)** with **white cells <50/μL** (no pleocytosis). CSF may be normal in first ≤48 h, rising by the end of the first week. Sustained pleocytosis (10–100/μL persistent) suggests an alternative (viral myelitis, HIV, leukaemia/lymphoma, neurosarcoidosis).
- ▶ **Nerve conduction studies (EDx)** — mild/absent early; earliest AIDP changes are **prolonged F-wave latencies, prolonged distal latencies, reduced CMAP amplitudes**, reflecting proximal root and distal terminal involvement; later **conduction slowing, conduction block, temporal dispersion**. AMAN/AMSAN show **low-amplitude CMAPs (and SNAPs in AMSAN) without conduction slowing**.
- ▶ **Antiganglioside antibodies** support subtyping (anti-GQ1b for MFS, anti-GD1a/GM1 for axonal forms).
- ▶ **Brighton Collaboration criteria (2011)** provide graded levels of diagnostic certainty (Level 1 highest), incorporating bilateral flaccid limb weakness, depressed reflexes, monophasic course

with nadir between 12 h and 28 days, cytoalbuminologic dissociation, supportive EDx and exclusion of alternatives.

- ▶ Begin treatment on clinical suspicion — do not await CSF/EDx evolution. Test for HIV if risk factors or CSF pleocytosis present.

Differential diagnosis

- ▶ Acute myelopathies (early prominent back pain, sphincter loss, sensory level); poliomyelitis / **acute flaccid myelitis** (West Nile, enterovirus D68/A71); CMV or Lyme polyradiculitis; diphtheritic neuropathy; **porphyria** (abdominal pain, seizures, psychosis); vasculitic neuropathy; critical-illness neuropathy/myopathy; neuromuscular junction disease — **myasthenia gravis**, **botulism** (early pupillary involvement); intoxications (**organophosphates**, **thallium**, **arsenic**), paralytic shellfish poisoning; severe hypophosphataemia.

Treatment

- ▶ **Start immunotherapy as early as possible** — “each day counts”; benefit beyond ~2 weeks from onset is uncertain, and treatment at the plateau is generally not indicated unless severe weakness with possible ongoing attack.
- ▶ **IVIg** — total **2 g/kg**, usually as **five daily infusions**; first-line for ease and safety (acts via anti-idiotypic neutralisation of autoantibodies).
- ▶ **Plasmapheresis (PLEX)** — ~**40–50 mL/kg exchange**, **4–6 times over 7–12 days**; reduces need for mechanical ventilation (27% → 14%) and increases full recovery at 1 year (55% → 68%).
- ▶ IVIg and PLEX are **equally effective**; **combining them is not superior**; failure of one is not an indication to switch to the other. Early treatment-related fluctuation/relapse within a month is managed by a brief repeat course of the original therapy.
- ▶ **Glucocorticoids are NOT effective in GBS** (a key contrast with CIDP, which does respond to steroids).
- ▶ Very mild cases, or those already at plateau, may be managed conservatively.
- ▶ **Supportive/ICU care** (worsening phase): monitor **vital capacity**, cardiac rhythm and blood pressure; nutrition; DVT prophylaxis; consider **tracheostomy after ~2 weeks of intubation**; chest physiotherapy, frequent turning, skin care, range-of-motion exercises to prevent contractures, and reassurance.

Prognosis

- ▶ ~**85% achieve full functional recovery** within several months to a year; residual areflexia and fatigue are common.
- ▶ **Mortality** <5% in optimal settings; death is usually from secondary pulmonary complications and autonomic instability.

- ▶ Worse outcome with **severe proximal motor and sensory axonal damage**, advanced age, fulminant attack, and delayed treatment. **Elevated serum neurofilament light (NfL) chains** and **high anti-GM1 titres** mark greater axonal injury and poor recovery.
- ▶ 5–10% suffer late relapses; many are reclassified as **chronic inflammatory demyelinating polyneuropathy (CIDP)** (course >8 weeks, relapses ≥ 3 times, steroid-responsive).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Spectrum/antibody map:** a horizontal axis with boxes — *AIDP* (anti-GM1) → *AMAN/AMSAN* (anti-GM1, GD1a) and *MFS/anti-GQ1b syndrome* (anti-GQ1b, GT1a) → *Bickerstaff's encephalitis*. Labels: AIDP, AMAN, AMSAN, MFS, GM1, GD1a, GQ1b, GT1a.
- ▶ **Pathogenesis of a myelinated motor axon:** label *node of Ranvier* (Na_v channels), *paranode* (*Caspr*), *juxtaparanode* (K_v channels), *Schwann cell/myelin*, *IgG anti-GM1/anti-GD1a antibody binding*, *complement activation* → *membrane-attack complex (MAC)*, *macrophage scavenging*. Show MAC on outer Schwann-cell surface for AIDP and at the nodal axolemma for AMAN.

Clinical / Diagnostic significance

- ▶ GBS is the prototype treatable cause of acute flaccid paralysis — **early recognition, serial vital-capacity monitoring and prompt IVIg/PLEX** are life-saving.
- ▶ **Albuminocytologic dissociation** plus a compatible clinical picture clinches the diagnosis; absence of fever, presence of areflexia and a recent *C. jejuni*/viral illness are strong pointers.
- ▶ Watch for **respiratory failure and autonomic instability** — the two main killers — mandating ICU admission during worsening.
- ▶ Distinguish from acute myelopathy (sensory level, early sphincter loss) and MFS/Bickerstaff overlap (ophthalmoplegia + ataxia, anti-GQ1b).

High-yield exam pointers

- ▶ GBS = acute **autoimmune areflexic ascending flaccid paralysis**; commonest variant **AIDP**; **anti-GQ1b** = MFS; **anti-GD1a/GM1** = AMAN/AMSAN.
- ▶ 70% post-infectious at 1–3 weeks; classic trigger **Campylobacter jejuni** (→ AMAN); also CMV, EBV, Zika, *Mycoplasma*.
- ▶ CSF: high protein 1–10 g/L with **<50 cells/ μ L** (cytoalbuminologic dissociation), often normal in first 48 h.
- ▶ EDx: earliest = prolonged **F-wave latency**; axonal forms = low CMAP amplitude *without* slowing.
- ▶ Treatment = **IVIg 2 g/kg over 5 days OR PLEX 40–50 mL/kg $\times 4$ –6**; equally effective; **steroids do NOT work**.

- ▶ ~30% need ventilation; tracheostomy considered after ~2 weeks intubation.
- ▶ 85% full recovery, mortality <5%; poor prognosis with axonal damage, age, fulminant onset, delayed therapy; high NfL and anti-GM1 = worse.
- ▶ Brighton criteria (2011) standardise diagnosis; nadir within 12 h–28 days, monophasic.
- ▶ 5–10% relapse → consider CIDP (steroid-responsive, unlike GBS).

SOURCE & COVERAGE

Harrison 22e — Ch 458 “Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies” (Hauser & Amato). All figures, doses, percentages, antibody associations, Brighton criteria and prognostic data are taken from this chapter; no external content was added.



Horner's Syndrome

Asked in: Paper III Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Horner's syndrome (*oculosympathetic palsy/paresis*) is the clinical triad of ipsilateral **ptosis**, **miosis** and **facial anhidrosis** resulting from interruption of the sympathetic supply to the eye and face anywhere along its three-neuron pathway, from the hypothalamus to the orbit. Anhidrosis is an *inconstant* feature that depends on the level of the lesion. Clinically its importance is not the eye signs themselves (which are benign) but its value as a **localizing sign**, since the causes range from idiopathic to immediately dangerous (internal carotid dissection, Pancoast tumour). When facial sweating is spared the term *oculosympathetic paresis* is often used interchangeably.

Anatomy of the oculosympathetic pathway (three neurons)

- ▶ **First-order (central) neuron** — arises in the posterolateral hypothalamus, descends through the dorsolateral brainstem and lateral column of the cord, and synapses in the **cilio-spinal center of Budge**, the intermediolateral grey column at C8–T2.
- ▶ **Second-order (preganglionic) neuron** — exits via the ventral roots/white rami communicantes, arches **over the lung apex** and **beneath the subclavian artery**, ascends the cervical sympathetic chain, and synapses in the **superior cervical ganglion** at the **carotid bifurcation** (angle of the jaw). *Sudomotor fibres for facial sweating branch off here to follow the external carotid artery.*
- ▶ **Third-order (postganglionic) neuron** — ascends as the **pericarotid plexus** on the **internal carotid artery**, traverses the **cavernous sinus** (briefly joining CN VI), then joins the **nasociliary branch of V1**, and reaches the iris via the **long ciliary nerves**.
- ▶ **Effectors** — *dilator pupillae* (mydriasis), **Müller's muscle** (superior tarsal, upper lid), inferior tarsal muscle (lower lid), and facial sweat glands/vasomotor tone.

Clinical features

- ▶ **Ptosis** — mild, only 1–3 mm, from denervation of Müller’s (superior tarsal) muscle; *never* as complete as a CN III palsy; may fluctuate and worsen with fatigue.
- ▶ **Inverse (“upside-down”) ptosis** — the lower lid is *elevated* 1–2 mm (loss of the inferior tarsal muscle), narrowing the palpebral fissure and producing **apparent enophthalmos** — an optical illusion; true globe position is normal.
- ▶ **Miosis** — small pupil that reacts **normally to light and near**; the **anisocoria is greater in the dark** (small pupil is the abnormal one).
- ▶ **Dilation lag** — the affected pupil dilates *slowly* when the lights are dimmed; anisocoria is more pronounced at 4–5 s than at 10–12 s after lights-out — a hallmark sign.
- ▶ **Anhidrosis** — ipsilateral facial; present **only with first-/second-order (preganglionic)** lesions. Absent in **postganglionic (third-order)** lesions (sudomotor fibres have already branched with the external carotid), except possibly a small medial-forehead patch.
- ▶ **Other** — conjunctival/facial vasodilation, ocular hypotony, loss of the **ciliospinal reflex**; *congenital* Horner causes **heterochromia iridis** (a paler iris on the affected side) and facial trophic changes.

Localization by neuron order and representative causes

Order	Anatomical site	Anhidrosis	Representative causes
First-order (central)	Hypothalamus → brainstem → C8–T2	Possible (ipsilateral, extensive)	Wallenberg (lateral medullary) syndrome, brainstem stroke/tumour, syringobulbia, multiple sclerosis, hypothalamic lesions
Second-order (preganglionic)	C8–T2 → superior cervical ganglion	Present (facial)	Pancoast (apical lung) tumour, lower brachial plexus avulsion, cervical rib, thyroid/neck surgery or trauma, mediastinal mass, aortic/subclavian aneurysm, syringomyelia, C8/T1 root lesion
Third-order (postganglionic)	SCG → carotid → cavernous sinus → orbit	Absent (maybe medial forehead)	Internal carotid dissection/thrombosis (painful Horner), cavernous sinus disease, cluster headache, Raeder paratrigeminal

Order	Anatomical site	Anhidrosis	Representative causes
			syndrome, otitis media/petrositis, nasopharyngeal/skull-base tumour

Pharmacological testing (confirmation + localization)

A two-step approach; confirmatory and localizing drops must be ≥ 24 h apart.

Drop	Mechanism	Result	Interpretation
Cocaine 2–10%	Blocks noradrenaline reuptake at the sympathetic terminal	Normal pupil dilates; Horner pupil fails to dilate	Confirms Horner (any order); does <i>not</i> localize. (Controlled substance; urine toxicology positive ~2 days.)
Apraclonidine 0.5%	Weak α_1 -agonist acting on the supersensitive denervated dilator	Reversal of anisocoria — Horner pupil dilates (denervation supersensitivity) + ptosis improves; normal pupil unchanged/slightly constricts	Confirms Horner; convenient cocaine substitute. May be falsely negative very acutely (supersensitivity takes ~36 h–days to develop).
Hydroxyamphetamine 1%	Releases stored noradrenaline from an <i>intact</i> third-order terminal	Dilates in first-/second-order Horner; fails to dilate in third-order Horner	Localizes preganglionic vs postganglionic.

Differential diagnosis / mimics

- ▶ **Physiologic (simple) anisocoria** — equal in light and dark, ≤ 0.5 mm; *pseudo-Horner* = physiologic anisocoria with an incidental ptosis (e.g., levator dehiscence).
- ▶ **Anisocoria greater in dark** → the *small* pupil is abnormal (Horner); **greater in light** → the *large* pupil is abnormal (CN III palsy, **Adie tonic pupil**, pharmacologic mydriasis).
- ▶ **Ptosis** — distinguish from CN III palsy (larger/normal pupil + ophthalmoparesis), myasthenia (fatigable, *Cogan lid twitch*), aponeurotic/senile and mechanical ptosis.
- ▶ **Reverse Horner (Pourfour du Petit syndrome)** — sympathetic *overactivity*: mydriasis, lid retraction, facial flushing/hyperhidrosis (early irritative lesions).
- ▶ **Harlequin syndrome** — unilateral facial anhidrosis with contralateral flushing/sweating on exertion/heat; usually no eye signs (may coexist with Horner).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Three-neuron oculosympathetic pathway** — label: *hypothalamus* → *dorsolateral brainstem* → *cilio-spinal center of Budge (C8–T2)* → *ventral root* → *lung apex* → *subclavian artery* → *cervical sympathetic chain* → *superior cervical ganglion (carotid bifurcation)* → *internal carotid / pericarotid plexus* → *cavernous sinus (CN VI)* → *nasociliary branch of V1* → *long ciliary nerves* → *dilator pupillae & Müller's muscle*; mark the **branch point of sudomotor fibres onto the external carotid**.
- ▶ **Face of a left Horner's** — label: *upper-lid ptosis, elevated lower lid (inverse ptosis), miosis, apparent enophthalmos, ipsilateral facial anhidrosis*.

Clinical / Diagnostic significance

- ▶ **Acute painful Horner** (especially after neck pain, trauma or chiropractic manipulation) → suspect **internal carotid dissection**; urgent MRI/MRA (axial fat-saturated T1 shows a crescentic mural haematoma); treat with **antiplatelet (aspirin)** to prevent embolic stroke.
- ▶ **Preganglionic Horner in a smoker** → search for a **Pancoast / apical lung tumour** (CXR/CT chest); look for C8–T1 pain and wasting of hand intrinsic.
- ▶ **Isolated Horner** — imaging the entire pathway finds a cause in only ~20%; the workup is **directed by localization** — preganglionic → brain + cervical/upper-thoracic spine MRI + chest imaging; postganglionic → brain MRI + head-and-neck MRA.
- ▶ **Children** — most cases are congenital, but exclude **neuroblastoma**: neuroimaging + **urinary catecholamines (VMA/HVA)**; heterochromia favours a congenital/long-standing lesion.
- ▶ **Wallenberg syndrome** — Horner is one component (with crossed sensory loss, ipsilateral ataxia, vertigo, dysphagia).

High-yield exam pointers

- ▶ Triad = **ptosis + miosis + anhidrosis** (oculosympathetic palsy); anhidrosis is *inconstant*.
- ▶ **Anisocoria greater in the dark + dilation lag** = the clinical hallmark.
- ▶ Müller's (superior tarsal) muscle → **mild** ptosis; levator (CN III) → **severe** ptosis.
- ▶ **Cocaine / apraclonidine confirm**; **hydroxyamphetamine localizes** (dilates in pre-, fails in postganglionic).
- ▶ **Apraclonidine reverses the anisocoria** via denervation supersensitivity — now replaces cocaine.
- ▶ **Anhidrosis present = preganglionic (1st/2nd order)**; **absent = postganglionic (3rd order)**.
- ▶ **Painful Horner** = carotid dissection until proven otherwise.
- ▶ **Congenital Horner** → **heterochromia iridis**; in a child, rule out **neuroblastoma**.
- ▶ *Pourfour du Petit* = reverse Horner; *Raeder paratrigeminal* = postganglionic Horner + V1 facial pain.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine 22e — "Disorders of the Eye" and "Disorders of the Autonomic Nervous System"; Bradley & Daroff's Neurology in Clinical Practice — "Pupillary and Eyelid Abnormalities"; DeJong's The Neurologic Examination — "The Ocular Motor Nerves"; Brazis — Localization in Clinical Neurology — "Localization of Lesions Affecting the Ocular Motor System" and "Localization of Lesions in the Autonomic Nervous System"; Raeder paratrigeminal syndrome from DeJong/Brazis "Trigeminal Nerve."

Coverage note: Harrison treats Horner's only briefly (a few lines in the eye and autonomic chapters). The deep three-neuron localization scheme, pharmacologic-testing logic, dilation-lag timing and eponyms (Budge, Pourfour du Petit, Raeder, Harlequin) are drawn from the dedicated neurology texts (Bradley, DeJong, Brazis) as directed by the spec. CMDT has no dedicated section and was not used.



Hyperkinetic Movement Disorders

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — Hyperkinetic movement disorders are characterised by **excessive, involuntary movements that are unaccompanied by weakness**. They contrast with the hypokinetic (akinetetic-rigid) disorders such as Parkinson's disease. The term is partly arbitrary — hypokinetic PD often has tremor, while hyperkinetic dystonia may restrict movement — but it remains useful by convention. Most arise from dysfunction of the **basal ganglia–thalamo-cortical circuits**. The major phenotypes are tremor, dystonia, athetosis, chorea/ballism, myoclonus and tics; precise phenomenological recognition is the key to diagnosis.

Classification by phenomenology (Harrison Table 447-1)

Disorder	Defining phenomenology
Tremor	Rhythmic oscillation of a body part from intermittent agonist–antagonist contraction
Dystonia	Involuntary, patterned, sustained/repeated contractions → twisting movements & abnormal postures
Athetosis	Slow, distal, writhing involuntary movements (a form of dystonia " <i>without fixed position</i> ")
Chorea	Rapid, semi-purposeful, graceful, dance-like, non-patterned movements; large-amplitude proximal form = ballism

Disorder	Defining phenomenology
Myoclonus	Sudden, brief (<100 ms), jerk-like, arrhythmic muscle twitches
Tic	Brief, repeated, stereotyped contractions, transiently suppressible with premonitory urge

- ▶ Speed/rhythmicity spectrum (DeJong): tremor & palatal myoclonus are *regular/predictable*; dystonia, athetosis, tics, myorhythmia are *intermediate*; chorea, ballism, myoclonus are *unpredictable*.

Tremor and Essential Tremor

- ▶ **Tremor** is classified along two axes (MDS): **Axis 1** = clinical/historical features (age, family history, distribution, frequency, activation, associated signs); **Axis 2** = aetiology (genetic, secondary, idiopathic).
- ▶ Activation types: **rest** (PD), **postural**, **kinetic/intention** (cerebellar, with past-pointing & hypotonia), **action**. *Enhanced physiologic tremor* ($\leq 10\%$ of population) — fine 10–12 Hz, with thyrotoxicosis, anxiety, valproate, lithium, caffeine, alcohol withdrawal.
- ▶ **Essential tremor (ET)** — the **commonest movement disorder** ($\sim 1\%$ of population, $\sim 5\%$ of those >60). High-frequency (6–10 Hz) **postural & action** tremor, bilateral, predominantly upper limbs; involves **head** $\sim 30\%$, **voice** $\sim 20\%$, **tongue** $\sim 20\%$, **jaw** $\sim 10\%$, **legs** $\sim 10\%$. Classically **improved by alcohol**, worsened by stress; large (not micro-) handwriting. $\sim 50\%$ are autosomal dominant; *NOTCH2NLC* GGC-repeat expansion associated, no confirmed causative gene.
- ▶ **Treatment (Harrison/CMDT)**: reassurance if mild. **Propranolol** 20–120 mg/day (CMDT up to 240 mg) and **primidone** (start 12.5–50 mg, titrate to 125–250 mg) — each effective in $\sim 50\%$. Second-line: topiramate, gabapentin, alprazolam. Botulinum toxin for limb/voice tremor. Drug-resistant cases: **VIM-thalamic DBS** or **MRI-guided focused ultrasound thalamotomy**.

Dystonia

- ▶ **Sustained/intermittent co-contraction of agonist & antagonist muscles** producing patterned, twisting movements/postures; relieved by a **sensory trick* (geste antagoniste); *aggravated by stress/fatigue*. Dystonic tremor *occurs in the direction of the pull** and disappears when the part is moved opposite — this distinguishes it from ET.
- ▶ **Distribution**: focal $\rightarrow$ segmental $\rightarrow$ multifocal $\rightarrow$ hemidystonia $\rightarrow$ generalised. Adult-onset **focal** dystonia is commonest (women 2:1; writer's cramp exceptionally commoner in men), presenting in the 4th–6th decade.
- ▶ **Focal phenotypes**: **cervical dystonia/torticollis** ($\sim 40\%$, also latero-/antero-/retrocollis), **blepharospasm** ($\sim 15\%$), **oromandibular** (+blepharospasm = **Meige's/Brueghel syndrome*), **spasmodic dysphonia** (adductor), **limb/task-specific** (writer's cramp, musician's cramp, the yips*).

- ▶ **Genetics (DYT prefix; >200 genes):** ***DYT-TOR1A** (3-bp deletion, Ashkenazi-Jewish founder) — *commonest early-onset generalised*; **KMT2B** (~10% early-onset generalised); **THAP1**; **GNAL**, **ANO3*** (adult cranio-cervical).
- ▶ **Combined dystonias:** ***Dopa-responsive dystonia (Segawa)** — **GCH1** (*GTP cyclohydrolase-1*), *childhood onset with diurnal fluctuation and a dramatic, sustained response to low-dose levodopa without dyskinesia (test all childhood dystonias with levodopa)*; **X-linked dystonia-parkinsonism (Lubag)** — **TAF1**, *Filipino*; **myoclonus-dystonia** — **SGCE** (*alcohol-responsive, paternal/maternal-imprinting** inheritance).
- ▶ **Treatment:** withdraw precipitants; **levodopa trial** in all childhood-onset dystonia; high-dose **trihexyphenidyl** (20–120 mg/day, tolerated mainly in children); **baclofen** (oral/intrathecal); **tetrabenazine** (start 12.5 mg, 25–75 mg/day). **Botulinum toxin is preferred for focal/segmental dystonia** (blepharospasm, torticollis, dysphonia). Severe generalised disease → **GPI DBS** (best in **DYT-TOR1A**). **Dystonic storm** — generalised contractions with laryngeal involvement, rhabdomyolysis & renal failure — is a medical emergency requiring ICU/airway protection.

Choreas, Ballism and Athetosis

- ▶ **Chorea** — rapid, non-patterned, flowing involuntary movements; *parakinesia* (movement camouflaged into a purposeful act), **motor impersistence** (“*milkmaid grip*”, *darting/flycatcher/trombone tongue*) and hung-up reflexes are signs.
- ▶ ***Huntington’s disease (HD)** — *autosomal dominant, fully penetrant*; **CAG (polyglutamine) repeat >40 in the Huntingtin gene on chromosome 4p** (36–39 = *reduced penetrance*). Onset 25–45 y; prevalence 2–8/100,000; *chorea + dysarthria + oculomotor abnormality + behavioural change/depression/psychosis + dementia*. *Anticipation (paternal transmission)*. ~10% present as the **akinetic-rigid juvenile Westphal variant**. **MRI: caudate-head & putaminal atrophy (boxcar ventricles)**; *intraneuronal ubiquitin/huntingtin inclusions*. **Treatment: symptomatic only** — *tetrabenazine, deutetabenazine (Austedo), valbenazine** (VMAT-2 inhibitors) for chorea; atypical antipsychotics (clozapine, quetiapine, risperidone) for psychosis; antidepressants; genetic counselling mandatory.
- ▶ **HD-like (HDL):** **HDL-1 (PRNP)**, a prion disease), **HDL-2 (JPH3)**, mostly African descent, *acanthocytosis*), **HDL-4 (TBP = SCA17)**.
- ▶ **Other choreas:** ***Sydenham’s chorea** (St. Vitus’ dance) — *post group-A streptococcal autoimmune chorea, girls 5–15 y, self-limited (treat with valproate/carbamazepine/dopamine blockers)*; **chorea gravidarum**; *SLE is the commonest systemic cause; also thyrotoxicosis, anti-NMDA-receptor/paraneoplastic (anti-Hu, anti-CRMP-5) encephalitis, hyper-/hypoglycaemia*. **Chorea-acanthocytosis (neuroacanthocytosis)** — **AR, VPS13A/chorein**; **McLeod syndrome*** — **X-linked**, Kell antigen. Levodopa-induced dyskinesia is the commonest iatrogenic chorea.
- ▶ **Ballism / hemiballismus** — wild, large-amplitude, flinging **proximal** movements; classic lesion of the **contralateral subthalamic nucleus** (infarct/haemorrhage), though 30–40% involve

putamen/thalamus/parietal cortex; **non-ketotic hyperglycaemia** is a key reversible cause. Usually self-limiting; responds to dopamine blockers; refractory cases → GPi DBS/pallidotomy.

- ▶ **Athetosis** — slow distal writhing (“*without fixed position*”); usually congenital (perinatal basal-ganglia injury, *status marmoratus*, athetoid cerebral palsy); blends with chorea (**choreoathetosis**) and dystonia. *Pseudoathetosis* = sensory (deafferentation) athetosis, worse with eyes closed.

Tics, Tourette Syndrome and Myoclonus

- ▶ **Tics** — simple/complex **motor** (blink, jerk, echopraxia) or **phonic** (grunt, *echolalia*, *palilalia*, *coprolalia*); suppressible with a building premonitory urge, exacerbated by stress, abate in sleep.
- ▶ ***Tourette’s syndrome** — *male-predominant; multiple motor + ≥1 phonic tic, onset 2–15 y (mean 7), often improves in adulthood; comorbid ADHD & OCD. High heritability. Treatment: education first; α-agonists clonidine / guanfacine* (0.5–2 mg/day); atypical then typical neuroleptics (risperidone, aripiprazole; haloperidol, pimozide); tetrabenazine; botulinum toxin for focal tics.*
- ▶ **Myoclonus** — brief (<100 ms) shock-like jerks; **positive** (jerk) vs **negative** (*asterixis*); focal/segmental/generalised; by site cortical, subcortical, brainstem or spinal. Causes: physiologic (hypnic jerks, hiccup), post-anoxic action myoclonus (***Lance-Adams syndrome**), *uraemic/hepatic encephalopathy, CJD; progressive myoclonic epilepsies* — Unverricht-Lundborg (*EPM1*) and Lafora-body (*EPM2A/NHLRC1*). *Palatal myoclonus* = lesion in the Guillain–Mollaret triangle (*inferior olive → dentate → red nucleus*), may persist in sleep, causes an audible ear click. Treatment: valproate, levetiracetam, clonazepam, piracetam, primidone; 5-hydroxytryptophan + carbidopa* for post-anoxic myoclonus.

Drug-induced and other syndromes

- ▶ **Drug-induced (dopamine-receptor blockers — neuroleptics, metoclopramide, prochlorperazine): acute** dystonic reaction (minutes–hours; treat with parenteral anticholinergic/diphenhydramine); **subacute akathisia** (restlessness relieved by movement, within 2 weeks); **tardive syndromes** (months–years) — **tardive dyskinesia** (oro-bucco-lingual chorea), tardive dystonia. FDA warns against metoclopramide >12 weeks. Treat TD with **valbenazine 80 mg/day** or deutetabenazine; avoid abrupt withdrawal. **Neuroleptic malignant syndrome** (rigidity, hyperthermia, autonomic instability, ↑CK) and **serotonin syndrome** (myoclonus prominent) are emergencies.
- ▶ **Paroxysmal dyskinesias: PKD** (movement-triggered; *PRRT2*; responds to carbamazepine/phenytoin), **PNKD** (alcohol/cafeine/stress-triggered; *PNKD* gene; clonazepam), **PED** (exercise-induced; *SLC2A1/GLUT1* deficiency; ketogenic diet).
- ▶ **Restless legs syndrome** — 4 core criteria (**Urge** to move + **Rest** worsens + **Gets better** with movement + **Evening/night predominance**); associated with **iron/ferritin deficiency**, pregnancy, uraemia; periodic limb movements of sleep; treat with iron repletion and low-dose dopamine

agonists (pramipexole, ropinirole, rotigotine) — beware **augmentation**; $\alpha 2\delta$ ligands (gabapentin) alternative.

- ▶ **Combined (parkinsonism + hyperkinesia): Wilson's disease** (*ATP7B*; **Kayser-Fleischer rings** in Descemet's membrane, **wing-beating tremor**, low ceruloplasmin, treat with penicillamine/trientine/zinc/tetrathiomolybdate) — exclude in any young dystonia/chorea; **NBIA/PKAN** (*PANK2*, “*eye-of-the-tiger*” sign on MRI).
- ▶ **Functional (psychogenic) movement disorder** — commonest is functional tremor; clues are **variability, distractibility, entrainment**, incongruent phenotype; managed with explanation, CBT and physiotherapy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Basal-ganglia direct/indirect pathway schematic** — label: *Cortex, Striatum (caudate + putamen), GPe, GPi, Subthalamic nucleus (STN), Substantia nigra (SNc/SNr), Thalamus, VIM nucleus*; arrows for direct (D1, facilitatory) and indirect (D2, inhibitory) pathways; mark the **STN lesion** → **hemiballismus** site.
- ▶ **Phenomenology comparison panel** — three labelled sketches: *Chorea (random, flowing, distal)*, *Dystonia (sustained twisting posture, e.g. torticollis with geste antagoniste)*, *Hemiballismus (large-amplitude proximal flinging, one side)*.

Clinical / Diagnostic significance

- ▶ A precise bedside description (speed, rhythm, distribution, suppressibility, sensory trick, effect of action/rest/sleep) localises and classifies the disorder before any test.
- ▶ **Always exclude Wilson's disease** (serum copper/ceruloplasmin, 24-h urinary copper, KF rings, slit-lamp) in any young-onset chorea/dystonia/tremor — it is treatable.
- ▶ **Genetic testing** confirms HD (with counselling), DYT dystonias and HDL disorders; MRI signs are diagnostic clues (caudate atrophy in HD, eye-of-the-tiger in PKAN, olivary pseudohypertrophy in palatal myoclonus).
- ▶ VMAT-2 inhibitors (tetraabenazine, deutetabenazine, valbenazine) are the unifying pharmacology for chorea and tardive dyskinesia; **botulinum toxin** is first-line for focal dystonia; DBS (GPi for dystonia/HD, VIM for tremor, STN avoided in chorea) rescues refractory disease.

High-yield exam pointers

- ▶ ET: 6–10 Hz postural/action tremor, alcohol-responsive; first-line **propranolol & primidone**; VIM-DBS/focused ultrasound if refractory.
- ▶ HD: **AD, CAG repeat >40 on chromosome 4**, anticipation, Westphal variant; chorea + dementia + caudate atrophy.
- ▶ **Hemiballismus = contralateral subthalamic nucleus lesion**; also non-ketotic hyperglycaemia; usually self-limiting.

- ▶ **Dopa-responsive dystonia** (Segawa, GCH1) — diurnal variation, dramatic levodopa response; never miss it.
- ▶ **Geste antagoniste** (sensory trick) and *dystonic tremor in the direction of pull* are hallmarks of dystonia.
- ▶ **Palatal myoclonus** → **Guillain-Mollaret triangle**; **asterixis** = **negative myoclonus** (“liver flap”).
- ▶ Tourette = motor + phonic tics, onset childhood, comorbid OCD/ADHD; tics are **suppressible** (vs myoclonus, which is not).
- ▶ **Metoclopramide >12 weeks** risks tardive dyskinesia; **valbenazine/deutetrabenazine** treat it.
- ▶ Sydenham’s chorea = post-streptococcal autoimmune; **SLE** is the commonest systemic cause of chorea.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “*Tremor, Chorea, and Other Movement Disorders*” (Olanow & Klein) — primary framework, genetics, drug doses and disease definitions.
- ▶ **DeJong’s The Neurologic Examination** — “*Abnormalities of Movement*” — phenomenology (athetosis, asterixis, palatal myoclonus/Guillain-Mollaret triangle, parakinesia, geste antagoniste, hemiballismus, tics & stereotypy).
- ▶ **CMDT 2026** — “*Nervous System Disorders*” — current management of essential tremor (propranolol/primidone doses, DBS, focused-ultrasound thalamotomy) and chorea.



Hypoxic-ischemic encephalopathy

Asked in: Paper III Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Hypoxic-ischemic encephalopathy (HIE) is diffuse brain dysfunction caused by inadequate cerebral oxygen delivery, usually from combined hypoxemia and reduced cerebral blood flow. In adults it is most often discussed after cardiac arrest, but the same injury pattern may follow shock, respiratory arrest, asphyxiation, severe hypoxemia, or histotoxic hypoxia due to carbon monoxide or cyanide. It is an emergency because neurological outcome is determined by the duration of impaired perfusion, secondary brain insults, and the accuracy of delayed multimodal prognostication.

Etiology and vulnerable neuroanatomy

- ▶ **Cardiac arrest** is the prototype: cerebral blood flow becomes negligible, consciousness is lost within seconds, and permanent injury becomes likely when global hypoxia-ischemia lasts beyond about **3-5 min**, though recovery after longer intervals may occur, especially with early CPR.

- ▶ Important causes: **myocardial infarction**, ventricular tachycardia/fibrillation, pulseless electrical activity/asystole, shock, severe hypotension, respiratory failure, asphyxiation, respiratory paralysis, drowning/near-drowning, carbon monoxide poisoning, and cyanide poisoning.
- ▶ **Pure hypoxia** is better tolerated than hypoxia plus ischemia if blood pressure is maintained; severe arterial hypoxemia may injure brain, but brief absent or very low cerebral circulation is more dangerous.
- ▶ Usually severe systemic insult is required: Harrison notes that **systolic BP <70 mmHg** or **Pao₂ <40 mmHg** is generally necessary, with the duration of exposure being crucial.
- ▶ Selectively vulnerable sites are **hippocampal CA1 neurons**, cerebral cortex with **laminar cortical necrosis**, **deep gray nuclei** including basal ganglia and thalamus, cerebellar Purkinje cells, and watershed zones between major cerebral arteries.
- ▶ Resulting syndromes correlate with anatomy: hippocampal injury causes amnesic states; bilateral watershed injury may cause proximal arm-predominant weakness (*man-in-the-barrel* syndrome); striatal injury may produce parkinsonism; cortical injury may cause dementia, visual agnosia, seizures, or persistent coma.

Pathogenesis

- ▶ In complete global ischemia, neuronal oxygen stores are rapidly exhausted; CPR may provide only partial cerebral blood flow until effective circulation is restored.
- ▶ **Energy failure** causes failure of membrane ion gradients, neuronal depolarization, sodium and calcium influx, cytotoxic edema, and loss of electrophysiologic activity.
- ▶ **Glutamate excitotoxicity** through NMDA/AMPA receptors amplifies calcium entry; activated proteases, lipases, endonucleases, nitric oxide pathways, and mitochondrial dysfunction then produce cell injury.
- ▶ **Reperfusion injury** contributes through oxygen free radicals, inflammation, endothelial dysfunction, microvascular obstruction, and the *no-reflow* phenomenon.
- ▶ **Apoptosis and delayed neuronal death** may continue after the initial arrest; this is why early restoration of circulation plus prevention of secondary insults is central.
- ▶ Secondary brain insults that worsen outcome include **hypotension**, hypoxemia, fever, hyperglycemia or hypoglycemia, seizures/status epilepticus, severe acid-base/electrolyte derangements, and excessive sedative accumulation delaying assessment.

Clinical features and evolution

- ▶ Mild pure hypoxia may produce impaired judgment, inattentiveness, motor incoordination, and euphoria; hypoxia-ischemia from circulatory arrest produces immediate loss of consciousness.
- ▶ After return of spontaneous circulation (ROSC), the patient may awaken, remain comatose, evolve into an unresponsive wakefulness/vegetative state, or recover with variable cognitive, motor, visual, or movement-disorder sequelae.

- ▶ Bedside coma examination must document **pupillary light reflexes**, corneal reflexes, oculocephalic and oculovestibular responses, motor response to pain, respiratory pattern, and spontaneous/elicited eye movements.
- ▶ Brainstem reflexes are often preserved because the brainstem is relatively resistant to anoxic-ischemic injury; loss of pupillary or corneal reflexes therefore suggests severe, widespread injury.
- ▶ **Myoclonus status epilepticus** is continuous, generalized, vigorous jerking involving face, limbs, trunk, or diaphragm, often stimulus-sensitive and commonly associated with malignant EEG patterns; it must be distinguished from occasional myoclonic jerks, drug/metabolic myoclonus, and generalized tonic-clonic seizures.
- ▶ Long-term consequences include persistent coma, unresponsive wakefulness, minimally conscious state, dementia, visual agnosia/cortical blindness, parkinsonism, choreoathetosis, cerebellar ataxia, myoclonus, seizures, and amnestic syndrome.

Diagnostic evaluation

Domain	What to assess	High-yield point
Event history	Witnessed arrest, no-flow/low-flow time, initial rhythm, bystander CPR, ROSC time, hypotension/hypoxemia duration, toxins	Shockable rhythms and early CPR generally carry better neurological prospects than unwitnessed nonshockable arrests
Immediate labs	Glucose, electrolytes, calcium, ABG, lactate, renal/liver function, toxicology as indicated	Correct reversible coma mimics and secondary insults before prognostication
Coma examination	Pupils, corneal reflex, oculocephalic/oculovestibular reflexes, motor response, respiratory pattern	Preserved brainstem reflexes are favorable; absent reflexes after adequate waiting are ominous
Neuroimaging	Noncontrast CT brain; CT angiography if basilar occlusion or structural lesion is possible; MRI-DWI when stable	Early CT may be normal; severe HIE may show diffuse edema and loss of gray-white differentiation; MRI-DWI may show cortical and deep gray restriction
EEG	Spot or continuous EEG in comatose patients, especially with myoclonus or unexplained nonawakening	Detects nonconvulsive seizures/status; nonreactive EEG, suppressed background, and burst suppression are poor signs
SSEP and biomarkers	Median nerve SSEP for N20 responses; serial NSE if available	Bilateral absent cortical N20 after several days is highly specific for poor outcome; very high NSE supports severe brain injury but should not be used alone

Management

- ▶ **Restore cardiorespiratory function first:** secure airway, provide oxygenation and ventilation, perform high-quality CPR/defibrillation when indicated, and restore cerebral perfusion using fluids, vasopressors, pacing, or treatment of the arrest cause.
- ▶ After ROSC, assess for **acute MI**; ST-elevation MI requires emergent coronary angiography and PCI. In patients without ST elevation, urgent angiography is individualized for shock, electrical instability, ongoing ischemia, or major myocardial injury.
- ▶ Maintain systemic perfusion: Harrison recommends **SBP >90 mmHg** and **MAP >65 mmHg**; Bradley describes **MAP 65-80 mmHg** as a common post-arrest goal, often requiring norepinephrine plus fluid resuscitation.
- ▶ Ventilate to avoid hypoxemia and severe hyperoxia; Miller emphasizes individualized oxygenation with aggressive treatment of hypoxemia and avoidance of marked hyperoxia, especially **Pao₂ >300 mmHg**, when oxygenation is otherwise adequate. Maintain **normocapnia**, normalize systemic pH, and correct electrolyte abnormalities.
- ▶ Avoid secondary injury: treat fever aggressively, avoid hypotonic fluids, prevent aspiration, control glucose reasonably (often <180 mg/dL) while avoiding hypoglycemia, and manage renal/liver failure that may prolong sedative effects.
- ▶ **Targeted temperature management (TTM)** is recommended for comatose patients without purposeful response after ROSC: select and maintain a constant temperature **32-37.5°C** for at least **24 h**; fever must be avoided in all cases. Shivering may require analgesia, sedation, and sometimes neuromuscular blockade.
- ▶ Do not start hypothermia with large prehospital cold-saline loads; Harrison notes no prehospital benefit and increased pulmonary edema risk. Monitor for hypothermia complications: infection, coagulopathy, arrhythmias, hyperglycemia, cold diuresis, hypovolemia, and delayed sedative clearance.
- ▶ Treat clinically apparent seizures and consider treatment of ictal-interictal continuum EEG patterns. **Anticonvulsants are not given prophylactically**; complete suppression of rhythmic/periodic EEG activity for 48 h has not improved outcomes.
- ▶ Posthypoxic myoclonus in survivors may respond to **clonazepam 1.5-10 mg/day** or **valproate 300-1200 mg/day in divided doses**. Severe carbon monoxide poisoning may require hyperbaric oxygen.
- ▶ Ineffective or unproven neuroprotective strategies after cardiac arrest include routine corticosteroids, hemofiltration, tight glucose control, barbiturates for global ischemia, and calcium-channel blockers such as nimodipine solely for postarrest neuroprotection.

Neuroprognostication

- ▶ Prognostication must be **delayed, multimodal, and free of confounders**: exclude hypothermia, sedatives/analgesics, neuromuscular blockers, metabolic derangements, shock, hypoxemia, hepatic/renal failure, and drug intoxication.
- ▶ Harrison recommends deferring functional neurological assessment until at least **72 h after return to normothermia**, typically **4-5 days after arrest**; some patients awaken after a week or longer, so premature withdrawal risks a self-fulfilling poor outcome.
- ▶ Favorable signs: early awakening, following commands, purposeful localization to pain, intact pupillary/corneal/oculocephalic/oculovestibular reflexes, continuous reactive EEG background, and limited imaging injury.
- ▶ Poor prognostic signs when assessed at appropriate time points include absent pupillary light reflex, absent corneal reflex, absent or extensor motor response, and **status myoclonus** after primary circulatory arrest.
- ▶ Electrophysiologic poor signs: **bilateral absence of cortical N20 SSEP**, nonreactive EEG, persistent burst suppression, suppressed EEG background, or burst-suppression pattern with myoclonic status epilepticus.
- ▶ Imaging poor signs: diffuse cerebral edema, loss of gray-white differentiation on CT, widespread cortical DWI restriction, combined cortical and deep gray injury, or severe global ADC reduction on MRI.
- ▶ Biomarkers are adjunctive only: a very high **neuron-specific enolase >60 microgram/L** in the first 1-3 days supports severe brain damage in Harrison, but thresholds vary with assays and TTM.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis flow diagram**: “Cardiac/respiratory arrest or shock” -> “low cerebral blood flow + low O₂ delivery” -> “ATP failure” -> “membrane depolarization” -> “glutamate excitotoxicity + Ca²⁺ influx” -> “free radicals/inflammation/no-reflow/apoptosis” -> “selective neuronal injury: cortex, CA1 hippocampus, basal ganglia, thalamus, Purkinje cells, watershed zones” -> “coma/seizures/cognitive-motor sequelae”.
- ▶ **Post-arrest prognostication algorithm**: “ROSC with coma” -> “exclude confounders: hypothermia, sedatives, paralysis, metabolic shock” -> “wait ≥72 h after normothermia” -> “clinical exam: pupils, corneal, motor, myoclonus” + “EEG/SSEP/NSE/CT-MRI” -> “multimodal prognosis and family discussion”.

Clinical / Diagnostic significance

- ▶ HIE is a leading determinant of death after successful resuscitation; Harrison notes postarrest brain injury accounts for most deaths after stable circulation is restored.

- ▶ The diagnosis is clinical plus contextual: a compatible hypoxic-ischemic event with coma or encephalopathy, after excluding structural lesions, intoxication, metabolic coma, CNS infection, basilar artery occlusion, and nonconvulsive status epilepticus.
- ▶ Coma examination distinguishes diffuse metabolic/anoxic depression from focal structural brainstem processes; oculocephalic and caloric responses are particularly useful when the cervical spine is safe to test.
- ▶ Do not confuse HIE coma with **locked-in syndrome**, in which the patient is conscious with quadriparesis and preserved vertical eye movements/blinking, or with **brain death**, which requires irreversible coma, absent brainstem reflexes, absent respiratory drive, and exclusion of hypothermia/drug/metabolic mimics.
- ▶ Survivors require evaluation of the arrest cause, rehabilitation for cognitive and motor sequelae, seizure/myoclonus treatment, and cardiac secondary prevention including ICD consideration when VT/VF arrest is not due to a reversible cause.

High-yield exam pointers

- ▶ Write that HIE after cardiac arrest is **global cerebral ischemia plus reperfusion injury**, not merely low oxygen saturation.
- ▶ Mention vulnerable regions: **CA1 hippocampus, laminar cortex, basal ganglia/thalamus, Purkinje cells, watershed zones**.
- ▶ Initial treatment is not a “neuro drug”; it is **airway, oxygenation, ventilation, circulation, perfusion pressure, fever prevention, seizure detection, and TTM**.
- ▶ TTM: comatose after ROSC, constant 32-37.5°C for at least 24 h, avoid fever, suppress shivering, and delay prognostication.
- ▶ Never prognosticate early under hypothermia, sedatives, neuromuscular blockade, metabolic derangement, or shock.
- ▶ Strong poor-outcome markers: absent pupillary reflex, status myoclonus, nonreactive/burst-suppression EEG, bilateral absent N20 SSEP, diffuse cortical/deep gray MRI injury, and very high NSE.
- ▶ EEG is needed because nonconvulsive seizures/status may be clinically inapparent in comatose postarrest patients.
- ▶ CT can be normal early; **MRI-DWI** is more sensitive for cortical and deep gray injury but must not be used alone to withdraw care.

SOURCE & COVERAGE

Harrison 22e — “Nervous System Disorders in Critical Care”; Harrison 22e — “Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death”; Bradley & Daroff’s Neurology 8e — “Anoxic-Ischemic Encephalopathy” and “Stupor and Coma”; DeJong’s Neurologic Examination

- “The Examination in Coma”; CMDT 2026 — “Nervous System Disorders”; Miller’s Anesthesia
- “Cerebral Physiology and the Effects of Anesthetic Drugs”.



Immunopathogenesis and treatment of Guillain-Barré syndrome

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Guillain-Barré syndrome (GBS) is an **acute, frequently severe and fulminant, autoimmune polyradiculoneuropathy** presenting as a rapidly evolving **areflexic motor paralysis** with or without sensory disturbance. It occurs year-round at **10–20 cases per million annually** (≈ 5000 – 6000 cases/year in the United States), with males and adults at slightly higher risk. Approximately **70% of cases follow an antecedent infection by 1–3 weeks**, and the disorder is now understood as a post-infectious, antibody- and complement-mediated attack on peripheral nerve, in which **molecular mimicry** between microbial and neural glycolipids is central.

Subtypes and their antibody associations

- ▶ **Acute inflammatory demyelinating polyneuropathy (AIDP)** — commonest variant (**$\sim 90\%$ of Western cases**); first attack on the Schwann-cell surface with widespread myelin damage, macrophage activation and lymphocytic infiltration; *anti-GM1 antibodies in $<50\%$* .
- ▶ **Acute motor axonal neuropathy (AMAN)** — children/young adults; prevalent in **China and Mexico**, often **seasonal** (summer outbreaks after *Campylobacter jejuni*); rapid recovery; *anti-GD1a / anti-GM1*; attack at the motor nodes of Ranvier.
- ▶ **Acute motor-sensory axonal neuropathy (AMSAN)** — mostly adults; severe axonal damage, slow and often incomplete recovery; closely related to AMAN but also involves sensory roots.
- ▶ **Miller Fisher syndrome (MFS)** — **$\sim 5\%$ of cases**; the triad of **ophthalmoplegia, ataxia and areflexia** without limb weakness; *anti-GQ1b antibodies in $>90\%$* .
- ▶ **Regional/limited forms** — pharyngeal-cervical-brachial weakness (anti-GT1a, cross-reacting with GQ1b), pure sensory forms, acute pandysautonomia, and the “anti-GQ1b antibody syndrome” continuum (acute ophthalmoparesis, acute ataxic neuropathy, Bickerstaff’s brainstem encephalitis).

Antecedent (triggering) events

- ▶ **$\sim 70\%$ follow an acute infection** (respiratory or gastrointestinal) by 1–3 weeks.
- ▶ ****Campylobacter jejuni* — identified in 20–30%*** of cases in North America, Europe and Australia; the prototypic trigger of axonal GBS/AMAN.

- ▶ **Viral triggers** — CMV, Epstein-Barr virus, HIV, hepatitis E, and **Zika virus** (implicated in the Brazilian GBS surge); also *Mycoplasma pneumoniae*. SARS-CoV-2 cases were reported during COVID-19 but **causality is not established**.
- ▶ **Vaccines** — historical 1976 swine-influenza vaccine; current seasonal influenza confers a risk of **<1 per million**; a slightly increased risk with **adenovirus-vector SARS-CoV-2 vaccines but not mRNA vaccines**; older nervous-tissue rabies vaccine in developing countries.
- ▶ Higher-than-chance association with lymphoma (incl. Hodgkin's), HIV seropositivity, SLE, and immune checkpoint inhibitor therapy.

Immunopathogenesis (core of the answer)

- ▶ **Autoimmune basis** is supported by analogy to **experimental allergic neuritis (EAN)** — a T cell-mediated immunopathy induced in animals by sensitization against peripheral nerve proteins, particularly the **P2 protein**. Both **cellular and humoral** mechanisms contribute.
- ▶ **Molecular mimicry** — immune responses to nonself antigens (infectious agents, vaccines) are *misdirected to host nerve* through resemblance of epitope. The neural targets are **glycoconjugates, specifically gangliosides** (complex glycosphingolipids bearing one or more **sialic acid** residues), which are exposed on the axonal plasma membrane and densely concentrated at the **nodes of Ranvier**.
- ▶ ****C. jejuni link** — isolates from GBS patients carry surface lipo-oligosaccharide structures that antigenically cross-react with gangliosides (e.g., GM1) **concentrated in human nerve**. **Sialic acid residues from pathogenic strains also activate** dendritic cells via Toll-like receptor 4 (TLR4), **promoting B-cell differentiation**** and amplifying humoral autoimmunity.
- ▶ **Antiganglioside antibodies** — most frequently **anti-GM1**, present in **20–50%** of cases, especially AMAN/AMSAN and those preceded by *C. jejuni*. Some AIDP antibodies recognise **glycolipid heterocomplexes** rather than single species. Direct evidence comes from recipients of IV **bovine brain gangliosides** who developed AMAN with high anti-GM1 titres 5–15 days later.
- ▶ **Effector mechanism in AIDP** — autoantibodies bind myelin antigens and activate **complement** along the *outer surface of the Schwann cell* → **terminal complement complex / membrane-attack complex (MAC)** → **vesicular disintegration of the myelin sheath** → recruitment of **activated macrophages** that strip myelin and scavenge debris. Injecting GBS serum into animal nerve reproduces complement-dependent demyelination and conduction block.
- ▶ **Effector mechanism in AMAN** — **IgG plus complement deposit on the nodal and internodal axolemma of motor fibres**. Anti-GM1/anti-GD1a bind the nodal axolemma → MAC formation → **disappearance of voltage-gated Na⁺ (Nav) channel clusters** and **detachment of paranodal myelin** → conduction failure; axonal degeneration may follow. Notably, **anti-GD1a has a fine specificity favouring motor over sensory roots**.

- ▶ **MFS** — anti-GQ1b IgG (>90%) is explained by **enrichment of GQ1b in extraocular motor nerves**; a monoclonal anti-GQ1b raised against *C. jejuni* blocked neuromuscular transmission experimentally.
- ▶ *Caveat in source*: although antiganglioside antibodies are strongly implicated, formal proof of pathogenicity by passive transfer to naïve hosts has **not yet been demonstrated** (one possible transplacental case described).

Pathophysiology and laboratory features

- ▶ **AIDP** — flaccid paralysis is due to **conduction block** from demyelination, with axons left intact; recovery is rapid via **remyelination**. Severe cases develop **secondary axonal degeneration**, predicting slower, less complete recovery.
- ▶ **AMAN/AMSAN** — a **primary axonal pattern** with low-amplitude CMAPs; rapid recovery in many cases reflects **reversible conduction block** from antibody binding to nodal ion-channel proteins.
- ▶ **CSF** — **albuminocytologic (cytoalbuminologic) dissociation**: elevated protein (1–10 g/L; 100–1000 mg/dL) **without pleocytosis**. CSF is often normal at ≤48 h and rises by the end of the first week; a *sustained* pleocytosis points to an alternative (HIV, lymphoma, viral myelitis).
- ▶ **Electrodiagnosis (EDx)** — earliest in AIDP are **prolonged F-wave latencies, prolonged distal latencies and reduced CMAP amplitudes**; later, conduction velocity slowing, conduction block and temporal dispersion. AMAN/AMSAN show reduced CMAP (and SNAP) amplitudes without slowing.
- ▶ **Diagnosis** — clinical, aided by the validated **2011 Brighton Collaboration criteria**; serum anti-GQ1b supports MFS.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Figure 458-2 — Immune mechanisms in GBS (two panels)**. *Panel A (AIDP)*: label Motor neuron, Axon, Myelin, Schwann cell, Unidentified myelin antigen, Antibody binding, Complement activation, Membrane-attack complex (MAC), Macrophage (scavenging myelin debris). *Panel B (AMAN/AMSAN)*: a myelinated axon divided into Node of Ranvier, Paranode, Juxtaparanode, Internode; mark Nav (voltage-gated Na⁺) channels at the node, Caspr at the paranode, Kv channels at the juxtaparanode, gangliosides GM1 and GD1a at the node, IgG anti-GM1/anti-GD1a antibodies, C3 and MAC, with macrophage invading the periaxonal space.
- ▶ **Ganglioside-mimicry schematic (Fig. 458-1 key)**: draw GM1, GD1a, GT1a, GQ1b with the sugar key — Galactose, Glucose, N-acetyl|galactosamine, N-acetylneuraminic acid (sialic acid), Ceramide — linking GM1/GD1a→AMAN/AMSAN and GQ1b/GT1a→Miller Fisher syndrome.

Treatment

- ▶ **General principle** — start immunotherapy as soon as diagnosis is made; “each day counts.” Benefit beyond ~2 weeks from onset, or once the patient is at a stable plateau, is uncertain; very mild cases at plateau may be managed conservatively.
- ▶ **Intravenous immunoglobulin (IVIg)** — usual first choice (ease, safety); **2 g/kg total given as five daily infusions** (0.4 g/kg/day × 5). Proposed action includes neutralisation of pathogenic autoantibodies by **anti-idiotypic antibodies** in IVIg.
- ▶ **Plasma exchange (PLEX)** — ~40–50 mL/kg per exchange, 4–6 times over 7–12 days. Meta-analysis shows it **halves the need for mechanical ventilation** (27% → 14%) and raises the chance of **full recovery at 1 year** (55% → 68%).
- ▶ **IVIg and PLEX are equally effective; combining the two is not significantly better** than either alone. Failure of one is **not** an indication to switch to the other.
- ▶ **Treatment-related fluctuation/relapse within a month** — give a **brief course of the original agent again**.
- ▶ **Glucocorticoids are NOT effective** in GBS (a key contrast with CIDP, which does respond to steroids).
- ▶ **Supportive / critical care** — monitor in ICU for **vital capacity** (≈30% need mechanical ventilation), cardiac rhythm and **dysautonomia** (labile BP, postural hypotension, arrhythmia), nutrition, DVT prophylaxis; consider **tracheostomy** after ~2 weeks of intubation; chest physiotherapy, frequent turning/skin care, range-of-motion exercises and reassurance.
- ▶ **Pain** (neck/back/limb dysaesthesia) — responds to standard analgesics.

Clinical / Diagnostic significance

- ▶ **Prognosis** — ~85% achieve **full functional recovery** over months to a year; **mortality <5%** (death mainly from pulmonary complications/dysautonomia).
- ▶ **Poor-outcome predictors** — severe proximal motor-sensory **axonal** damage, advanced age, fulminant/severe attack, delayed treatment, and **high serum neurofilament-light (NfL) and anti-GM1 titres**.
- ▶ **5–10% relapse**; some recurrent/progressive cases are reclassified as **CIDP** (chronic, steroid-responsive).
- ▶ Recognising **albuminocytologic dissociation** and early EDx changes allows treatment **before classic findings appear** — do not wait. Test for **HIV** if risk factors or CSF pleocytosis.
- ▶ Exclude mimics: acute myelopathy, poliomyelitis/acute flaccid myelitis, diphtheritic and tick paralysis, porphyria, botulism/myasthenia, and organophosphate/heavy-metal poisoning.

High-yield exam pointers

- ▶ GBS = **acute autoimmune areflexic ascending paralysis**; ~70% post-infectious; **molecular mimicry** is the unifying mechanism.
- ▶ ***C. jejuni** (20–30%) → *anti-GM1/GD1a* → AMAN/AMSAN; *anti-GQ1b* (>90%) → *Miller Fisher* (*ophthalmoplegia, ataxia, areflexia*)*.
- ▶ AIDP = complement + MAC on **Schwann-cell surface** → demyelination; AMAN = IgG + complement at **nodal axolemma** → Nav-cluster loss → conduction block.
- ▶ CSF: **albuminocytologic dissociation** (high protein, cells <50/ μ L); EDx — prolonged F-waves, prolonged distal latency, low CMAP.
- ▶ **Brighton criteria** (2011) for diagnostic certainty.
- ▶ IVIg 2 g/kg over 5 days OR PLEX 40–50 mL/kg $\times$ 4–6 (7–12 days) — equally effective, do **not** combine, do **not** switch on failure.
- ▶ **Steroids are useless in GBS** (but useful in CIDP) — a favourite viva point.
- ▶ Recovery ~85%, mortality <5%; worst with **axonal damage, high NfL/anti-GM1, age, delay**.

SOURCE & COVERAGE

Harrison 22e — Ch 458 “Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies” (Hauser & Amato). All classifications, antibody targets, mechanisms, doses and outcome figures are taken from this chapter. *Coverage note*: the chapter fully supports the asked union (immunopathogenesis + treatment); no fabrication required. The CIDP material in the same chapter is referenced only for the steroid-responsiveness contrast.



Multiple sclerosis

Asked in: Paper III Dec 2023 · Paper IV Nov 2022 (2×) — RGUHS MD General Medicine

Definition / Introduction — Multiple sclerosis (MS) is a chronic autoimmune inflammatory demyelinating disease of the CNS, with **demyelination, gliosis, plaques and axonal-neuronal loss** in brain, spinal cord and optic nerves. Lesions occur at different CNS sites and at different times; therefore the diagnostic principle is **dissemination in space and time**, after excluding better explanations. The course may be relapsing or progressive, and disability reflects both focal inflammatory attacks and cumulative neurodegeneration.

Etiopathogenesis and pathology

- ▶ **Epidemiology**: usual onset is in young adults, commonly 20–40 years; relapsing MS shows a female predominance of about 2–3:1, while primary progressive MS has a more even sex distribution and later onset. MS is commoner in temperate zones and higher latitudes.

- ▶ **Risk factors:** genetic susceptibility, especially **HLA-DRB11501*, **interacts with environmental factors:** previous Epstein-Barr virus** infection/infectious mononucleosis, low sunlight or vitamin D deficiency, cigarette smoking, and probably childhood obesity/microbiome factors.
- ▶ **Pathology:** plaques are sharply demarcated, often **perivenular**, with mononuclear inflammation, macrophages, T cells, B cells/plasma cells, complement activation, myelin loss, astrocytic gliosis and variable axonal loss. Chronic active plaques, cortical demyelination and meningeal lymphoid aggregates are important in progressive disease.
- ▶ **Immunology:** B cells are central; clonally restricted B cells and plasma cells in CNS/CSF produce **oligoclonal IgG bands**. Autoreactive T cells, especially myelin-reactive T cells, inflammatory cytokines, CD8 cells at plaque edges and microglial activation contribute to tissue injury.
- ▶ **Physiology:** demyelination causes conduction block, slowed conduction and temperature-dependent failure. This explains **Uhthoff phenomenon** and pseudoexacerbations with fever, infection or heat.

Clinical features

- ▶ **Optic neuritis:** subacute unilateral visual loss, central scotoma, impaired colour vision, pain on eye movement and relative afferent pupillary defect; fundus may be normal in retrobulbar neuritis or show papillitis, followed later by optic pallor.
- ▶ **Sensory symptoms:** numbness, tingling, pins-and-needles, burning dysesthesia, reduced vibration/joint position, patchy sensory loss, a spinal sensory level and a band-like truncal tightness or *MS hug*. **Lhermitte sign** is an electric shock sensation down the spine on neck flexion.
- ▶ **Motor and pyramidal signs:** limb weakness, loss of dexterity, spastic paraparesis, brisk reflexes, clonus and extensor plantar responses. Exercise-induced weakness is typical; severe spasticity may cause painful spasms but may also help standing in advanced disease.
- ▶ **Brainstem/cerebellar disease:** diplopia, sixth nerve palsy, **internuclear ophthalmoplegia** from medial longitudinal fasciculus lesions, bilateral INO, nystagmus, vertigo, ataxic gait, intention tremor and scanning dysarthria.
- ▶ **Paroxysmal symptoms:** brief stereotyped events lasting seconds to minutes, often many times per day: tonic spasms, paroxysmal dysarthria-ataxia, sensory attacks, trigeminal neuralgia, hemifacial spasm or facial myokymia.
- ▶ **Autonomic, cognitive and affective symptoms:** urinary urgency, frequency, hesitancy, retention, recurrent UTI, constipation, sexual dysfunction, fatigue, slowed information processing, memory/executive difficulty, depression and pseudobulbar affect.

Disease course and phenotypes

Phenotype	Exam definition	Key point
Clinically isolated syndrome (CIS)	First typical demyelinating clinical event not yet fulfilling MS criteria	High-risk CIS with MRI/CSF activity may be treated early
Radiologically isolated syndrome (RIS)	Incidental MRI lesions typical of MS without clinical attack	Follow clinically and by MRI; some convert to clinical MS
Relapsing-remitting MS (RRMS)	Clearly defined attacks with full or partial recovery and no progression between attacks	Accounts for most onset cases; current term relapsing MS includes active SPMS
Secondary progressive MS (SPMS)	Initial RRMS followed by gradual progression independent of relapses	Produces more fixed disability; classify as active/inactive and progressing/not progressing
Primary progressive MS (PPMS)	Progression from onset, with possible plateaus or minor improvement	About 10% of cases; later onset; faster disability relative to first symptom
Fulminant variants	Tumefactive MS, Marburg variant, Balo concentric sclerosis	May mimic tumour or rapidly progressive encephalomyelitis

Diagnosis and investigations

- ▶ **Core rule:** do not diagnose MS from a single lesion or MRI alone. Demonstrate **dissemination in space (DIS)** and **dissemination in time (DIT)**, and exclude mimics.
- ▶ **2017 McDonald criteria, simplified:** two attacks plus objective evidence of two lesions need no further data; two attacks plus one lesion need DIS; one attack plus two lesions need DIT; one attack plus one lesion needs both DIS and DIT.
- ▶ **DIS by MRI:** at least one T2 lesion in at least two of four typical sites: **periventricular, cortical/juxtacortical, infratentorial or spinal cord**.
- ▶ **DIT by MRI/CSF:** simultaneous gadolinium-enhancing and non-enhancing lesions, or a new T2/gadolinium lesion on follow-up MRI, or a second clinical attack; in a patient with one clinical event meeting DIS, **CSF-specific oligoclonal bands can substitute for DIT**.
- ▶ **PPMS criteria:** at least 1 year of progression plus two of: typical brain lesion, at least two spinal cord lesions, or positive CSF oligoclonal bands/elevated IgG index.
- ▶ **MRI:** most sensitive test; shows ovoid T2/FLAIR plaques, **Dawson fingers** perpendicular to ventricles, corpus callosum, juxtacortical, infratentorial and cord lesions. Gadolinium enhancement marks active BBB breakdown, usually for less than 1 month; T1 black holes suggest irreversible demyelination/axonal loss.
- ▶ **CSF:** normal opening pressure, normal or mildly raised protein, mild lymphocytic pleocytosis, increased IgG index/synthesis and **two or more CSF-restricted oligoclonal bands** in >90% in Harrison. Red flags against MS are polymorphs, CSF cells >75/microL, or protein >1 g/L.

- ▶ **Evoked potentials/OCT:** VEP, SSEP and BAER may detect clinically silent lesions; delayed VEP P100 supports demyelination. OCT quantifies retinal nerve fibre layer axonal loss after optic neuritis but is not diagnostic.

Differential diagnosis

- ▶ **Inflammatory demyelinating mimics: neuromyelitis optica spectrum disorder and MOG antibody-associated disease,** especially with bilateral/severe optic neuritis, poor recovery or longitudinally extensive transverse myelitis; acute disseminated encephalomyelitis after infection/vaccination.
- ▶ **Systemic inflammatory disease:** SLE, Sjögren syndrome, sarcoidosis, Behçet disease, antiphospholipid syndrome and primary CNS/systemic vasculitis.
- ▶ **Infective/metabolic/vascular:** HIV, HTLV-1 tropical spastic paraparesis, Lyme disease, syphilis, vitamin B12 deficiency, CADASIL, stroke/small-vessel disease and spinal dural AV fistula.
- ▶ **Structural/neoplastic:** compressive myelopathy, Chiari malformation, lymphoma, glioma, meningioma and tumefactive demyelination.
- ▶ **Red flags:** onset age <15 or >60 years, progressive course from onset without typical attacks, symptoms confined to one anatomic site, fever/headache/seizures/coma, peripheral neuropathy, severe muscular atrophy, atypical MRI or inflammatory CSF.

Management

- ▶ **Acute relapse:** first exclude pseudoexacerbation due to fever, UTI, heat or metabolic stress. Treat disabling relapses with high-dose methylprednisolone **500-1000 mg IV daily for 3-5 days** or equivalent high-dose oral therapy; optional oral prednisone taper may follow. Steroids hasten recovery but do not improve final recovery or prevent future relapses; long-term steroids are not useful.
- ▶ **Steroid-refractory severe relapse:** **plasma exchange** is useful, especially for severe motor, brainstem or optic-spinal relapses unresponsive to corticosteroids. ACTH is an alternative where available.
- ▶ **Disease-modifying therapy (DMT):** start in all diagnosed relapsing MS and high-risk CIS after counselling. Current high-efficacy first-line choices include anti-CD20 therapy **ocrelizumab, ofatumumab or ublituximab**; rituximab is used where approved options are unavailable. **Natalizumab** is highly effective in JCV-negative patients but requires PML risk surveillance.
- ▶ **Other DMTs:** S1P modulators (fingolimod, ozanimod, ponesimod, siponimod), fumarates (dimethyl/diroximel fumarate), cladribine, alemtuzumab, teriflunomide, interferon-beta and glatiramer acetate. Choice depends on disease activity, pregnancy plans, infection risk, monitoring burden and patient preference.
- ▶ **Progressive MS:** **ocrelizumab** is the only convincingly disease-modifying drug for PPMS; active SPMS may be treated with ocrelizumab or siponimod, with

cladribine/ponesimod/ofatumumab/ozanimod used in active secondary progressive disease in appropriate settings.

- ▶ **Symptomatic care:** physiotherapy, occupational therapy, exercise and fall prevention. Spasticity: stretching, baclofen **20-120 mg/day**, tizanidine **8-32 mg/day**, benzodiazepines, dantrolene or intrathecal baclofen. Gait: dalfampridine **10 mg twice daily** if no seizure risk. Bladder: timed voiding, urodynamics, mirabegron **25-50 mg/day**, vibegron **75 mg/day**, anticholinergics, botulinum toxin or intermittent catheterization. Pain/paroxysms: carbamazepine, gabapentin, pregabalin or other membrane-stabilising drugs. Fatigue: treat sleep, nocturia, depression and spasticity first; modafinil/methylphenidate may help selected patients. Screen and treat depression and suicidality.
- ▶ **Pregnancy and prevention:** relapse rate falls during pregnancy, especially third trimester, and rises in the first 3 months postpartum. Avoid abrupt withdrawal of natalizumab/S1P drugs without planning because rebound can occur. Correct vitamin D deficiency, stop smoking and vaccinate before B-cell-depleting or other immunosuppressive DMTs when possible.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology diagram:** normal myelinated axon with node of Ranvier and saltatory conduction; demyelinated axon with exposed potassium channels, redistributed sodium channels, conduction block/slow conduction; labels: myelin sheath, axon, node of Ranvier, Na⁺ channels, demyelinated plaque, conduction block, continuous conduction.
- ▶ **MRI/clinical course diagram:** sagittal brain showing periventricular **Dawson fingers**, corpus callosum lesions, juxtacortical lesion, infratentorial lesion and short-segment spinal cord plaque; alongside a course graph labelled CIS/RRMS/SPMS/PPMS, relapses, MRI activity and progression.

Clinical / Diagnostic significance

- ▶ Optic neuritis, partial myelitis and brainstem syndromes in a young adult should prompt MRI brain and spinal cord with gadolinium and CSF when needed.
- ▶ Bilateral INO, Lhermitte sign, Uhthoff phenomenon and paroxysmal tonic spasms are highly suggestive clinical clues but are not pathognomonic.
- ▶ Severe bilateral optic neuritis, longitudinally extensive myelitis, area postrema syndrome or poor visual recovery should trigger AQP4-IgG and MOG-IgG testing rather than assuming MS.
- ▶ MRI lesions must be interpreted in clinical context; migraine, ageing and small-vessel disease can produce nonspecific T2 hyperintensities.
- ▶ A true relapse lasts >24 hours and is separated from prior relapse by at least about 1 month; fever/UTI/heat-related worsening is a pseudoexacerbation and should not be treated with steroids alone.

- ▶ Early high-efficacy DMT reduces relapse/MRI activity and may improve long-term disability, but treatment requires infection, vaccination, pregnancy and monitoring planning.

High-yield exam pointers

- ▶ Write the definition: autoimmune CNS disease with **demyelination + gliosis + axonal loss**, disseminated in time and space.
- ▶ Mention common onset: young adult woman; optic neuritis, sensory symptoms and UMN weakness are classic first presentations.
- ▶ Must list the four MRI DIS sites: **periventricular, cortical/juxtacortical, infratentorial, spinal cord**.
- ▶ CSF-specific **oligoclonal bands** can substitute for DIT in the 2017 McDonald criteria.
- ▶ Dawson fingers, gadolinium enhancement and T1 black holes carry diagnostic/prognostic value.
- ▶ Always exclude NMO/MOGAD, B12 deficiency, infections, connective-tissue disease, sarcoidosis, lymphoma and compressive myelopathy.
- ▶ Acute relapse: high-dose methylprednisolone; severe steroid-resistant relapse: plasma exchange.
- ▶ DMT: anti-CD20 therapy/natalizumab are high-efficacy options; **ocrelizumab** is key for PPMS.
- ▶ Do not miss symptomatic management: bladder, spasticity, gait, pain, fatigue, cognition, mood and pregnancy counselling.

SOURCE & COVERAGE

Harrison 22e — “Multiple Sclerosis”; Bradley & Daroff’s Neurology 8e — “Multiple Sclerosis and Other Inflammatory Demyelinating Diseases of the Central Nervous System”; Brazis Localization — “The Localization of Lesions Affecting the Ocular Motor System”; DeJong’s Neurologic Examination — “The Trigeminal Nerve”, “The Facial Nerve”, “The Spinal Cord Level”; CMDT 2026 — “Nervous System Disorders” and “Disorders of the Eyes & Lids”.



Muscular Dystrophies: Genetics, Pathogenesis and Clinical Implications

Asked in: Paper I Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — The **muscular dystrophies** are a genetically determined group of progressive, degenerative myopathies caused by mutations in genes encoding **structural, membrane, nuclear-envelope, enzymatic or RNA-binding proteins** of the muscle fibre. They are characterised clinically by progressive (usually proximal, limb-girdle) weakness with preserved sensation and reflexes, elevated serum creatine kinase (CK), myopathic EMG, and dystrophic features on biopsy. Each subtype has a unique phenotype–genotype signature; cardiac and ventilatory muscle involvement are the chief determinants of mortality. Genetic testing is now the gold standard for diagnosis.

Normal muscle architecture and the dystrophin–glycoprotein complex (DGC)

- ▶ The contractile actin–myosin apparatus of the sarcomere is anchored, via the cytoskeleton, to the extracellular matrix by a chain of proteins; loss of any link destabilises the **sarcolemma**.
- ▶ **Dystrophin** (427 kD) lies on the cytoplasmic face of the sarcolemma — its **amino terminus** binds F-actin and its **carboxyl terminus** links to **β-dystroglycan**.
- ▶ **β-Dystroglycan** spans the membrane and connects to **α-dystroglycan**, which (after enzymatic glycosylation) binds **laminin-α2 (merosin)** in the basal lamina.
- ▶ The **sarcoglycan complex** (**α, β, γ, δ**) and **sarcospan** also span the sarcolemma and stabilise the dystroglycan–dystrophin unit.
- ▶ Together — dystrophin, dystroglycans, sarcoglycans and merosin — form the DGC, transmitting contractile force and protecting the membrane from mechanical stress. Defects at *any* point produce a dystrophy.

Molecular mechanisms of pathogenesis (genetics → disease)

- ▶ **Sarcolemmal/structural-protein loss (DGC dystrophies)**: absence of dystrophin (DMD/BMD), sarcoglycans, dysferlin or merosin renders the membrane fragile → unregulated **Ca²⁺ influx** → activation of proteases → cycles of fibre **necrosis–regeneration** → exhaustion of satellite cells → fibro-fatty replacement.
- ▶ **Defective glycosylation of α-dystroglycan** (fukutin, FKR, POMT1/2, POMGnT1) — “dystroglycanopathies” — disrupt merosin binding; severe forms cause congenital muscular dystrophy with brain/eye anomalies, milder forms an LGMD.
- ▶ **Nuclear-envelope protein defects** (emerin, lamin A/C, nesprin-1/2, LUMA) destabilise the inner nuclear membrane → Emery-Dreifuss MD and LGMD1B, with prominent cardiac conduction disease.
- ▶ **Toxic RNA gain-of-function from non-coding repeat expansions**: in myotonic dystrophy the mutant mRNA forms **intranuclear inclusions that sequester RNA-splicing proteins**, causing mis-splicing of multiple downstream transcripts (multisystem disease).
- ▶ **Epigenetic de-repression**: in FSHD, contraction of the D4Z4 array → **hypomethylation** → aberrant **toxic expression of DUX4** transcription factor in muscle.
- ▶ **Protein aggregation**: in OPMD, an expanded polyalanine tract makes PABP2 resistant to proteasomal degradation → toxic intranuclear aggregates.

Genetic classification of the major muscular dystrophies

Dystrophy	Inheritance	Gene / locus	Protein	Hallmark feature
Duchenne / Becker (DMD/BMD)	X-linked recessive	DMD / Xp21	Dystrophin	Calf pseudohypertrophy,

Dystrophy	Inheritance	Gene / locus	Protein	Hallmark feature
				Gowers sign, very high CK
Limb-girdle (LGMD “D”/”R”)	AD (D) or AR (R)	<i>CAPN3, DYSF, SGCA-D, FKRP, ANO5, TTN...</i>	Calpain-3, dysferlin, sarcoglycans, FKRP, anoctamin-5	Proximal limb-girdle weakness, often indistinguishable from DMD/BMD
Emery-Dreifuss (EDMD)	XLR / AD / AR	<i>EMD, LMNA, SYNE1/2, FHL1, TMEM43</i>	Emerin, lamin A/C, nesprins, FHL1, LUMA	Early contractures + cardiac conduction block / sudden death
Myotonic dystrophy 1 (DM1)	AD	<i>DMPK</i> / 19q13 — CTG repeat	DMPK	Grip myotonia, hatchet face, frontal balding, multisystem
Myotonic dystrophy 2 (PRODM / DM2)	AD	<i>CNBP (ZNF9)</i> — CCTG repeat, intron 1	CNBP	Proximal weakness, milder, no congenital form
Facioscapulohumeral (FSHD)	AD (FSHD1, 95%)	<i>D4Z4</i> / 4q35, <i>DUX4</i>	DUX4 (toxic)	Facial weakness, scapular winging, asymmetric
Oculopharyngeal (OPMD)	AD	<i>PABPN1</i> — GCG / polyalanine	PABP2	Late ptosis + dysphagia; rimmed vacuoles

Duchenne and Becker muscular dystrophy (the prototype dystrophinopathy)

- **Genetics:** X-linked recessive; the *DMD* gene at Xp21 is the largest human gene (~2.5 million bp, 79 exons). ~65–75% of cases are deletions/duplications (hot-spots between exons 44–52); the remainder are point/nonsense mutations. Roughly **one-third are sporadic** (new mutations); germline mosaicism gives a recurrence risk up to ~14% even when the mother tests negative.
- **The reading-frame (Monaco) rule — the key concept:** in-frame mutations preserve the triplet reading frame → a shortened but partly functional dystrophin → **milder Becker phenotype**; out-of-frame (frameshift) mutations destroy the frame → absent dystrophin → **severe Duchenne**.
- **DMD clinical course:** boys normal at birth; proximal lower-limb weakness from ~3–5 yr, **Gowers sign**, toe-walking, waddling gait, firm **calf pseudohypertrophy**; loss of ambulation ~8–12 yr; progressive contractures, scoliosis. **Cardiomyopathy in ~1/3 by age 14 and virtually all by 18**; respiratory failure. Intellectual disability may occur.

- ▶ **BMD:** later onset, ambulation usually retained beyond 15 yr, survival into 4th–5th decade; cardiomyopathy may dominate (occasionally heart failure is the only manifestation) and may require transplantation.
- ▶ **Labs:** CK markedly elevated (often >10,000 IU/L in DMD, lower in BMD); myopathic EMG; immunostain/Western blot — dystrophin absent in DMD, reduced/altered in BMD (immunoblot needed in BMD as staining can look normal).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Dystrophin–glycoprotein complex (DGC):** Draw the sarcolemma as a bilayer. Label, from inside out: *F-actin / cytoskeleton* → *Dystrophin (N-terminus to actin, C-terminus to β -dystroglycan)* → *β -Dystroglycan (transmembrane)* → *α -Dystroglycan (extracellular)* → *Laminin- α 2 (merosin) in basal lamina*; show the **Sarcoglycan complex** (α , β , γ , δ) + **sarcospan** spanning the membrane beside dystroglycan; mark *Calpain-3*, *Dysferlin*, *Caveolin-3* and the *nuclear envelope (emerin, lamin A/C, nesprin)* to show where different dystrophies localise.
- ▶ **Diagram 2 — Gowers sign:** Sequential figures of a child rising from the floor by “climbing up the legs” — turning prone, pushing onto hands and feet, then walking the hands up the thighs to stand. Label *Gowers manoeuvre = proximal (hip/trunk) weakness*.

Clinical / Diagnostic significance

- ▶ **Pattern recognition localises the diagnosis:** limb-girdle (most dystrophies) vs facial weakness + scapular winging (FSHD) vs facial/distal weakness + grip myotonia (DM1) vs ptosis + dysphagia (OPMD) vs early contractures + heart block (EDMD).
- ▶ **Investigations:** serum CK (screening; very high in dystrophinopathies/Miyoshi, normal-mildly raised in FSHD/EDMD/OPMD); EMG (myopathic, short-duration small-amplitude polyphasic MUAPs; myotonic discharges in DM); **muscle MRI/ultrasound** for pattern of involvement; **immunohistochemistry/immunoblot** (dystrophin, sarcoglycans, dysferlin, α -dystroglycan, emerin); **genetic testing** is definitive (MLPA/array CGH for deletions-duplications, then next-generation sequencing for point mutations).
- ▶ **Multisystem surveillance (high-yield):** annual ECG + echo/cardiac MRI in DMD/BMD and EDMD/laminopathy; FVC monitoring for respiratory failure; cataracts, conduction block, insulin resistance, testicular atrophy and hypersomnia in DM1; aspiration risk in OPMD.
- ▶ **Management — largely supportive but evolving:**
 - **Glucocorticoids** (prednisone ~0.75 mg/kg/day or deflazacort ~0.9 mg/kg/day) slow progression and prolong ambulation in DMD.

- **Cardiac:** ACE-inhibitor/ARB (start ~age 10 in DMD), beta-blockers, afterload reduction; **pacemaker/ICD** is potentially life-saving in EDMD/laminopathy and significant DM conduction disease; cardiac transplant in selected BMD.
 - **Respiratory/orthopaedic:** non-invasive ventilation (BiPAP), physiotherapy, stretching/bracing, ankle-foot orthoses for foot-drop, scoliosis surgery, scapular fixation in FSHD, cricopharyngeal myotomy in OPMD.
 - **Molecular therapies (DMD):** **exon-skipping antisense oligonucleotides** (e.g., eteplirsen — exon 51 skipping, converts DMD toward a BMD phenotype) and **stop-codon read-through** agents (ataluren for nonsense mutations); DUX4-suppression trials ongoing in FSHD.
 - **Symptomatic myotonia:** **mexiletine** in DM1/DM2; modafinil for hypersomnia.
- ▶ **Genetic counselling** is integral: carrier testing of female relatives in X-linked DMD/BMD/EDMD; recognition of **anticipation** in DM1 and **maternal transmission of the congenital form**; prenatal/germline-mosaicism counselling.

High-yield exam pointers

- ▶ **DMD/BMD** — X-linked, *Xp21* dystrophin; **reading-frame rule:** in-frame → Becker, out-of-frame → Duchenne.
- ▶ **Gowers sign + calf pseudohypertrophy + CK >10,000** = think Duchenne; death from cardiomyopathy/respiratory failure.
- ▶ **DM1** — AD, CTG expansion in *DMPK* (19q13); **genetic anticipation**; congenital form from **affected mothers**; grip/percussion myotonia, hatchet face, frontal balding, cataracts, heart block. **DM2 (PROMM)** = CCTG in *CNBP*, proximal, no congenital form.
- ▶ **FSHD1** — contraction of **D4Z4 repeat at 4q35** (<35 kb) → toxic **DUX4** expression; facial weakness + scapular winging; heart spared.
- ▶ **EDMD triad** — early **contractures**, humero-peroneal weakness, **cardiac conduction defects/sudden death**; emerin (X-linked) or lamin A/C (AD).
- ▶ **OPMD** — AD, GCG/polyalanine expansion in *PABPN1*; late ptosis + dysphagia; **rimmed vacuoles**, 8.5-nm intranuclear tubular filaments.
- ▶ **LGMD** — new ENMC nomenclature: AD = **LGMD-D**, AR = **LGMD-R**; commonest adult types — calpainopathy (R1), FKRP (R9), anoctaminopathy (R12).
- ▶ **Always exclude treatable mimics** — immune-mediated necrotising myopathy (anti-HMGCR/anti-SRP) can mimic LGMD.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Muscular Dystrophies and Other Muscle Diseases” (Amato & Brown).

- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Disorders of Skeletal Muscle” (dystrophin–glycoprotein complex, *DMD* gene structure/hot-spots, reading-frame rule, *DMD/BMD* clinical course and therapy including exon-skipping/ataluren, *LGMD* classification).



Myasthenia gravis

Asked in: Paper III Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Myasthenia gravis (MG) is the commonest primary disorder of the neuromuscular junction (NMJ), an **antibody-mediated autoimmune disease** characterised by **fatigable weakness of skeletal muscle**. The fundamental defect is a **reduction in the number of functioning acetylcholine receptors (AChRs)** at the post-synaptic muscle membrane, most often caused by anti-AChR antibodies, producing weakness that worsens with repeated activity and improves with rest. It is eminently treatable, with contemporary mortality falling from ~70% a century ago to the present 1–5%.

Pathophysiology and immunopathology

- **Normal transmission:** acetylcholine (ACh) is synthesised in the motor nerve terminal and stored in vesicles (quanta); a nerve action potential releases ACh from **150–200 vesicles**, which binds AChRs packed on the crests of post-synaptic folds. The **AChR is a pentamer (2 α , 1 β , 1 δ , and 1 γ or ϵ)** around a central cation pore; ACh binding opens the channel, Na⁺ entry depolarises the end-plate, and if large enough triggers a muscle action potential. Transmission is terminated by **acetylcholinesterase (AChE)**.
- **Clustering machinery:** presynaptic **agrin** binds **LRP4**; the agrin–LRP4 complex activates **MuSK** (muscle-specific tyrosine kinase), which recruits **DOK7** and **rapsyn** to cluster AChRs. These molecules underlie both autoimmune MG and the congenital myasthenic syndromes.
- **Core defect in MG:** fewer available AChRs **plus flattened, “simplified” post-synaptic folds** and a widened synaptic cleft → small end-plate potentials that fail to reach threshold → transmission failure. Normal **presynaptic “rundown”** (declining ACh release on repetitive activity) superimposed on this margin recruits fewer fibres with each impulse → clinical **fatigue** and the **decremental response** on repetitive nerve stimulation (RNS).
- **Anti-AChR antibodies (IgG, T-cell dependent)** reduce receptors by three mechanisms: (1) **cross-linking and accelerated endocytosis/turnover** of AChRs; (2) **complement-mediated lysis** of the post-synaptic membrane; (3) **direct blockade** of the ACh-binding site.
- **MuSK antibodies** are **IgG4** — they **do not fix complement** (hence anti-MuSK MG does not respond to complement inhibitors); they block MuSK–LRP4 binding. **LRP4 antibodies** are **IgG1**, complement-activating, like AChR antibodies.

- ▶ **Thymus:** abnormal in ~75% of AChR-antibody-positive patients — ~65% **hyperplastic** (germinal centres), ~10–15% **thymoma**. Thymic **myoid cells** express surface AChR and may initiate autosensitisation; **Treg deficiency/dysfunction** permits escape of autoreactive lymphocytes.

Clinical features and subtypes

- ▶ **Cardinal feature:** painless, **fatigable weakness** — worse with use and late in the day, better after rest/sleep; **fluctuating** course with exacerbations and remissions, especially in the first 1–3 years.
- ▶ **Ocular (initial in ~two-thirds):** **ptosis and diplopia**; if weakness stays confined to ocular muscles for ≥ 2 –3 years, generalisation is unlikely (**ocular MG**, ~10–15%; up to ~50–58% in Asians).
- ▶ **Bulbar/facial:** “snarling”/**myasthenic sneer** on smiling, **nasal regurgitation**, dysphagia, nasal or “mushy” dysarthria, hoarseness, fatigable chewing.
- ▶ **Axial/limb:** neck-extensor weakness $\rightarrow$ “**dropped-head**”; limb weakness typically **proximal and** may be asymmetric; **deep-tendon reflexes preserved**; **sensation normal**.
- ▶ **Generalisation** occurs in ~85% within ~3 years. **MuSK-MG:** prominent **bulbar, neck and respiratory** weakness with **muscle atrophy**, female predominance, often poor/worsening response to anticholinesterases.

Subtype	Onset / sex	Antibody	Thymus
Ocular	Any; childhood in Asia	AChR (~50%)	Usually normal
Early-onset (EOMG)	<50 y; F>M	AChR	Hyperplasia
Late-onset (LOMG)	>50 y; M>F	AChR $\pm$ titin, ryanodine	Normal/atrophic
Thymomatous	Peak ~50 y; M=F	AChR + striational (titin, ryanodine)	Thymoma
MuSK	30–50 y; marked F	MuSK (IgG4)	Normal/minimal
LRP4 / seronegative	Often younger	LRP4 (IgG1) / none detectable	Hyperplasia in some

MGFA clinical classification

- ▶ **Class I** — ocular weakness only ($\pm$ eyelid-closure weakness), all other muscles normal.
- ▶ **Class II** — mild generalised weakness; **III** — moderate; **IV** — severe generalised (each subdivided **a** = limb/axial predominant, **b** = bulbar/respiratory predominant).
- ▶ **Class V** — intubation (with or without ventilation) = **myasthenic crisis**. (*Harrison/landmark trials enrol “class II–IV” gMG and grade severity with MGADL and QMG scores.*)

Diagnosis and evaluation

- ▶ **Bedside provocation / clinical signs:** sustained upgaze provokes **ptosis**; Cogan’s “**lid twitch**” (lid overshoot on saccade from down- to up-gaze); **enhanced ptosis** / “**curtain sign**” (lifting one lid

worsens the other); “peek sign” and inability to “bury the eyelashes” on forced closure; **pseudo-internuclear ophthalmoplegia**; the **ice-pack test** — 2 min of cooling a ptotic lid producing ≥ 2 mm lid rise (high sensitivity).

- **Serology: anti-AChR antibody** (radioimmunoassay) — **~85% positive in generalised**, **~50% in ocular MG**; virtually diagnostic but a negative test does **not** exclude MG. **Anti-MuSK** in **~40% of AChR-negative generalised MG**; **anti-LRP4** in a small proportion of double-seronegatives. **Striational antibodies (titin, ryanodine)** are non-pathogenic but flag **thymoma/older or severe disease**.
- **Electrodiagnosis: RNS at 2–3 Hz shows a decrement >10%** (test weak/proximal muscles); **single-fibre EMG — increased jitter and blocking with normal fibre density** — is the most sensitive test (confirmatory but not specific).
- **Anticholinesterase test: edrophonium** historically (rapid onset/short action); now largely abandoned for serology/EMG.
- **Search for associated disease: chest CT/MRI** (thymoma — present in ~10–15%); **thyroid function** (hyper-/hypothyroidism in ~3–8%); screen for SLE/RA, and pre-immunosuppression work-up — TB, hepatitis, glucose/HbA1c, blood pressure, bone densitometry; baseline spirometry (FVC, MIP/MEP).

Differential diagnosis

Disorder	Distinguishing features
Lambert–Eaton myasthenic syndrome (LEMS)	Proximal lower-limb weakness, areflexia, autonomic symptoms (dry mouth, orthostasis); P/Q-type VGCC antibody; RNS shows decrement at low rate but $\geq 100\%$ increment at high rate (20–50 Hz)/post-exercise; ~paraneoplastic with SCLC. Treat with 3,4-DAP (amifampridine) + pyridostigmine
Congenital myasthenic syndromes	Non-autoimmune; onset infancy/childhood; seronegative ; >30 genes (commonest <i>CHRNε</i> , also <i>RAPSN</i> , <i>COLQ</i> , <i>DOK7</i>)
Botulism	Descending paralysis, dilated/poorly reactive pupils , autonomic features; incremental CMAP at high-rate RNS
Drug-induced / ICI-related MG	Penicillamine; checkpoint inhibitors (overlap myositis/myocarditis , high mortality)
Others	Graves’/thyroid ophthalmopathy, intracranial compressive lesion, oculopharyngeal dystrophy, mitochondrial PEO/Kearns–Sayre

Treatment

- ▶ **Symptomatic — anticholinesterase:** pyridostigmine 30–60 mg every 4–8 h (max ~360–480 mg/day); onset 15–30 min, lasts 3–4 h; muscarinic side effects (cramps, diarrhoea, salivation) countered by glycopyrrolate/loperamide. **Anti-MuSK patients respond poorly and may worsen.**
- ▶ **Thymectomy:** mandatory for **thymoma**; the MGTX trial showed extended trans-sternal thymectomy in **non-thymomatous, AChR-positive generalised MG** improves strength, lowers prednisone/second-line needs and hospitalisations — offer to patients <65 y unless purely ocular. Not established for MuSK/seronegative MG. Optimise strength (IVIg/PLEX) before surgery; **never an emergency procedure.**
- ▶ **Chronic immunosuppression: corticosteroids** — start low and up-titrate (or pre-treat with IVIg/PLEX before high dose to avoid early steroid worsening). **Steroid-sparing:** azathioprine (2–3 mg/kg; *avoid allopurinol*), mycophenolate mofetil (1–1.5 g bid), calcineurin inhibitors (cyclosporine/tacrolimus). **Rituximab** (anti-CD20) is **highly effective in MuSK-MG** and beneficial in new-onset disease (RINOMAX/RITUXIMAB data).
- ▶ **Newer targeted agents** — work within weeks, used as bridge or in refractory disease:
 - **Complement (C5) inhibitors:** eculizumab, ravulizumab (IV mAbs), zilucoplan (SC peptide) — only for **AChR-positive generalised MG**; **meningococcal vaccination required** (B + ACWY).
 - **FcRn antagonists:** efgartigimod (IV/SC), rozanolixizumab (SC; the **only one approved for both AChR- and MuSK-positive MG**) — increase IgG catabolism, lowering pathogenic antibody.
- ▶ **Rapid rescue:** plasmapheresis (5–6 exchanges) and IVIg 2 g/kg over 2–5 days — equally effective for crisis or peri-operative optimisation.

Myasthenic crisis and drugs to avoid

- ▶ **Myasthenic crisis** = exacerbation severe enough to threaten life, usually **ventilatory failure** needing intubation/NIV (= MGFA class V). Commonest trigger is **intercurrent infection**; manage in ICU with airway support, treat infection, and **PLEX or IVIg**. Distinguish from **cholinergic crisis** (anticholinesterase excess — now rare).
- ▶ **Drugs that worsen MG (avoid):** aminoglycosides, fluoroquinolones, macrolides; non-depolarising neuromuscular blockers; β -blockers; procainamide, quinine/quinidine, chloroquine/mefloquine; IV magnesium; penicillamine (can cause MG); botulinum toxin; immune-checkpoint inhibitors.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Normal vs myasthenic NMJ (side-by-side):** label *motor axon terminal*, *ACh vesicles (quanta)*, *active zone*, *voltage-gated Ca^{2+} channel*, *synaptic cleft*, *AChR on crests of post-synaptic folds*, *AChE*, *voltage-gated Na^{+} channels*, *agrin-LRP4-MuSK-DOK7-rapsyn*

clustering complex. On the MG side label: **reduced AChR number, flattened/simplified post-synaptic folds, widened synaptic cleft, AChR autoantibody + complement (membrane attack complex)**.

- ▶ **Diagram 2 — Myasthenic facies:** label **bilateral ptosis, compensatory frontalis contraction/raised eyebrow, myasthenic “snarl/sneer” on smiling, head drop**.

Clinical / Diagnostic significance

- ▶ **Pattern recognition:** fatigable, fluctuating weakness with **ocular onset, preserved reflexes and normal sensation** is the clinical signature; confirm with serology + RNS/SFEMG before committing to long-term immunotherapy and surgery.
- ▶ **Antibody status guides therapy:** MuSK-MG (IgG4) ignores complement inhibitors but responds to rituximab/rozanolixizumab; AChR-MG suits **complement inhibitors**.
- ▶ **Always image the chest** — thymoma changes management (mandatory thymectomy, striational-antibody association).
- ▶ **Monitor FVC/MIP/MEP serially;** falling vital capacity heralds crisis. **Vaccinate against meningococcus** before C5 inhibitors.
- ▶ **~20% achieve sustained remission;** thymectomy improves the odds in AChR-positive disease.

High-yield exam pointers

- ▶ Pentameric AChR ($2\alpha\beta\delta\gamma\epsilon$); ACh from 150–200 vesicles per impulse.
- ▶ Anti-AChR: 85% generalised / 50% ocular; anti-MuSK = ~40% of AChR-negative generalised MG (IgG4, no complement).
- ▶ RNS decrement >10% at 2–3 Hz; SFEMG jitter = most sensitive. MG decrements; LEMS increments.
- ▶ **Ice-pack test:** ≥ 2 mm lid rise after 2 min cooling. **Cogan lid-twitch, curtain sign, peek sign** are clinical clues.
- ▶ **Thymoma** in ~10–15%; **thymic hyperplasia** in ~65% of AChR-positive MG; F:M $\approx$ 3:2.
- ▶ **MGTX trial:** thymectomy benefits non-thymomatous AChR-positive generalised MG.
- ▶ **Crisis** = ventilatory failure $\rightarrow$ ICU + PLEX/IVIg; commonest trigger = infection.
- ▶ **Avoid:** aminoglycosides, quinolones, macrolides, β -blockers, magnesium, penicillamine, neuromuscular blockers, checkpoint inhibitors.
- ▶ MuSK-MG often worsens with anticholinesterases; treat with rituximab.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Myasthenia Gravis and Other Diseases of the Neuromuscular Junction” (pathophysiology, antibody mechanisms, diagnostic table, MGTX, complement/FcRn agents, crisis, drugs to avoid).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Disorders of Neuromuscular Transmission” (clinical subtypes, ocular signs — lid twitch, curtain/peek sign, pseudo-INO; immunopathology, electrodiagnosis, HLA associations).
- ▶ **CMDT 2026** — “Nervous System Disorders: Myasthenia Gravis” (current drug doses, thymectomy and FcRn/complement-inhibitor management).

Coverage note: The full MGFA clinical classification (classes I–V with a/b subdivisions) is standard internal medicine; the corpus references MGFA “class II–IV” and the MGADL/QMG severity scores but does not tabulate every subclass. The older **Osserman classification** is not in the corpus and is omitted.



Narcolepsy

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — Narcolepsy is a chronic, lifelong **central disorder of hypersomnolence** characterised by difficulty sustaining wakefulness, dysregulation of REM sleep (intrusion of REM phenomena into wakefulness) and disturbed nocturnal sleep. The cardinal feature is **excessive daytime sleepiness (EDS)** present in 100% of patients, classically accompanied by the *narcoleptic tetrad* of cataplexy, sleep paralysis and hypnagogic hallucinations. It results from selective loss of the hypothalamic **orexin (hypocretin)** neurons and affects about **1 in 2000** people, with onset typically between 10–30 years of age.

Pathophysiology — the orexin (hypocretin) deficiency

- ▶ Caused by **loss of the lateral/posterior hypothalamic neurons that produce orexin-A and orexin-B (hypocretin-1 and -2)** neuropeptides. Orexins normally promote long episodes of wakefulness and suppress REM sleep by exciting the wake-promoting monoaminergic nuclei (noradrenergic locus coeruleus, serotonergic raphe, histaminergic tuberomammillary nucleus).
- ▶ Loss of orexin signalling **destabilises the sleep–wake “flip-flop” switch** → frequent intrusions of sleep into wakefulness and **untimed REM sleep** (causing cataplexy, sleep paralysis, hallucinations).
- ▶ **Type 1 narcolepsy** (with cataplexy): near-complete (~90%) loss of orexin neurons → **very low/undetectable CSF orexin (hypocretin-1)**. **Type 2** (without cataplexy): orexin levels usually normal; partial neuronal loss or other uncharacterised mechanisms.

- ▶ **Autoimmune mechanism** (strongly supported): narcolepsy has the **strongest known HLA association** of any disease — ***HLA DQB1\06:02 is present in >90% of type 1 patients (CMDT: 85–95%) versus only 12–25% of the general population.** Hypothesised molecular mimicry*: *immune response to influenza, Streptococcus or other infections cross-reacts with orexin neurons in genetically susceptible (DQB1\06:02+) individuals*; patients show heightened T-cell responses (CD4⁺/CD8⁺) against orexin peptides.
- ▶ A documented **8- to 12-fold rise in childhood narcolepsy** followed the *Pandemrix* H1N1 influenza vaccine (AS03-adjuvanted) in Europe — supporting the infection/vaccine-triggered autoimmune model.
- ▶ **Secondary (“symptomatic”) narcolepsy**: damage to the hypothalamic orexin neurons or their projections by anti-Ma2 **paraneoplastic antibodies**, severe traumatic brain injury, diencephalic/midbrain tumours, strokes, multiple sclerosis, encephalitis or **Niemann-Pick disease type C**.

Clinical features — the narcoleptic tetrad and beyond

Feature	Frequency	Key clinical points
Excessive daytime sleepiness / sleep attacks	100%	Irresistible sleep at inappropriate times (talking, driving, eating); naps last minutes–20–30 min; patient wakes refreshed (unlike OSA)
Cataplexy	~60–70%	Sudden bilateral loss of muscle tone, consciousness retained ; triggered by strong emotion (laughter, excitement, anger >95%); spares respiratory and ocular muscles
Sleep paralysis	25–50%	Inability to move/speak at sleep onset (hypnagogic) or on waking (hypnopompic); lasts up to 15–20 min; frightening
Hypnagogic/hypnopompic hallucinations	20–40%	Vivid, often frightening visual (also auditory/vestibular) imagery at sleep–wake transition
Disturbed nocturnal sleep	70–80%	Fragmented sleep with frequent awakenings
Automatic behaviour	20–40%	Semi-purposeful acts (e.g., writing nonsense, driving to wrong place) with amnesia, from microsleeps

- ▶ **Cataplexy in detail:** muscle weakness from **decreased noradrenergic excitation + increased GABA/glycinergic inhibition of spinal motor neurons** — essentially REM atonia intruding into wakefulness. During the attack, muscle stretch reflexes, **H-reflex and F-responses are reduced/absent**; EEG shows wakefulness (if >1–2 min, REM appears). Usually appears months–years after sleep attacks; **status cataplecticus** may follow abrupt withdrawal of anticataplectic drugs.
- ▶ The full tetrad (all four) occurs in only ~10%; three of four in ~30%. **Cataplexy is the most specific symptom** — it occurs in almost no other disorder, hence it defines type 1.
- ▶ **Children** may present atypically with hyperactivity, prolonged nocturnal sleep, *cataplectic facies* (facial hypotonia, ptosis, tongue protrusion) or perioral dystonic movements unrelated to emotion.
- ▶ **Comorbidities:** obesity/raised BMI, type 2 diabetes, REM sleep behaviour disorder (up to 36%, often drug-induced), periodic limb movements (10–60%), sleep apnoea (~30%, often central), depression and anxiety.

Classification (ICSD-3) and diagnostic criteria

Narcolepsy is part of the **Central Disorders of Hypersomnolence** (ICSD-3, AASM 2014), which also include idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia due to a medical/medication/psychiatric disorder, and insufficient sleep syndrome.

Parameter	Narcolepsy type 1 (NT1)	Narcolepsy type 2 (NT2)
Older name	Narcolepsy with cataplexy / hypocretin-deficiency syndrome	Narcolepsy without cataplexy
Cataplexy	Present	Absent
CSF hypocretin-1	≤110 pg/mL (or ≤⅓ of normal mean)	>110 pg/mL (normal)
MSLT	Mean sleep latency ≤8 min + ≥2 SOREMPs (1 may be a sleep-onset REM on prior PSG)	Same MSLT criterion
HLA DQB1*06:02	~100% positive	~25% positive

- ▶ **Reclassification rule:** an NT2 patient later found to have CSF hypocretin-1 ≤110 pg/mL is reclassified as NT1.
- ▶ **Diagnostic workup:** clinical history (chronic EDS + cataplexy is often sufficient); quantify sleepiness with the **Epworth Sleepiness Scale**; confirm objectively with **overnight polysomnography (PSG)** followed next day by the **Multiple Sleep Latency Test (MSLT)**.
- ▶ **MSLT protocol:** five 20-minute nap opportunities every 2 hours; positive when **mean sleep latency <8 min and REM (SOREMP) in ≥2 naps**. A sleep-onset REM period within 15 min at

night is also supportive. **Stop stimulants 1 week and antidepressants 3 weeks** before the test (they suppress REM); ensure adequate prior sleep.

Differential diagnosis

- ▶ **Of sleep attacks / EDS:** obstructive sleep apnoea (most common cause; un-refreshing naps, snoring, obesity), insufficient sleep syndrome, **idiopathic hypersomnia** (prolonged un-refreshing sleep, “sleep drunkenness”, **no SOREMPs**, no cataplexy), Kleine-Levin syndrome (recurrent hypersomnia + hyperphagia + hypersexuality in young males), circadian rhythm disorders, drug/alcohol-related hypersomnolence.
- ▶ **Of cataplexy:** partial complex seizure (altered consciousness, postictal confusion, epileptiform EEG), absence and atonic seizures, drop attacks, syncope, vertebrobasilar insufficiency, basilar migraine, and **pseudocataplexy** (functional, triggered by negative thoughts, lasting minutes–hours).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hypnogram comparison (healthy vs narcolepsy)** — two stacked sleep-stage tracings against clock time. Labels: *Awake, REM, N1, N2, N3*; *clock time 20:00 → 16:00*; “**sleep-onset REM period (SOREMP) <15 min**”, “fragmented nocturnal sleep”, “frequent daytime naps containing REM” on the narcolepsy trace; “normal long NREM-before-REM latency” on the healthy trace.
- ▶ **Orexin pathophysiology schematic** — *lateral/posterior hypothalamus* with **orexin (hypocretin) neurons** projecting to wake-promoting nuclei (*locus coeruleus – NE; raphe – 5-HT; tuberomammillary nucleus – histamine*) and inhibiting **VLPO**. Show **autoimmune destruction** (label: *HLA DQB1*06:02, CD4⁺/CD8⁺ T cells, molecular mimicry, H1N1/Streptococcus**) → loss of orexin → unstable sleep–wake switch → “**EDS + REM intrusion (cataplexy, sleep paralysis, hallucinations)**”.

Clinical / Diagnostic significance

- ▶ **Investigations:** PSG + MSLT are the diagnostic standard; **CSF hypocretin-1 ≤ 110 pg/mL** is highly specific for NT1 and useful when MSLT is equivocal or REM-suppressing drugs cannot be stopped; ***HLA DQB1*06:02*** typing supports (but does not confirm — common in healthy people) the diagnosis. Screen for secondary causes (anti-Ma2, neuroimaging) if onset is atypical or focal signs are present.
- ▶ **Treatment is symptomatic** — there is no cure. Non-pharmacological: regular adequate nocturnal sleep, **scheduled 15–20 min afternoon naps**, sleep hygiene, support groups, and **driving counselling** (legal/safety responsibility — advise against driving until effectively treated).

Target	Drug (dose)	Class / mechanism
EDS	Modafinil 200–400 mg every morning	Wake-promoting agent (first line)
	Armodafinil 150–250 mg morning	R-isomer of modafinil, longer-acting
	Methylphenidate 10–20 mg bid; dextroamphetamine 10 mg bid	Stimulants (abuse/sympathomimetic risk)
	Solriamfetol 75–150 mg/day	Norepinephrine–dopamine reuptake inhibitor
	Pitolisant 8.9–35.6 mg/day	Selective histamine H3 receptor antagonist/inverse agonist
Cataplexy	Venlafaxine 37.5–150 mg; fluoxetine 10–40 mg	SNRI / SSRI (suppress REM)
	Protriptyline 10–40 mg/d; clomipramine 25–50 mg/d (imipramine)	TCAs (anticholinergic limits use)
Both EDS + cataplexy + fragmented sleep	Sodium oxybate (gamma-hydroxybutyrate) 3–9 g in 2 nightly divided doses (bedtime + 2.5–4 h later); low-sodium (calcium/magnesium/potassium/sodium oxybate) versions	Consolidates slow-wave sleep

- ▶ No antidepressant is FDA-approved specifically for narcolepsy, though they are standard for cataplexy. **Pitolisant and oxybates** uniquely improve both sleepiness and cataplexy.

High-yield exam pointers

- ▶ **Narcoleptic tetrad** = EDS + cataplexy + sleep paralysis + hypnagogic hallucinations; only ~10% have all four, EDS is universal.
- ▶ **NT1** = cataplexy + CSF hypocretin-1 ≤ 110 pg/mL; **NT2** = no cataplexy, normal hypocretin.
- ▶ ***HLA DQB1*06:02**** — strongest HLA disease association; >90% of NT1 but present in 12–25% of normals (not diagnostic alone).
- ▶ **MSLT diagnostic**: mean sleep latency <8 min + ≥ 2 SOREMPs; SOREMP <15 min at night supportive.
- ▶ **Cataplexy** = sudden emotion-triggered atonia with **preserved consciousness**, spares respiratory/ocular muscles; abolished reflexes; most specific feature.
- ▶ **Pandemrix H1N1 vaccine** and influenza/*Streptococcus* → autoimmune trigger via molecular mimicry.
- ▶ **First-line for EDS** = modafinil; newer agents **pitolisant** (H3 inverse agonist) and **solriamfetol** (NDRI).

- ▶ Sodium oxybate (GHB) treats EDS, cataplexy and disrupted night sleep together.
- ▶ Stop stimulants 1 week and antidepressants 3 weeks before MSLT to avoid REM suppression.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Sleep Disorders" (orexin/hypocretin pathophysiology, HLA DQB1*06:02, type 1 vs type 2, MSLT, treatment regimens).
- ▶ Bradley & Daroff's Neurology in Clinical Practice, 8e — "Sleep and Its Disorders" (ICSD-3 classification, clinical-feature frequencies, cataplexy mechanism/cataplectic facies, CSF hypocretin-1 ≤ 110 pg/mL diagnostic table, drug doses, differential diagnosis).
- ▶ CMDT 2026 — "Psychiatric Disorders" (narcolepsy criteria and current management — modafinil/armodafinil dosing, HLA 85–95%).



Orthostatic hypotension

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Orthostatic (postural) hypotension (OH) is defined (Freeman *et al.*, 2011 consensus) as a sustained fall in systolic blood pressure (SBP) ≥ 20 mmHg or in diastolic blood pressure (DBP) ≥ 10 mmHg within 3 minutes of active standing or of head-up tilt (HUT) $\geq 60^\circ$. In patients with supine hypertension a drop of $\geq 30/15$ mmHg is used. It is a cardinal sign of sympathetic vasoconstrictor (autonomic) failure and a major cause of orthostatic intolerance, falls, syncope and increased mortality, especially in the elderly and in neurodegenerative disease. Prevalence rises from $<5\%$ below age 50 to $\sim 20\%$ above age 70.

Normal orthostatic homeostasis and pathophysiology

- ▶ On standing, ~ 500 – 700 mL of blood (Bradley: 300 – 800 mL) pools in the lower limbs and splanchnic venous bed, reducing venous return, cardiac filling and stroke volume.
- ▶ The fall in BP unloads aortic/carotid baroreceptors $\rightarrow$ reduced afferent traffic to the *nucleus tractus solitarius* $\rightarrow$ reflex sympathetic activation (arteriolar + venoconstriction, $\uparrow$ heart rate, $\uparrow$ contractility) and vagal withdrawal.
- ▶ Net normal response: SBP changes little (falls ~ 10 mmHg), DBP rises ~ 5 mmHg, heart rate rises 5 – 20 beats/min; the leg and abdominal muscle pump aids venous return.
- ▶ OH results when this reflex arc fails at any level — afferent (baroreceptors), central integration, efferent sympathetic outflow, or peripheral release of norepinephrine — or when cardiac output/intravascular volume is inadequate.
- ▶ The hallmark of neurogenic OH (NOH) is inadequate peripheral norepinephrine release $\rightarrow$ failure of vasoconstriction, with a blunted compensatory tachycardia.

Diagnostic criteria and variants

Variant	Defining features
Classical OH	Sustained $\downarrow$ SBP ≥ 20 or $\downarrow$ DBP ≥ 10 mmHg within 3 min of standing/HUT
OH with supine hypertension	Orthostatic drop $\geq 30/15$ mmHg
Initial OH	Transient $\downarrow$ SBP > 40 / $\downarrow$ DBP > 20 mmHg within 15–30 s, recovering by 45 s; young subjects; cardiac output–vascular resistance mismatch (not autonomic failure)
Delayed (late) OH	SBP steady for first 3–5 min then falls (sometimes only after 10 min tilt); early/mild adrenergic failure
Postprandial OH	BP fall within ~ 2 h of a large, high-carbohydrate meal $\pm$ alcohol (splanchnic pooling); elderly/autonomic patients

- **Neurogenic vs non-neurogenic OH** — a compensatory HR rise > 15 beats/min indicates *non-neurogenic* OH (volume depletion, drugs, cardiac); HR rise < 15 beats/min suggests **neurogenic OH**.
- A more accurate marker is the $\Delta\text{HR}/\Delta\text{SBP}$ ratio (cardiac baroreflex gain): < 0.5 beats/min/mmHg after 3 min strongly indicates NOH.

Etiology

Neurogenic OH (autonomic failure)	Non-neurogenic OH
Primary (synucleinopathies): Multiple system atrophy (MSA / Shy-Drager), Parkinson's disease with autonomic failure, Dementia with Lewy bodies, Pure autonomic failure (Bradbury-Eggleston)	Volume depletion: haemorrhage, vomiting/diarrhoea, dehydration, over-diuresis, dialysis
Secondary peripheral autonomic neuropathies: Diabetic autonomic neuropathy, amyloidosis (AL & hereditary ATTR), autoimmune autonomic ganglionopathy (anti-g-AChR $\alpha 3$), paraneoplastic, Sjögren, GBS, HIV, porphyria, alcoholic, B12 deficiency	Cardiac: heart failure, chronotropic incompetence, bradyarrhythmias
Hereditary: Familial dysautonomia (Riley-Day / HSAN III), dopamine β -hydroxylase (DBH) deficiency	Drug-induced (very common): α -blockers, diuretics, nitrates/vasodilators, tricyclics, phenothiazines/antipsychotics, dopamine agonists, antihypertensives
Spinal cord: traumatic quadriplegia, syringomyelia, MS	Endocrine: Addison disease, hypoadosteronism, pheochromocytoma; vasodilator excess (mastocytosis, carcinoid)

Clinical features

- ▶ **Cerebral hypoperfusion:** lightheadedness/dizziness on standing (commonest), presyncope, blurred or tunnel vision, cognitive slowing/"brain fog", **syncope and falls**.
- ▶ **Regional ischaemia:** "coat-hanger" neck/shoulder/sub-occipital pain (cervical-trapezius muscle ischaemia); **platypnea** (orthostatic dyspnoea from apical lung hypoperfusion); orthostatic angina; orthostatic headache.
- ▶ **Triggers:** rising in the morning (worst after bed rest), large meals/alcohol, heat, fever, exercise, hyperventilation, sepsis, surgery, intensified antihypertensives.
- ▶ Many patients — especially with chronic NOH — are **asymptomatic or present only with falls**, because cerebral autoregulation compensates; symptom reports alone are unreliable in the elderly.
- ▶ **Supine hypertension** coexists in >50% of autonomic-failure OH (baroreflex impairment), giving "reverse dipping" (higher nocturnal than morning BP) and end-organ damage.
- ▶ **Functional classes I–IV** grade severity from asymptomatic (class I) to severe daily disabling symptoms (class IV).

Investigations / autonomic testing

- ▶ **Bedside orthostatic vitals** — supine BP/HR, then BP/HR at **1 and 3 min** of standing (gold-standard bedside test); repeat as a single reading may mislead.
- ▶ **Tilt-table testing (60–70°)** with beat-to-beat finger arterial pressure — detects OH/NOH and distinguishes vasovagal, vasodepressor and cardioinhibitory syncope; pharmacologic provocation (nitroglycerin/isoproterenol) increases sensitivity.
- ▶ **Cardiovascular autonomic reflexes:** heart-rate variation to deep breathing and the **Valsalva manoeuvre/ratio** (parasympathetic/baroreflex), BP response to Valsalva (sympathetic adrenergic).
- ▶ **Sudomotor tests:** **QSART** (postganglionic sudomotor), **thermoregulatory sweat test** (pre- + postganglionic); **skin punch biopsy** for epidermal nerve fibre density and **phosphorylated α -synuclein** deposits (synucleinopathy).
- ▶ **Plasma catecholamines (supine + upright):** central/preganglionic NOH — normal supine NE that fails to rise on standing; peripheral/postganglionic — **low supine NE** (PAF often <200, even <100 pg/mL) failing to rise.
- ▶ **Bloods to find a cause:** CBC, metabolic panel, HbA1c/2-h GTT, B12, ferritin, vitamin D; serum free light chains/SPEP (amyloid); ganglionic AChR & paraneoplastic antibodies; TTR gene testing; fat-pad aspirate if amyloid suspected.

Management

Non-pharmacologic (first-line, often sufficient in mild/early OH):

- ▶ **Withdraw/reduce offending drugs** (diuretics, α -blockers, nitrates, tricyclics, antipsychotics, dopamine agonists) and correct iron/B12/D deficiency, anaemia, volume depletion.
- ▶ **↑Fluid to ~2–3 L/day and salt to 2 g, 2–3×/day**; a rapid **500 mL water bolus** gives a useful short-term pressor response.
- ▶ **Staged posture changes, physical counter-manoevres** (leg-crossing, leg/abdominal muscle tensing, squatting), **waist-high compression stockings** and an **abdominal binder** (reduces splanchnic pooling).
- ▶ **Head-of-bed elevation 30° at night** — reduces supine hypertension, nocturnal natriuresis and nocturia.

Drug	Class / action	Dose	Caution
Fludrocortisone	Mineralocorticoid — volume expansion + mild α -effect	0.1–0.2 (up to 0.4) mg morning	Supine HTN, hypokalaemia, oedema; check bone density long-term
Midodrine	Direct α_1 -agonist	2.5 mg TID → 15 mg TID (usual 7.5–10)	Onset 30–60 min, lasts ~4 h; last dose before 6 pm ; scalp tingling, piloerection, urinary urgency, supine HTN
Droxidopa	Norepinephrine precursor (newest agent, approved for NOH)	100 → 400–600 mg TID	Supine HTN; reduces falls in PD
Pyridostigmine	Cholinesterase inhibitor (↑ganglionic transmission)	30 → 60 mg TID	No supine HTN ; helps GI hypomotility; cramps/diarrhoea
Atomoxetine	NE-reuptake inhibitor (adjuvant)	18 mg morning	CNS stimulation, tremor, anxiety
Desmopressin (DDAVP)	↑water reabsorption	low oral/nasal at night	Reduces nocturia; monitor for hyponatraemia

- ▶ **Supine hypertension** complicating treatment: keep head of bed up, short-acting bedtime antihypertensive, monitor end-organ function; avoid long-acting pressors late in the day.
- ▶ **DBH deficiency** is uniquely treated by **droxidopa** (replaces absent norepinephrine).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Baroreflex arc on standing**: label — *gravitational blood pooling (lower limbs + splanchnic bed), ↓venous return / ↓stroke volume, aortic & carotid sinus baroreceptors, nucleus tractus solitarius (medulla), sympathetic efferent (norepinephrine → vasoconstriction, ↑HR,*

↑*contractility*), *vagal withdrawal*; mark the **site of failure in neurogenic OH** (reduced peripheral NE release).

- ▶ **Tilt-table tracing (BP & HR vs time):** label — *supine baseline (with supine hypertension ~175 mmHg), tilt-up, progressive sustained fall in SBP ≥ 20 mmHg, blunted/absent compensatory HR rise (< 15 bpm) = neurogenic OH* (contrast with POTS: HR rise ≥ 30 bpm without sustained OH).

Clinical / Diagnostic significance

- ▶ OH is an **independent predictor of falls, fractures, coronary heart disease, heart failure, stroke and death**; NOH carries a grim prognosis — mortality ~44% at 30 months and >60% at 10 years (Bradley: 64% 10-year mortality), mostly from synucleinopathies and diabetes.
- ▶ It is a **key early clue to MSA** (symptomatic OH within 2 years, poor levodopa response, “hot cross bun” pons sign, glial cytoplasmic α -synuclein inclusions; cardiac MIBG uptake preserved in MSA but reduced in PD/DLB/PAF).
- ▶ Distinguish from **POTS** (chronic orthostatic intolerance + HR rise ≥ 30 bpm [≥ 40 if < 19 yr] without sustained OH) and from **reflex/vasovagal syncope**.
- ▶ Always **measure both supine and standing BP at 1 and 3 min** in any patient with falls, syncope, dizziness, frailty or polypharmacy — the diagnosis is easily missed.

High-yield exam pointers

- ▶ OH = $\downarrow$ SBP ≥ 20 or $\downarrow$ DBP ≥ 10 mmHg within 3 min of standing/tilt ($\geq 30/15$ if supine HTN) — Freeman 2011 consensus.
- ▶ **Neurogenic vs non-neurogenic:** HR rise < 15 bpm or $\Delta\text{HR}/\Delta\text{SBP} < 0.5$ bpm/mmHg = neurogenic.
- ▶ **Initial OH** ($> 40/20$ mmHg, < 30 s, young, recovers by 45 s) is **not** autonomic failure; **delayed OH** is beyond 3 min.
- ▶ **Coat-hanger headache** (neck/shoulder muscle ischaemia) and **platypnea** are characteristic clues.
- ▶ Commonest **primary** cause = **synucleinopathies** (MSA/Shy-Drager, PD, DLB, PAF); commonest **secondary** = diabetic autonomic neuropathy; commonest **reversible** cause = **drugs**.
- ▶ **>50% of autonomic-failure OH have supine hypertension** (“reverse dipping”).
- ▶ First-line drugs: **fludrocortisone** and **midodrine**; **droxidopa** for NOH; **pyridostigmine** avoids supine HTN.
- ▶ **Midodrine last dose before 6 pm**; salt 2 g TID, fluids 2–3 L/day, **500 mL water bolus** = rapid pressor; **head-up tilt 30°** at night.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Disorders of the Autonomic Nervous System” (definition, variants, neurogenic vs non-neurogenic criteria, autonomic testing, full pharmacology and doses) and “Syncope” (orthostatic hypotension as sympathetic vasoconstrictor failure, causes, treatment algorithm).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Disorders of the Autonomic Nervous System” (normal orthostatic physiology, consensus criteria, differential diagnosis, 10-year mortality data, pure autonomic failure, DBH deficiency, drug-induced dysautonomia).
- ▶ **DeJong's The Neurologic Examination, 8e** — sympathetic/parasympathetic effector table.



Posterior circulation stroke

Asked in: Paper III May 2022 · Paper II May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — *Posterior (vertebrobasilar) circulation stroke* is ischemic infarction within the territory supplied by the paired **vertebral arteries**, the **basilar artery** and the paired **posterior cerebral arteries (PCAs)**, which together perfuse the brainstem, cerebellum, thalamus, occipital lobes and medial temporal lobes. Because the brainstem packs long tracts, cranial-nerve nuclei and reticular structures in close apposition, occlusion of each vessel produces its own distinctive, often eponymous syndrome. The hallmark of brainstem ischemia is “**crossed**” **findings** — ipsilateral cranial-nerve signs with contralateral long-tract (motor/sensory) signs. Basilar occlusion in particular is a treatable but potentially devastating emergency carrying high mortality.

Vascular anatomy (basis of localization)

- ▶ **Vertebral artery** — arises from the innominate artery on the right and the subclavian artery on the left; four segments: **V1** (origin to C6 transverse foramen), **V2** (C6→C2), **V3** (around the atlas to pierce dura at the foramen magnum), **V4** (intracranial). The two vertebrals join to form the basilar at the **pontomedullary junction**; only **V4** gives branches to brainstem/cerebellum.
- ▶ **Posterior inferior cerebellar artery (PICA)** — proximal segment supplies the **lateral medulla**; distal branches supply the inferior cerebellar surface.
- ▶ **Basilar artery** — supplies the base of the pons and superior cerebellum via **three branch groups**: (1) **paramedian** (7–10) → medial pontine wedge; (2) **short circumferential** (5–7) → lateral two-thirds of pons + middle/superior cerebellar peduncles; (3) **bilateral long circumferential** = **superior cerebellar (SCA)** and **anterior inferior cerebellar (AICA)** arteries → cerebellar hemispheres. The basilar divides into two PCAs in the **interpeduncular fossa**.
- ▶ **PCA origin variants** — both PCAs arise from the basilar bifurcation in **75%**; in **20%**, one arises from the ipsilateral ICA via the posterior communicating artery (“**fetal**” PCA); in **5%**, both arise

from the ICAs. PCA divides at the posterior communicating artery into a proximal **P1** (precommunal) and distal **P2** segment.

Aetiology and mechanisms

- ▶ **Atherothrombosis** — predilection for **V1 and V4** segments of the vertebral artery; basilar atheroma is most frequent in the **proximal basilar and distal vertebral** segments. In-situ thrombosis of small penetrating (perforator) branches causes lacunar brainstem strokes.
- ▶ **Embolism** — cardiac or artery-to-artery emboli from proximal vertebral/basilar lodge at the **top of the basilar** (“top-of-the-basilar” syndrome) or at the PCA.
- ▶ **Arterial dissection** — vertebral artery dissection (V2/V3 mobile segments; spontaneous, traumatic, or after **spinal manipulative therapy**); a vertebral dissection may extend into the basilar.
- ▶ **Fibromuscular dysplasia** and, rarely, **osteophytic** encroachment in the vertebral foramina.
- ▶ **Subclavian steal** — subclavian occlusion proximal to the vertebral origin reverses ipsilateral vertebral flow; ipsilateral arm exercise “steals” flow and provokes posterior-circulation TIAs.

Clinical syndromes by arterial territory

Artery / territory	Eponym	Key clinical features (source-grounded)
PCA – P1 (midbrain/thalamus)	Weber	Ipsilateral CN III palsy + contralateral hemiplegia (cerebral peduncle)
PCA – P1	Claude	Ipsilateral CN III palsy + contralateral cerebellar ataxia (red nucleus/dentatothalamic tract)
PCA – thalamogeniculate perforators	Déjérine-Roussy	Contralateral hemisensory loss → later searing/burning thalamic pain
PCA – artery of Percheron	—	Bilateral paramedian thalamic infarct: upgaze paresis, drowsiness, abulia
PCA – P2 (occipitotemporal)	—	Contralateral homonymous hemianopia (without macular sparing) ; alexia without agraphia; amnesia; peduncular hallucinosis
Bilateral distal PCA	Anton / Balint	Cortical blindness with denial (Anton); disordered visual scanning (Balint)

Artery / territory	Eponym	Key clinical features (source-grounded)
Vertebral/PICA – lateral medulla	Wallenberg	(see focused box)
Vertebral – medial medulla	Dejerine medial medullary	Contralateral hemiparesis sparing face + position-sense loss + ipsilateral tongue weakness (CN XII)
Basilar – complete	Locked-in	Quadriplegia + bilateral cranial-nerve signs, preserved consciousness
SCA	—	Severe ipsilateral cerebellar ataxia, N/V, dysarthria; contralateral pain/temp loss (limbs, body, face)
AICA	—	Ipsilateral deafness, facial weakness, vertigo, tinnitus, ataxia, Horner; contralateral pain/temp loss

Lateral medullary (Wallenberg) syndrome — high-yield focus

- **Cause** — embolic occlusion/thrombosis of the **V4 vertebral segment** in most cases; **PICA** occlusion in the remainder.
- **Ipsilateral** — facial pain/numbness (descending trigeminal tract), **Horner's syndrome** (descending sympathetic tract), cerebellar ataxia/falling to side of lesion, **dysphagia, hoarseness, palatal/vocal-cord palsy, diminished gag** (CN IX–X, nucleus ambiguus), vertigo/nystagmus (vestibular nuclei).
- **Contralateral** — impaired pain and temperature over the body (spinothalamic tract).
- **Key pearl** — **hemiparesis is NOT typical**; its presence points elsewhere. Dysphagia and aspiration risk dominate management.

Top-of-the-basilar and basilar occlusion

- **Top-of-the-basilar (embolic)** — sudden **bilateral** signs: ptosis, pupillary asymmetry/unreactive pupils, somnolence; vertical-gaze palsy; posturing and **myoclonic jerks simulating seizure**; visual and behavioural disturbances.
- **Complete basilar occlusion** — constellation of **bilateral long-tract signs (motor + sensory) with cranial-nerve and cerebellar dysfunction**; a “**locked-in**” state (preserved awareness, quadriplegia, anarthria, vertical eye/blink-only communication) indicates complete pontine + lower midbrain infarction. Carries **high mortality**.

- ▶ **Warning prodrome** — repetitive short-lived TIAs (5–30 min, several/day) with vertigo, diplopia, dysarthria, circumoral numbness; a “**herald hemiparesis**” may precede basilar occlusion. Recognising impending basilar occlusion *before* infarction is the therapeutic goal.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Posterior circulation arterial tree (Harrison Fig. 437-6):** Draw the two vertebral arteries uniting into the **basilar artery**, then the basilar bifurcating into both **posterior cerebral arteries**. Label: *Vertebral artery, Basilar artery, Posterior inferior cerebellar artery (PICA), Anterior inferior cerebellar artery (AICA), Superior cerebellar artery (SCA), Posterior cerebral artery (PCA), Posterior communicating artery, Deep penetrating (paramedian) branches of the basilar artery.*
- ▶ **Diagram 2 — Axial medulla for Wallenberg syndrome (Fig. 437-7):** Cross-section of medulla labelling the shaded **lateral medullary zone**: *Spinothalamic tract, Descending sympathetic tract (Horner), Nucleus ambiguus (CN IX–X), Vestibular nucleus, Spinal tract/nucleus of CN V, Inferior cerebellar peduncle (restiform body), Inferior olive, Pyramid (medial — spared).*

Clinical / Diagnostic significance

- ▶ **Imaging** — Non-contrast CT excludes haemorrhage but **frequently misses posterior-fossa infarcts** owing to bone (beam-hardening) artefact; look for the **hyperdense basilar artery sign** (intraluminal thrombus). CTA (aortic arch to vertex) confirms vertebral/basilar occlusion and selects thrombectomy targets. **MRI with DWI** is markedly superior to CT for brainstem/cerebellar ischemia.
- ▶ **Acute reperfusion** — **IV thrombolysis** with alteplase (rtPA 0.9 mg/kg, max 90 mg; 10% bolus) or tenecteplase 0.25 mg/kg IV bolus within 4.5 h of last-known-well, after excluding haemorrhage. **Endovascular mechanical thrombectomy** for large-vessel occlusion (ICA/M1–M2 or **basilar artery**) up to 24 h with perfusion-imaging selection in the 6–24 h window; **basilar thrombectomy can be life-saving**.
- ▶ **Cerebellar infarction is a neurosurgical emergency** — may mimic labyrinthitis (vertigo, vomiting); even small oedema obstructs the 4th ventricle/aqueduct causing **hydrocephalus** and **brainstem compression** → **coma and respiratory arrest**. **Suboccipital (posterior-fossa) decompression** is recommended for deteriorating patients and should precede significant brainstem compression. Head/neck pain should prompt suspicion of **vertebral dissection**.
- ▶ **Secondary prevention** — antiplatelet therapy / risk-factor control for atherothrombotic disease; anticoagulation for cardioembolism; dissection managed with antithrombotics. **Déjérine-Roussy thalamic pain** responds poorly to analgesics — use **carbamazepine, gabapentin, or tricyclic antidepressants**.

High-yield exam pointers

- ▶ Posterior circulation = **vertebrals + basilar + PCAs**; vertebrals fuse at the **pontomedullary junction**, basilar splits at the **interpeduncular fossa**.
- ▶ **Crossed signs** (ipsilateral CN + contralateral long tract) localize to the brainstem.
- ▶ **Wallenberg** = V4/PICA; vertigo, ipsilateral Horner + bulbar palsy + facial sensory loss, contralateral body pain/temp loss, **no hemiparesis**.
- ▶ **Weber** = CN III + contralateral hemiplegia; **Claude** = CN III + contralateral ataxia; **Benedikt-type** features (red nucleus tremor) overlap.
- ▶ **PCA P2** → homonymous hemianopia **without macular sparing**; bilateral → **Anton's syndrome** (cortical blindness with denial).
- ▶ **Locked-in syndrome** = ventral pontine infarct; conscious, quadriplegic, communicates by **vertical eye movements/blinking**.
- ▶ **Hyperdense basilar artery sign**; CT misses posterior-fossa strokes — get MRI-DWI.
- ▶ **Cerebellar infarct** → watch for hydrocephalus/herniation → **suboccipital decompression**.
- ▶ Reperfusion: **thrombolysis ≤4.5 h**, **thrombectomy ≤24 h** (basilar occlusion can be salvaged).

SOURCE & COVERAGE

Harrison 22e — Ch 437 “Introduction to Cerebrovascular Diseases” (posterior-circulation anatomy and clinical syndromes, Figs. 437-5 to 437-11) + Ch 438 “Ischemic Stroke” (thrombolysis, thrombectomy, cerebellar-infarct decompression). Coverage note: All territory syndromes, eponyms, anatomy, imaging and acute-management points above are sourced from these two chapters. *Benedikt's syndrome* is named as a standard textbook overlap of the P1 midbrain syndrome (red-nucleus involvement) but is not given that eponym verbatim in the provided text; the underlying lesion (dentatorubrothalamic/red nucleus with rubral tremor) is described. Vertebral-artery segmental anatomy detail and Brazis-style localization tables corroborate the same content.



Posterior Reversible Encephalopathy Syndrome

Asked in: Paper III Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Posterior Reversible Encephalopathy Syndrome (PRES) is a clinico-radiological syndrome of acute neurological dysfunction (headache, seizures, altered consciousness, visual loss) accompanied by characteristic **vasogenic oedema** that predominantly affects the **posterior (parieto-occipital) white matter**. Harrison groups it among the **hyperperfusion disorders**, in which seemingly diverse conditions — hypertensive encephalopathy, eclampsia, post-carotid endarterectomy syndrome and calcineurin-inhibitor/drug toxicity — share a final common pathway of **hyperperfusion**.

due to endothelial dysfunction. The term is partly a misnomer: the syndrome is *not always reversible* and is *not always limited to the posterior brain*.

Pathophysiology

- ▶ The brain maintains nearly **constant cerebral blood flow (CBF)** across a wide range of systemic pressures by **autoregulation** — arteriolar vasodilation when systemic BP falls and arteriolar vasoconstriction when it rises. **Cerebral perfusion pressure (CPP) = MAP – ICP**.
- ▶ Beyond the upper limit of autoregulation, flow becomes **pressure-dependent**, producing hyperperfusion. **Vasogenic oedema** is the primary process causing neurological dysfunction.
- ▶ Two mechanisms are proposed (both probably contribute in every case):
 - **Exceeding the cerebral autoregulatory threshold** → increased CBF with **capillary leakage of fluid into the interstitium** (the “increased-pressure / breakthrough” model).
 - **Direct impairment of the blood–brain barrier (BBB)** itself by toxic or autoimmune endothelial injury (the “endothelial-dysfunction” model).
- ▶ **Why posterior predilection?** The posterior (vertebrobasilar) circulation is postulated to have a **lower threshold for autoregulatory breakthrough** and/or a **vasculopathy that is more common in these vessels**, owing to relatively sparse sympathetic innervation.
- ▶ A **noninflammatory vasculopathy** (vascular narrowing, especially in the posterior circulation) may be seen on vessel imaging; whether it is a primary cause of the oedema or a secondary phenomenon remains unclear.

Etiology / Classification

Harrison (Table 318-3) divides the causes mechanistically into those dominated by **raised capillary pressure** and those dominated by **endothelial dysfunction**.

Mechanism	Representative etiologies
Increased capillary pressure dominates	Hypertensive encephalopathy, including secondary causes — renovascular hypertension, pheochromocytoma, cocaine use
	Post-carotid endarterectomy syndrome
	Pre-eclampsia / eclampsia
Endothelial dysfunction dominates	Calcineurin-inhibitor toxicity — cyclosporine, tacrolimus
	Chemotherapeutic agent toxicity — cytarabine, azathioprine, 5-fluorouracil, cisplatin, methotrexate, TNF- α antagonists
	HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)

Mechanism	Representative etiologies
	Hemolytic-uremic syndrome (HUS)

- ▶ **Drug culprits behave atypically:** cyclosporine (and other agents) can precipitate PRES even at low doses or after years of treatment, and a normal serum drug level does not exclude the drug as the trigger.
- ▶ **Rapidity of BP rise, rather than the absolute value of pressure, appears to be the most important risk factor** — explaining why PRES can occur at modest BP in previously normotensive patients (e.g., eclampsia, post-transplant).

Clinical features

- ▶ **Headache** — non-specific, ranging from mild to severe; no characteristic quality.
- ▶ **Seizures** — frequent and often the presenting event; of multiple types depending on the severity and location of oedema. **Nonconvulsive seizures occur**, so a **low threshold for EEG** must be maintained.
- ▶ **Altered consciousness** — a spectrum from confusion to coma.
- ▶ **Focal neurological deficits** — the typical deficit is **cortical visual loss** (cortical blindness), reflecting the **occipital-lobe** involvement; visual hallucinations and field defects may occur.
- ▶ **Any focal deficit can occur** depending on the territory affected — e.g., after carotid endarterectomy, deficits referable to the **ipsilateral, newly reperfused hemisphere**.

Investigations / Neuroimaging

- ▶ **MRI is the investigation of choice.** Classically shows **high T2 / FLAIR signal of oedema, predominantly in the posterior occipital lobes, not respecting any single vascular territory** (Harrison Fig. 318-7 — a patient on cyclosporine after liver transplant presenting with seizures, headache and cortical blindness, with bilateral occipital white-matter signal change).
- ▶ **CT is less sensitive** but may show **patchy hypodensity** in the involved territory.
- ▶ **Vessel imaging** (MRA/CTA/angiography) may demonstrate **vascular narrowing, especially in the posterior circulation** (the noninflammatory vasculopathy).
- ▶ **CSF analysis** is often performed to exclude mimics but **yields nonspecific results**.
- ▶ **EEG** — used liberally because nonconvulsive status epilepticus is common; **continuous EEG monitoring** is often required.
- ▶ Serum studies to identify the precipitant (BP trend, renal/hepatic function, platelets and LDH for HELLP/HUS, pregnancy status); remember that **normal calcineurin-inhibitor levels do not exclude drug-induced PRES**.

Management

- ▶ **Treat the precipitant and lower the blood pressure judiciously** — the two pillars of therapy.

- ▶ **Antihypertensive therapy (when BP is elevated):** use titratable IV agents — **labetalol** or **nicardipine** (per Ch 318). In the broader setting of a **hypertensive emergency** (SBP/DBP $\geq 180/100$ with end-organ damage), Harrison (Ch 288) lists **IV nicardipine** (most commonly used; avoid in severe aortic stenosis), **IV labetalol** (avoid in obstructive airways disease/COPD, bradycardia, second-/third-degree block) and **IV sodium nitroprusside**.
- ▶ **Controlled, not abrupt, BP reduction:** if BP is very high, **lower the MAP by ~20% initially**. Over-aggressive lowering may drop perfusion **below the patient's autoregulatory range and precipitate secondary ischaemia/infarction**. Aim for reduction rather than immediate normalisation, then transition to oral agents.
- ▶ **Remove / reduce the offending drug:** lower the dose of or discontinue the **calcineurin inhibitor** (cyclosporine, tacrolimus); **sirolimus** (few recorded neurotoxic cases) may be a reasonable alternative in transplant patients.
- ▶ **Seizure control:** identify and treat seizures; **anticonvulsants are effective** when seizure activity is documented. In the **special case of eclampsia**, **magnesium sulfate** is the agent of choice for seizure control (and definitive treatment is delivery of the fetus).
- ▶ **Treat the underlying medical condition** — e.g., delivery in eclampsia, management of HELLP/HUS, withdrawal of cocaine/sympathomimetics, resection of pheochromocytoma.
- ▶ **Supportive neurocritical care** — control of cerebral oedema and seizures, with serial imaging to confirm radiological resolution.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Axial brain MRI (FLAIR) in PRES** — draw both cerebral hemispheres at the occipital level; shade **bilateral, symmetric high-signal (white) areas in the parieto-occipital white matter**. Labels: *Occipital lobe (parieto-occipital white matter oedema), Bilateral / symmetric, Vasogenic oedema — high T2/FLAIR signal, Does not respect a single vascular territory, Relative cortical sparing, Posterior > anterior distribution.*
- ▶ **Cerebral autoregulation curve** — plot CBF (y-axis) against MAP/CPP (x-axis). Labels: *Autoregulatory plateau (constant CBF), Lower limit (below which CBF falls — ischaemia), Upper limit / breakthrough (above which CBF rises — hyperperfusion → vasogenic oedema → PRES), Arteriolar vasodilation (low BP), Arteriolar vasoconstriction (high BP).*

Clinical / Diagnostic significance

- ▶ PRES is a **treatable, frequently reversible cause of acute encephalopathy/seizures/cortical blindness** — prompt recognition and BP/drug control usually reverse the clinical and radiological abnormalities; delayed or excessive BP lowering risks **infarction and irreversible deficits**.

- ▶ **High-yield clinical contexts:** eclampsia/HELLP in obstetrics, post-transplant patients on calcineurin inhibitors, chemotherapy recipients, hypertensive emergency, renovascular hypertension and pheochromocytoma, and cocaine/sympathomimetic use.
- ▶ Always **review the full medication list** in any transplant or oncology patient presenting with headache, seizures or focal deficits — calcineurin-inhibitor PRES can occur with normal drug levels.
- ▶ Differentiate from **acute ischaemic stroke** (PRES oedema is bilateral, posterior and crosses vascular territories) and from **cerebral venous sinus thrombosis, vasculitis, and infective/autoimmune encephalitis**.

High-yield exam pointers

- ▶ PRES = vasogenic oedema of the posterior brain from hyperperfusion / endothelial dysfunction that breaches the upper limit of cerebral autoregulation or the BBB.
- ▶ **Tetrad:** headache, seizures, altered mentation, **cortical (occipital) visual loss**.
- ▶ **Two mechanistic classes:** *raised capillary pressure* (hypertensive encephalopathy, eclampsia, post-CEA) vs *endothelial dysfunction* (calcineurin inhibitors, chemotherapy, HELLP, HUS).
- ▶ **MRI:** bilateral parieto-occipital T2/FLAIR hyperintensity **not confined to one vascular territory**; CT less sensitive.
- ▶ **Rate of BP rise matters more than the absolute BP** — PRES can occur at near-normal pressures.
- ▶ **Treatment:** judicious IV BP control (labetalol / nicardipine; nitroprusside), **lower MAP by ~20% initially**, withdraw the offending drug, control seizures (**magnesium sulfate in eclampsia**).
- ▶ **“Reversible” is conditional** — irreversibility/infarction follows delayed treatment or over-aggressive BP lowering.
- ▶ **Normal calcineurin-inhibitor serum levels do not exclude drug-induced PRES.**

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 318 “Nervous System Disorders in Critical Care”** (Hyperperfusion Disorders / PRES section, Table 318-3, Fig. 318-7, and the cerebral-autoregulation/CPP discussion) and **Ch 288 “Hypertension”** (hypertensive urgencies and emergencies; IV nicardipine/labetalol/sodium nitroprusside, reduction-not-normalisation principle). **Coverage note:** the topic spec flags PRES as thinly covered; Harrison presents PRES under “hyperperfusion disorders” rather than as a stand-alone chapter, and does not give formal epidemiology, an exact MAP/BP autoregulatory cut-off, or DWI/ADC criteria. The statement that PRES oedema is **vasogenic** (facilitated rather than restricted diffusion on DWI/ADC, distinguishing it from cytotoxic infarction) is universally accepted standard neuroradiology added for completeness but is not stated verbatim in the provided chapters.



Primary headaches

Asked in: Paper III Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Primary headaches are disorders in which headache and its associated features constitute the disease itself, without an exogenous structural, infective, vascular, metabolic, or toxic cause. The major groups are **migraine**, **tension-type headache (TTH)**, **trigeminal autonomic cephalalgias (TACs)**, and other primary headache disorders. Diagnosis is clinical, but the first duty in an examination answer and in practice is to exclude secondary headache when red flags are present.

Classification

ICHD-3 group	Important subtypes	Examination anchors
Migraine	Without aura; with aura; brainstem aura; hemiplegic migraine; retinal migraine; chronic migraine; complications such as status migrainosus and migrainous infarction	Recurrent 4-72 h attacks; nausea/vomiting or photophobia-phonophobia; aggravated by activity; normal examination between attacks
Tension-type headache	Infrequent episodic; frequent episodic; chronic; probable TTH	Bilateral tight/band-like pressure, mild-moderate, no vomiting, not worsened by routine activity
TACs	Cluster headache; paroxysmal hemicrania; SUNCT/SUNA; hemicrania continua	Strictly unilateral orbital/temporal pain with ipsilateral cranial autonomic signs
Other primary headaches	Cough, exercise, sexual-activity, thunderclap, cold-stimulus, external-pressure, primary stabbing, nummular, hypnic, new daily persistent headache	Diagnosis only after excluding mimics appropriate to the trigger and phenotype

- ▶ Chronic daily headache means headache on **15 or more days/month**; it is descriptive, not one diagnosis. Important primary causes are chronic migraine, chronic TTH, hemicrania continua, hypnic headache, SUNCT/SUNA, and new daily persistent headache.
- ▶ **Medication-overuse headache** is not a primary subtype but commonly complicates migraine or chronic daily headache and must be actively looked for.

Pathophysiology

- ▶ Pain-sensitive cranial structures include scalp, meningeal arteries, dural venous sinuses, falx, and proximal large pial arteries.
- ▶ Primary headache pathways center on the **trigeminovascular/trigeminocervical system**: meningeal and cervical afferents project through the trigeminal ganglion to the trigeminal

nucleus caudalis and upper cervical cord, then to thalamic, hypothalamic, brainstem, and cortical networks.

- ▶ In **migraine**, brainstem and hypothalamic sensory-modulation dysfunction produces abnormal sensitivity to light, sound, movement, smell, and cutaneous input. Trigeminal activation releases CGRP, PACAP and other neuropeptides, explaining the efficacy of gepants and CGRP monoclonal antibodies.
- ▶ Migraine aura is best explained by **cortical spreading depression**, a slowly propagating wave of neuronal and glial depolarization followed by suppression, typically beginning in occipital cortex.
- ▶ In TACs, pain is trigeminal, while ipsilateral lacrimation, conjunctival injection, nasal congestion, rhinorrhea, aural fullness, ptosis or miosis reflect cranial parasympathetic activation and sympathetic dysfunction. Cluster headache is linked to posterior hypothalamic/circadian mechanisms.
- ▶ Primary headaches are **not simply vascular headaches**; vascular changes are secondary epiphenomena and do not predict treatment response.

Migraine

- ▶ **Clinical phases**: premonitory phase with yawning, sleepiness, fatigue, cognitive fog, mood change, neck discomfort, polyuria/polydipsia or cravings; aura in about one-quarter to one-third; headache phase; and postdrome with tiredness and impaired concentration.
- ▶ **Diagnostic criteria**: repeated attacks lasting 4-72 h, normal examination, no better cause, with at least two of unilateral pain, throbbing quality, moderate/severe intensity, aggravation by movement; and at least one of nausea/vomiting or photophobia and phonophobia.
- ▶ **Aura** is usually visual, with scintillating scotoma, zigzags or field defects spreading over minutes and resolving within 60 min; sensory, language, brainstem and hemiplegic auras are recognized. Aura without headache may mimic TIA, especially after 40 years.
- ▶ **Triggers/activators**: altered sleep, missed meals, let-down after stress, exertion, weather change, menstruation, alcohol, nitrates, odors, glare and noise.
- ▶ **Acute treatment**: treat early, use adequate dose, avoid repeated ineffective dosing and overuse. Options include NSAIDs; acetaminophen-aspirin-caffeine for mild-moderate attacks; triptans; ergots; gepants; lasmiditan; dopamine antagonists; and selected neuromodulation.

Acute class	Examples and key points
NSAIDs/analgesics	Ibuprofen 400 mg, naproxen 220-550 mg, diclofenac K 50 mg; best early; simple analgesics limited to ≤15 days/month
Triptans	Sumatriptan 50-100 mg PO or 3-6 mg SC; rizatriptan 5-10 mg; zolmitriptan 2.5 mg PO or 5 mg

Acute class	Examples and key points
	nasal; avoid in ischemic cardiac/cerebrovascular/peripheral vascular disease and uncontrolled hypertension
Gepants	Rimegepant 75 mg ODT; ubrogepant 50-100 mg, repeat after 2 h if needed; zavegepant 10 mg intranasal
Ditans	Lasmiditan 50-200 mg once; no vasoconstriction; no driving for 8 h
Antiemetic/prokinetic	Metoclopramide 10-20 mg IV/PO, prochlorperazine 5-10 mg; useful with nausea, vomiting, gastric stasis, ED migraine

- ▶ **Prevention** is indicated for frequent or disabling attacks, increasing frequency, poor acute response, contraindications to abortives, or chronic migraine. Harrison suggests considering prevention at **≥ 4 migraine days/month**; CMDT uses more than 2-3/month or significant disability.
- ▶ Preventives include propranolol 40-120 mg bid, metoprolol 25-100 mg bid, amitriptyline 10-75 mg nocte, venlafaxine 75-150 mg/day, topiramate 25-200 mg/day, valproate 400-600 mg bid, candesartan 4-24 mg/day, CGRP monoclonal antibodies, rimegepant alternate-day, atogepant daily, and onabotulinum toxin A for chronic migraine.
- ▶ Start low, titrate, allow **2-12 weeks** or longer, continue about **6-12 months** after stabilization, then consider slow taper. Avoid or use topiramate/valproate cautiously in women of reproductive age.

Tension-type headache

- ▶ **Phenotype**: bilateral tight, pressing, band-like discomfort that builds slowly, fluctuates, and may persist for days; often generalized or occipitocervical; pericranial tenderness may occur.
- ▶ **Episodic vs chronic**: chronic TTH is headache on **≥ 15 days/month**; it may persist for years and overlap clinically with chronic migraine.
- ▶ **Diagnostic distinction from migraine**: pure TTH lacks nausea, vomiting, photophobia, phonophobia, osmophobia, throbbing, focal neurologic symptoms, and aggravation by routine activity.
- ▶ **Treatment**: simple analgesics such as acetaminophen, aspirin or NSAIDs for occasional attacks; avoid frequent combination analgesics, opioids and barbiturates. Relaxation, sleep hygiene, physical therapy, biofeedback and management of anxiety/depression help selected patients.
- ▶ **Prevention**: amitriptyline is the best-supported drug for chronic TTH; other tricyclics may be tried if not tolerated. Triptans do not help pure TTH, although they may help when apparent TTH occurs in a patient with comorbid migraine.

Trigeminal autonomic cephalalgias

Disorder	Attack pattern	Autonomic features	Specific treatment clue
Cluster headache	Excruciating unilateral orbital/temporal pain, 15-180 min, 1 every other day to 8/day; bouts for weeks with remission; nocturnal attacks common	Ipsilateral lacrimation, conjunctival injection, rhinorrhea/nasal congestion, aural fullness, ptosis/miosis; restlessness	Acute: 100% oxygen 10-12 L/min for 15-20 min, sumatriptan 6 mg SC, sumatriptan 20 mg or zolmitriptan 5 mg nasal. Prevent: verapamil 160-960 mg/day with ECG monitoring; prednisone bridge, occipital steroid injection, galcanezumab, topiramate, lithium, melatonin
Paroxysmal hemicrania	Severe unilateral orbital/temporal attacks, 2-45 min, usually >5/day	Prominent ipsilateral autonomic signs	Complete response to indomethacin 25-75 mg tid is diagnostic and therapeutic
SUNCT/SUNA	Very short unilateral orbital/temporal stabs, 5-240 s, often many/day	SUNCT has conjunctival injection and tearing; SUNA has cranial autonomic symptoms without both	Acute therapy usually impractical; IV lidocaine in hospital; prevention with lamotrigine 200-400 mg/day, topiramate or gabapentin
Hemicrania continua	Continuous unilateral moderate pain with severe exacerbations	May have conjunctival injection, lacrimation, photophobia on pain side	Complete response to indomethacin; trial 25 mg tid escalating to 50-75 mg tid

- ▶ TACs are often misdiagnosed as sinus headache because of nasal congestion and rhinorrhea; decongestants are ineffective.
- ▶ Consider MRI brain with pituitary views and pituitary function tests in atypical, refractory, bilateral or suspicious TACs.

Other primary headaches and medication overuse

- ▶ **Primary cough headache:** sudden generalized pain precipitated by cough, sneeze, straining, laughing or stooping, lasting seconds to minutes; diagnose only after excluding Chiari malformation, posterior fossa lesions, aneurysm, CSF leak and other causes. Indomethacin 25-50 mg two to three times daily, or 75-150 mg/day, is effective.
- ▶ **Primary exercise headache:** bilateral throbbing precipitated by sustained exercise, lasting up to 48 h; exclude SAH, intracranial hypertension, pheochromocytoma and **cardiac cephalalgia**.

- ▶ **Sexual-activity headache:** dull bilateral ache increasing with excitement or explosive orgasmic headache; exclude SAH, dissection, RCVS and pheochromocytoma. Options include stopping activity, propranolol 40-200 mg/day, diltiazem 60 mg tid, or pre-emptive indomethacin 25-50 mg/triptan/gepant.
- ▶ **Primary thunderclap headache** is a diagnosis of exclusion after CT/MRI, vascular imaging as indicated and CSF examination exclude SAH, RCVS, dissection, venous thrombosis and pituitary apoplexy.
- ▶ **Primary stabbing headache** causes seconds-long irregular “ice-pick” pains without autonomic features; reassurance is often enough, with indomethacin for frequent disabling attacks.
- ▶ **Hypnic headache** wakes older patients from sleep, usually without autonomic features; bedtime caffeine, lithium 200-600 mg, indomethacin or melatonin may help.
- ▶ **New daily persistent headache** begins abruptly and remains daily from onset; exclude secondary causes such as CSF leak and cerebral venous sinus thrombosis, then treat according to migraine or TTH phenotype.
- ▶ **Medication overuse:** opioids, barbiturate combinations, ergots and triptans over >10 days/month, and acetaminophen/aspirin/NSAIDs over >15 days/month, can perpetuate daily headache. Treat by withdrawal/taper, diary, bridge therapy where appropriate, and early prevention for the underlying headache.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Trigeminovascular pathway:** dura/meningeal vessels -> trigeminal ganglion -> trigeminocervical complex -> quintothalamic tract -> thalamus -> cortex; modulators labelled hypothalamus, dorsal raphe, locus coeruleus, nucleus raphe magnus, superior salivatory nucleus, sphenopalatine ganglion, CGRP release.
- ▶ **Migraine attack timeline:** prodrome -> aura -> headache phase -> postdrome; label yawning/food craving/polyuria, scintillating scotoma, unilateral throbbing pain with nausea-photophobia-phonophobia, fatigue/cognitive fog.

Clinical / Diagnostic significance

- ▶ Always screen for **SNNOOP10** red flags: systemic symptoms, neoplasm, neurologic deficit, sudden onset, older age >50, pattern change, positional headache, cough/exertion trigger, papilledema, progressive atypical headache, pregnancy/puerperium, painful eye with autonomic features, trauma, immunosuppression, and painkiller overuse/new drug.
- ▶ Neuroimaging is urgent for abnormal neurologic examination, altered mental status, papilledema, meningeal signs, thunderclap headache, new headache in HIV, or new headache after 50. LP follows imaging when meningitis or SAH remains possible.

- ▶ A normal examination between attacks supports primary headache, but does not by itself exclude secondary headache when the history is new, abrupt, progressive, positional, exertional, cancer-related, febrile, immunosuppressed, pregnant/postpartum, or associated with visual loss.
- ▶ Migraine is often mistaken for sinus headache because facial pain and autonomic symptoms can occur. Cluster headache is distinguished by shorter attacks, periodicity, ipsilateral autonomic features and restlessness.
- ▶ Examine temporal arteries, fundus, ocular movements, pupils, neck stiffness, BP, visual fields, and cranial nerves; Horner syndrome with acute pain suggests cluster headache but also carotid dissection.

High-yield exam pointers

- ▶ Define primary headache as headache without exogenous cause, then classify into **migraine**, **TTH**, **TACs** and **other primary headaches**.
- ▶ Write migraine diagnostic criteria: **4-72 h**, at least 2 pain features, at least 1 associated feature, normal examination/no better cause.
- ▶ Mention migraine phases and that **aura occurs in only a minority**, so absence of aura does not exclude migraine.
- ▶ Do not call migraine a vascular headache; write **brain disorder of sensory processing with trigeminovascular CGRP biology**.
- ▶ Cluster headache: **male predominance**, **orbital pain**, **15-180 min**, **autonomic signs**, **restlessness**, **oxygen + SC sumatriptan**, **verapamil with ECG**.
- ▶ Paroxysmal hemicrania and hemicrania continua are **indomethacin-responsive**; SUNCT/SUNA responds best preventively to **lamotrigine**.
- ▶ Chronic migraine is **≥ 15 headache days/month with ≥ 8 migraine days/month**; chronic daily headache always needs medication-overuse assessment.
- ▶ Avoid opioids and butalbital combinations in recurrent headache; they promote rebound and medication-overuse headache.
- ▶ First presentation of thunderclap, cough, exertional or sexual headache is not “primary” until dangerous secondary causes are excluded.

SOURCE & COVERAGE

Harrison 22e — “Headache”; “Migraine and Other Primary Headache Disorders”; Bradley & Daroff’s Neurology in Clinical Practice — “Headache and Other Craniofacial Pain”; DeJong’s The Neurologic Examination — “The Trigeminal Nerve”; CMDT 2026 — “Common Symptoms” and “Nervous System Disorders”.



Recent Advances in the Management of Migraine

Asked in: Paper III Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Migraine is a recurring syndrome of headache (typically unilateral, throbbing, lasting 4–72 h, aggravated by movement) associated with neurologic dysfunction in varying admixtures — nausea/vomiting, photophobia, phonophobia, osmophobia and, in ~20–25%, aura. It is the most common disabling neurologic disorder worldwide, affecting ~15% of women and ~6% of men annually. The last decade has transformed its treatment: clarification of the **calcitonin gene-related peptide (CGRP)** pathway and of serotonin-receptor subtypes has produced four mechanism-specific drug classes — *gepants*, *ditans*, *CGRP monoclonal antibodies* — plus several non-invasive neuromodulation devices, giving the first migraine-specific options that are safe in vascular disease.

Pathophysiological basis driving new therapy

- ▶ Migraine is a disorder of **sensory processing**: dysfunction of monoaminergic/brainstem and hypothalamic control systems (locus coeruleus, dorsal raphe, periaqueductal grey) and activation of the **trigeminovascular system** (trigeminal ganglion → trigeminocervical complex → quintothalamic tract → thalamus).
- ▶ Activated trigeminal neurons release vasoactive neuropeptides — **CGRP** and **pituitary adenylate cyclase-activating polypeptide (PACAP)**. Jugular venous CGRP rises during an attack and normalises with sumatriptan; IV CGRP infusion triggers migraine in migraineurs but not controls — the rationale for anti-CGRP drugs.
- ▶ **Serotonin (5-HT) receptors**: triptans are 5-HT_{1B/1D} agonists (1B = cranial vasoconstriction; 1D = neuronal); the 5-HT_{1F} receptor lies on neural (not vascular) tissue — selectively targeted by *ditans*, allowing efficacy without vasoconstriction.
- ▶ **Dopamine** hypersensitivity explains premonitory symptoms and the utility of dopamine antagonists.
- ▶ *Familial hemiplegic migraine (FHM)* genetics confirm a channelopathy: **CACNA1A** (Cav2.1 P/Q calcium channel) = FHM1 (~50%); **ATP1A2** (Na⁺/K⁺-ATPase) = FHM2 (~20%); **SCN1A** (neuronal Na⁺ channel) = FHM3. Aura correlates with cortical spreading depression.

Principles & goals of modern management

- ▶ **Assess disability** with the validated *Migraine Disability Assessment Score (MIDAS)*: Grade I 0–5, II 6–10, III 11–20, IV >20.
- ▶ **Two arms** — *acute (abortive)* for individual attacks and *preventive (prophylactic)*. Treat acutely **early and adequately**; if relief is incomplete by 60 min, escalate dose or switch class for future attacks.
- ▶ **Start preventives** when there are **≥4 migraine days/month**, or attacks that are prolonged, disabling or poorly responsive to acute drugs. Titrate slowly; expect a 2–12 week lag; continue 6–12 months then taper. Target **≥50% reduction** in headache days.

- ▶ **Patient education**, trigger management, regular sleep/meals/hydration, avoidance of the “let-down” effect, biofeedback and a headache diary remain foundational and reduce medication-overuse risk.
- ▶ **Chronic migraine** = headache on ≥ 15 days/month, ≥ 8 of them migrainous, for ≥ 3 months.

Recent advances in ACUTE therapy

Class / Agent	Mechanism	Dose	Key point
Gepants (oral) — rimegepant; ubrogepant	Small-molecule CGRP-receptor antagonists	Rimegepant 75 mg ODT; ubrogepant 50/100 mg, may repeat at 2 h	No vasoconstriction; very well tolerated; effective on repeat dosing (unlike triptans); safe in CVD
Gepant (nasal) — zavegepant	CGRP-receptor antagonist	10 mg intranasal, single spray	Rapid; useful for early nausea/vomiting
Ditan — lasmiditan	Selective 5-HT _{1F} agonist	50/100/200 mg PO, once/24 h	No vascular effect → fills the gap for cardio- /cerebrovascular disease; dizziness ~15%, somnolence ~6%; no driving for 8 h
Newer triptan/ergot routes	5-HT _{1B/1D} agonists	DHE inhaled/nasal (Trudhesa); SC sumatriptan via needle-free device	Improved absorption/onset; co-give naproxen 500 mg with sumatriptan to cut recurrence
Dopamine antagonists	D ₂ blockade + prokinetic	Metoclopramide/prochlorperazine 10 mg IV	Prochlorperazine superior to hydromorphone in the ED
Neuromodulation (acute)	Device-based	sTMS, nVNS, remote electrical neuromodulation (REN, upper- arm), supraorbital, eCOT-NS	FDA-cleared, drug- free; useful when drugs fail or are contraindicated

- ▶ Gepants and ditans render significantly more patients **pain-free at 2 h** and **most-bothersome-symptom-free** than placebo in phase-3 trials; gepants achieve pain freedom in ~20% and pain relief in ~60% within 2 h.
- ▶ **Opioids and butalbital are discouraged** — they do not treat the mechanism, blunt future triptan response and drive medication-overuse headache.

Recent advances in PREVENTIVE therapy

Agent	Target	Regimen
Erenumab	CGRP receptor (only mAb against the receptor)	70 or 140 mg SC monthly
Fremanezumab	CGRP ligand	225 mg SC monthly <i>or</i> 675 mg SC q3 months
Galcanezumab	CGRP ligand	240 mg loading, then 120 mg SC monthly
Eptinezumab	CGRP ligand	100 or 300 mg IV every 3 months
Atogepant (oral gepant)	CGRP receptor	10/30/60 mg once daily
Rimegepant (oral gepant)	CGRP receptor	75 mg every other day (also acute — first dual-use drug)
OnabotulinumtoxinA	Blocks glutamate/peptide release	155 U (PREEMPT protocol) q12 weeks — chronic migraine only

- ▶ The **CGRP monoclonal antibodies** are the headline advance: efficacy often **within the first month**, monthly/quarterly dosing, excellent tolerability (main effect = injection-site reaction ± constipation), and they **work even after failure of up to four prior preventives**. Approved for both episodic and chronic migraine.
- ▶ *AHS consensus criteria* for starting CGRP-targeted prevention: 4–7 monthly headache days with moderate disability after ≥2 trials of established preventives; 8–14 days at any disability after ≥2 trials; chronic migraine after 2 oral preventive trials or 2 onabotulinumtoxinA cycles.
- ▶ **Traditional preventives still first-line / cost-effective**: propranolol/metoprolol/timolol, topiramate, sodium valproate (FDA-approved); amitriptyline, candesartan, flunarizine, venlafaxine. *Topiramate and valproate are now avoided in reproductive-age women* (teratogenicity — neural-tube defects, reduced cognition).
- ▶ **Preventive neuromodulation** (sTMS, nVNS, REN, supraorbital stimulation) is FDA-cleared and well tolerated.
- ▶ onabotulinumtoxinA is effective only in **chronic** migraine (PREEMPT 1 & 2: –8.4 vs –6.6 headache days); **negative in episodic** migraine.

Special situations

- ▶ **Menstrual migraine**: short-term *perimenstrual prophylaxis* (days –2/–3 to +3) with naproxen, a long-acting triptan (frovatriptan/naratriptan/zolmitriptan), oestrogen patch, or **rimegepant during menses**.
- ▶ **Status migrainosus**: IV valproate, IV prochlorperazine + DHE; IV **dexamethasone 10 mg** reduces recurrence; avoid opioids.

- ▶ **Medication-overuse headache (MOH):** caution if ≥ 2 headache days/week. Limit simple analgesics to ≤ 15 days/month and triptans/ergots/opioids/combination analgesics to ≤ 9 –10 days/month; lasmiditan and gepants are **not** linked to MOH; early CGRP-directed prevention aids analgesic withdrawal.
- ▶ **Cardiovascular disease / migraine-with-aura:** avoid triptans and ergots (vasoconstriction) and combined oral contraceptives (stroke risk, OR ~ 6 with aura); prefer **ditans, gepants and CGRP mAbs** (though CGRP's physiologic vasodilatory role warrants caution pending long-term data).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Trigeminovascular pathway (label):** meningeal/dural vessels $\rightarrow$ *trigeminal ganglion* $\rightarrow$ *trigemino-cervical complex (TCC)* $\rightarrow$ *quintothalamic tract* (decussating) $\rightarrow$ *thalamus* $\rightarrow$ cortex; modulators *dorsal raphe nucleus, locus coeruleus, nucleus raphe magnus, hypothalamus, periaqueductal grey*; mark **CGRP/PACAP** release at vascular terminals — annotate drug sites: triptans/ditans at TCC, gepants/anti-CGRP mAbs at the peptide/receptor.
- ▶ **Management algorithm box:** *Acute* (NSAID $\rightarrow$ triptan/gepant/ditan $\rightarrow$ DHE/SC sumatriptan/neuromodulation) vs *Preventive* (β -blocker/topiramate/amitriptyline/candesartan $\rightarrow$ CGRP mAb / atogepant / rimegepant; onabotulinumtoxinA 155 U for chronic migraine).

Clinical / Diagnostic significance

- ▶ Diagnosis is clinical (IHS/ICHD-3 criteria); imaging only for red flags. Migraine with aura is an independent **stroke risk factor**, magnified by smoking and oestrogen-containing contraceptives.
- ▶ The new classes resolve two long-standing problems: a **vascular-safe acute option** (ditans, gepants) and **rapid, tolerable, mechanism-specific prevention** (CGRP mAbs, oral gepants).
- ▶ A single drug — **rimegepant** — now serves both acute and preventive roles, simplifying regimens.

High-yield exam pointers

- ▶ **CGRP** is the central therapeutic target: jugular CGRP rises in attacks; IV CGRP provokes migraine.
- ▶ **Gepants** = small-molecule CGRP-receptor antagonists (rimegepant, ubrogepant, zavegepant); acute *and* preventive use; no vasoconstriction.
- ▶ **Ditans** = lasmiditan, selective 5-HT_{1F} agonist; safe in CVD; dizziness/somnolence; no driving 8 h.
- ▶ **CGRP mAbs:** erenumab targets the **receptor**; fremanezumab, galcanezumab, eptinezumab target the **ligand**; eptinezumab is the only IV one.
- ▶ **onabotulinumtoxinA 155 U (PREEMPT)** — chronic migraine only; ineffective in episodic.

- ▶ Start prevention at ≥ 4 migraine days/month; chronic migraine = ≥ 15 headache/ ≥ 8 migraine days/month for ≥ 3 months.
- ▶ FHM genes: CACNA1A (1), ATP1A2 (2), SCN1A (3) — a channelopathy.
- ▶ Avoid opioids/butalbital; topiramate/valproate avoided in reproductive-age women.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Migraine and Other Primary Headache Disorders” (pathophysiology, CGRP/PACAP, 5-HT_{1F}/ditans, gepants, CGRP monoclonal antibodies, acute and preventive treatment tables, neuromodulation, MIDAS, FHM genetics).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Headache and Other Craniofacial Pain” (CGRP-targeted therapies, AHS consensus criteria, PREEMPT/onabotulinumtoxinA, chronic and menstrual migraine, medication-overuse headache).
- ▶ **CMDT 2026** — “Nervous System Disorders” (current acute drug doses, lasmiditan, gepant dosing, Table 27–1 pharmacologic prophylaxis including CGRP mAbs/gepants, neuromodulation, MOH thresholds).



Restless Legs Syndrome (Willis–Ekbom Disease)

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — Restless legs syndrome (RLS), also called *Willis–Ekbom disease*, is a common sensorimotor neurological disorder characterised by an **irresistible urge to move the legs**, usually accompanied by an unpleasant deep “creepy-crawly” sensation, that appears at **rest**, is **relieved by movement**, and shows a **circadian (evening/night) predominance**. It was first described by the English physician *Thomas Willis* in the seventeenth century and is now recognised as a bona-fide movement disorder. It affects roughly **5–10% of adults** (1–5% by some series; rare in Asians), is commoner in **women and older adults**, and in ~80% of patients coexists with **periodic limb movements (PLMs)** of sleep. The neurological examination is characteristically normal, and diagnosis is **clinical**.

Clinical features and the IRLSSG essential criteria

RLS is a **clinical diagnosis**; the *International Restless Legs Syndrome Study Group (IRLSSG)* requires **five essential criteria** (mnemonic **URGE** — Urge to move, Rest-induced, Gets better with movement, Evening worsening, plus an exclusion clause):

#	Essential criterion (IRLSSG)
1	An urge to move the legs , usually but not always accompanied by uncomfortable/unpleasant leg sensations
2	Urge begins or worsens during rest or inactivity (lying down, sitting)
3	Urge is partially or totally relieved by movement (walking, stretching), at least as long as activity continues
4	Urge occurs only or is worse in the evening/night than during the day (circadian pattern)
5	The features are not solely accounted for by another condition (leg cramps, myalgia, arthritis, venous stasis, positional discomfort, habitual foot tapping)

- ▶ The dysaesthesia is typically a **creepy-crawly, tingling, pulling or deep aching** discomfort in the calves/thighs; 30–50% report frank pain (an ache rather than a sharp burning).
- ▶ Symptoms usually **begin in the legs** but may spread to or begin in the **upper limbs** in severe disease; usually **bilateral**.
- ▶ **Supportive features** (aid diagnosis in doubtful cases): PLMs in sleep/wakefulness greater than expected for age, **response to dopaminergic therapy**, **positive family history** in first-degree relatives, and **lack of profound daytime sleepiness**.
- ▶ **Course specifiers**: *Intermittent* (<2 episodes/week on average) vs *Chronic-persistent* (≥2/week for the past year). The DSM-5 additionally requires symptoms ≥3 times/week for ≥3 months.
- ▶ Consequences: chronic **sleep-onset/maintenance insomnia**, poor-quality sleep, daytime sleepiness, and association with **depression, anxiety and hypertension**.

Classification and aetiology (primary vs secondary)

Type	Features / Causes
Primary (idiopathic)	Often familial (≈1/3 have affected relatives), early onset in the third decade; strong genetic component; >150 risk variants identified — strongest in MEIS1, BTBD9, PTPRD (also MAP2K5/LBXCOR)
Secondary / comorbid	Iron deficiency / ferritin deficiency (commonest treatable cause), pregnancy , uraemia / chronic renal failure , peripheral neuropathy (diabetic, uraemic), Parkinson disease, multiple sclerosis, ALS, myelopathy/radiculopathy, rheumatoid arthritis, hypothyroidism, gastrectomy, anaemia (folate)

Type	Features / Causes
Drug-induced / aggravating	Antidepressants (TCAs, SSRIs, venlafaxine — <i>not</i> bupropion), antihistamines, dopamine antagonists (neuroleptics, antiemetics), lithium, some calcium-channel blockers (nifedipine), caffeine, alcohol, nicotine

Pathophysiology — the iron–dopamine hypothesis

- ▶ The site of CNS dysfunction is not fully defined, but the leading model is **brain iron deficiency coupled with dopaminergic dysfunction** (the *iron–dopamine connection*).
- ▶ **Iron** is an essential cofactor for **tyrosine hydroxylase**, the rate-limiting enzyme of dopamine synthesis; low CNS iron reduces dopamine output and decreases the number of **D2 receptor** binding sites — explaining why iron deficiency precipitates RLS and dopaminergics relieve it.
- ▶ CSF analysis, special-sequence MRI (reduced R2 *in* substantia nigra *and* red nucleus) *and neuropathology show reduced regional brain iron / ferritin** despite often-normal peripheral iron.
- ▶ Neurophysiology (increased cortical excitability, reduced subcortical inhibition, increased spinal flexor-reflex excitability during sleep) localises dysfunction to **subcortical and spinal** circuits; the spinal mechanism helps explain PLMs.
- ▶ A genetic predisposition interacts with iron/dopamine handling — notably **no genetic linkage to iron metabolism genes** has been found despite the iron phenotype.

Periodic limb movements (PLMs) and PLMD

- ▶ ~80% of RLS patients have **periodic limb movements of sleep (PLMS)**; many also have PLMs of wakefulness (PLMW).
- ▶ PLMS are **stereotyped, repetitive movements** resembling a *triple-flexion reflex* — extension of the great toe with **dorsiflexion of the ankle**, sometimes knee/hip flexion.
- ▶ Polysomnographic definition: duration **0.5–10 s**, recurring every **20–40 s** (range 5–90 s), in runs of **≥4 consecutive** movements, predominantly during **NREM** sleep; they cause brief EEG **arousals** that fragment sleep.
- ▶ **Periodic limb movement disorder (PLMD)** is a *separate* ICSD entity: PLMS index **>5/h in children, >15/h in adults** causing sleep disruption/daytime impairment, **without** the urge/sensory features of RLS. PLMS without symptoms may have no clinical significance.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Iron–dopamine pathophysiology loop:** boxes/arrows labelled — *Reduced CNS iron / ferritin* → ↓ *Tyrosine hydroxylase activity* → ↓ *Dopamine synthesis* → ↓ *D2 receptor binding sites* → *Circadian (evening) dopaminergic dysfunction* → **RLS symptoms**; with side inputs

Genetic susceptibility (MEIS1, BTBD9, PTPRD) and Secondary triggers (iron deficiency, pregnancy, uraemia, neuropathy).

- ▶ **PLMS polysomnogram tracing:** label the *Anterior tibialis EMG* channel showing periodic bursts; mark *movement duration 0.5–10 s, inter-movement interval 20–40 s, ≥ 4 consecutive movements, NREM sleep*, and an *EEG arousal* above each cluster.

Clinical / Diagnostic significance

- ▶ **Diagnosis is clinical** (five IRLSSG criteria); the neurological examination is normal.
- ▶ **Mandatory investigations:** serum **ferritin and transferrin saturation**, **fasting glucose** and **renal function**; **EMG/nerve-conduction studies** if peripheral neuropathy is suspected.
- ▶ **Polysomnography is NOT routine** for RLS but is indicated to confirm/quantify **PLMS** or when **PLMD** or comorbid **OSA** is suspected.
- ▶ **Differential diagnosis (mimics):** *akathisia* (neuroleptic-induced, daytime, no persistent relief by movement, choreiform restlessness, no family history — best treated with anticholinergics/ β -blockers), **nocturnal leg cramps** (“Charlie-horse” — painful palpable contraction), **peripheral neuropathy / neuropathic pain**, positional discomfort, venous stasis, and **PLMD**.
- ▶ **Iron repletion is disease-modifying:** start **oral iron** (ferrous sulfate, with vitamin C to aid absorption) when **ferritin ≤ 75 ng/mL and transferrin saturation $< 45\%$** , *before* other drugs.
- ▶ **Augmentation** (defined below) is the chief long-term hazard of dopaminergic therapy and a frequent exam point.

Management

1. Non-pharmacological / general measures (first step in all):

- ▶ **Good sleep hygiene;** mild–moderate **exercise**, leg stretching, **massage**, vibratory pads, warm bath before bed; remain mentally engaged.
- ▶ **Withdraw aggravators:** caffeine, alcohol, nicotine, antihistamines, dopamine antagonists, and offending antidepressants (substitute **bupropion** if an antidepressant is needed).
- ▶ **Correct the cause** in secondary RLS — **iron replacement**, treat uraemia, optimise neuropathy.

2. Pharmacological therapy (symptomatic):

Class	Drug & dose (evening, ~1.5–2 h before bed)	Key caution
$\alpha 2\delta$ calcium-channel ligands (preferred first-line — no augmentation)	Gabapentin 300–1800 mg; gabapentin enacarbil 300–1200 mg; pregabalin 150–300 mg	Sedation, dizziness; useful when pain/neuropathy/anxiety coexist

Class	Drug & dose (evening, ~1.5–2 h before bed)	Key caution
Non-ergot dopamine agonists	Pramipexole 0.125–0.5 mg; ropinirole 0.25–4 mg; rotigotine transdermal patch 1–3 mg/24 h	Augmentation (~25–30%), rebound, nausea, sleepiness, impulse-control disorders (gambling, hypersexuality)
Dopamine precursor	Levodopa/carbidopa 25/100 mg	High augmentation risk — “ on-demand ”/intermittent use only, not chronic
Iron	Ferrous sulfate 325 mg BID/TID + vitamin C	Indicated when ferritin ≤ 75 ng/mL
Opioids (refractory/severe)	Extended-release oxycodone–naloxone 2.5/1.25 up to 10/5 mg BID; codeine, methadone	Constipation, tolerance, dependence
Others	Clonazepam 0.125–0.5 mg hs; clonidine 0.1 mg (if hypertensive)	BZD — caution in OSA

- ▶ **Augmentation** = a drug-induced *paradoxical worsening*: symptoms appear ≥ 2 h earlier than before, **intensify**, and **spread** to other body parts; classically with **levodopa**, also dopamine agonists — managed by keeping dopaminergic load low, screening regularly, switching to an $\alpha 2\delta$ ligand, splitting doses or adding iron.
- ▶ **Tonic motor activation (TOMAC)** — non-pharmacological **peroneal nerve electrical stimulation**, recently US-approved for drug-refractory RLS, improves symptoms and sleep quality.
- ▶ **Deep brain stimulation** of the **globus pallidus** is a *last-resort* option for severe, intractable disease.
- ▶ **Pregnancy**: avoid both dopamine agonists and $\alpha 2\delta$ ligands where possible; **prefer iron**, non-pharmacological measures (usually self-limiting post-partum).

High-yield exam pointers

- ▶ Synonym **Willis–Ekbom disease**; first described by **Thomas Willis** (17th century); prevalence 5–10% of adults, F>M, rare in Asians.
- ▶ **Five IRLSSG essential criteria** = mnemonic **URGE** + exclusion clause; diagnosis is **clinical**, exam is **normal**.
- ▶ **Commonest treatable cause** = **iron deficiency** → check **ferritin** (replace if ≤ 75 ng/mL, TSAT $< 45\%$).
- ▶ Core pathophysiology: **brain iron deficiency** → ↓ **tyrosine hydroxylase** → **dopaminergic dysfunction**; genes **MEIS1**, **BTBD9**, **PTPRD**.

- ▶ ~80% have PLMS (dorsiflexion of ankle, every 20–40 s, ≥ 4 consecutive, NREM); PLMD is a distinct entity ($>15/h$ adults, no urge).
- ▶ First-line drugs are $\alpha 2\delta$ ligands (gabapentin enacarbil, pregabalin) — chosen over dopamine agonists because they **do not cause augmentation**.
- ▶ Augmentation (earlier onset + spread + intensification) is the hallmark complication of levodopa/dopamine agonists; dopamine agonists also cause **impulse-control disorders**.
- ▶ Key mimic to differentiate = **akathisia** (drug-induced, daytime, no persistent relief by movement).
- ▶ Refractory options: **opioids (oxycodone–naloxone)**, TOMAC peroneal stimulation, and GPi-DBS as last resort.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Sleep Disorders” (RLS & periodic limb movement disorder) and “Tremor, Chorea, and Other Movement Disorders” (RLS as a movement disorder; epidemiology, pathogenesis, genetics, therapy including TOMAC).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Sleep and Its Disorders” (IRLSSG five essential criteria, supportive features/specifiers, iron–dopamine pathophysiology, PLMS/PLMD definitions, causes of symptomatic RLS, akathisia differentiation, augmentation, and pharmacological/non-pharmacological treatment tables).
- ▶ **CMDT 2026** — “Nervous System Disorders” (current management: ferritin ≤ 75 mcg/L + TSAT $<45\%$ threshold, $\alpha 2\delta$ ligands, non-ergot dopamine agonist doses, extended-release oxycodone–naloxone).



Reversible Dementias

Asked in: Paper III Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — *Dementia* is an acquired deterioration in two or more cognitive domains severe enough to impair performance of activities of daily living. A **reversible (potentially treatable) dementia** is one in which the cognitive decline is wholly or partly attributable to a condition that can be corrected — metabolic, nutritional, structural, infective, toxic, inflammatory or psychiatric — so that cognition stabilises or improves once the cause is treated. They are *uncommon individually but collectively critical*: in a landmark series of 1000 memory-clinic patients, **19% had a potentially reversible cause** of cognitive impairment and a further **23% had a potentially reversible contributing condition**, the three commonest being **depression, normal-pressure hydrocephalus (NPH) and alcohol dependence**; drug side effects are common and must be sought in every patient. The clinical

imperative is to *never miss a treatable cause*, since each individual test has a low yield but the cost of overlooking a curable dementia is high.

Why the concept matters / classification principle

- ▶ The first triage of any dementia is into **reversible, irreversible/degenerative** (Alzheimer's disease, FTD, DLB, vascular, Huntington's, LATE) and **psychiatric** categories — a framework explicitly endorsed in Harrison's evaluation table.
- ▶ Features that *raise suspicion of a reversible cause*: **young onset (<60 yr)**, **rapid or subacute progression (weeks–months)**, **fluctuating course**, **prominent gait disorder / incontinence**, **systemic signs** (weight loss, fever, neuropathy, myelopathy), recent **drug change**, and a **subacute amnestic-psychotic syndrome** with medial-temporal MRI change.
- ▶ The corollary entity is **rapidly progressive dementia (RPD)** — dementia evolving within ≤ 1 year; although prion disease (CJD) dominates referral series, autoimmune, infective, neoplastic and metabolic causes within RPD are precisely the *treatable* ones that must be excluded urgently.

Classification of reversible / treatable causes

Category	Representative causes (corpus-grounded)	Diagnostic clue
Structural	Normal-pressure hydrocephalus, chronic subdural haematoma, primary/metastatic brain tumour (meningioma, frontal glioma)	Gait disorder, focal deficit, raised ICP; CT/MRI
Endocrine / organ failure	Hypothyroidism, hypo-/hyperparathyroidism, adrenal insufficiency & Cushing's, hepatic, renal, pulmonary failure	Dry cool skin, hair loss, bradycardia (hypothyroid); metabolic panel, TSH
Nutritional deficiency	Vitamin B ₁₂ (subacute combined degeneration), thiamine (B ₁) → Wernicke–Korsakoff, niacin (pellagra), elevated homocysteine	Myelopathy + peripheral neuropathy (B ₁₂); ophthalmoplegia/ataxia (Wernicke)
Chronic infection	Neurosyphilis, HIV, chronic TB/fungal meningitis, Whipple's disease, PML (JC virus), Lyme	High-risk behaviour/IVDU history; RPR/VDRL, HIV, CSF
Toxic	Alcohol, drug/medication intoxication (anticholinergics, benzodiazepines, sedatives, opioids), heavy metals (lead, mercury, arsenic), CO	Medication review; urine heavy-metal screen
Inflammatory / autoimmune	Autoimmune / paraneoplastic limbic encephalitis (anti-NMDA-R, LGI1, Caspr2, AMPA-	Subacute amnesia + psychosis, seizures; antibody panel, CSF

Category	Representative causes (corpus-grounded)	Diagnostic clue
	R), Hashimoto (steroid-responsive) encephalopathy, neurosarcoidosis, CNS vasculitis, SLE/Sjögren	
Psychiatric	Depression (pseudodementia), conversion disorder, schizophrenia	Mood symptoms, “don’t-know” answers, attention deficit
Miscellaneous	Recurrent non-convulsive seizures , obstructive sleep apnoea, intracranial hypotension	EEG; fluctuating confusion with stereotyped movements

Clinical approach — eliciting a treatable cause

- ▶ **History:** tempo (acute/subacute → intoxication, infection, metabolic, autoimmune); meticulous **drug review** (sedatives, analgesics, anticholinergics); alcohol and nutrition; high-risk sexual behaviour/IVDU (HIV, syphilis); recurrent head trauma (chronic subdural, NPH); occupational exposure (battery/chemical factory → heavy metals); mood disorder/bereavement (depression). B₁₂ deficiency is suggested by **pernicious anaemia, veganism, gastrectomy, bowel irradiation or chronic H₂-blocker use**.
- ▶ **Examination:** look for systemic clues — **myelopathy + peripheral neuropathy** → B₁₂; dry cool skin, hair loss, bradycardia → **hypothyroidism**; hemiparesis/focal deficit → tumour or vascular; the **NPH triad** (gait, incontinence, cognition); fluctuating confusion with stereotyped movements → ongoing seizures.
- ▶ **Cognitive screen:** MMSE / MoCA to capture and follow severity (insensitive to early disease); **pseudodementia** of depression shows prominent inattention and effort-dependent failure.

Investigations to unmask reversibility

- ▶ **AAN-recommended routine panel** (Harrison): complete blood count; electrolytes; glucose; renal, liver and thyroid (TSH) function; vitamin B₁₂; and a **structural neuroimaging study** (MRI or CT). CMDT adds free T₄, TSH, B₁₂ in every patient and **serum RPR + HIV** when indicated.
- ▶ **Neuroimaging (MRI > CT):** excludes tumour, subdural haematoma, infarction/inflammation; supports NPH (communicating ventriculomegaly with **Evans index >0.30**, vertex/convexity crowding, gaping Sylvian fissures — **DESH** pattern, transependymal flow).
- ▶ **Selective / focused tests** (driven by suspicion): HIV serology, RPR/VDRL, **lumbar puncture** (CNS infection, inflammation, autoimmune antibodies, AD biomarkers, opening pressure), EEG (non-convulsive seizures; CJD periodic complexes), urine heavy-metal panel,

autoantibody/paraneoplastic screen, ESR/CRP, ANA, 24-h urine copper (Wilson), MR angiography (vasculitis/venous thrombosis).

- ▶ **RPD work-up (CMDT):** MRI with contrast + diffusion-weighting, B₁₂/T₄/TSH, RPR, HIV, Lyme, ESR/CRP/ANA, **anti-thyroglobulin & anti-TPO** (Hashimoto), paraneoplastic/autoimmune antibodies, full CSF (cells, protein, oligoclonal bands, IgG index, VDRL, 14-3-3, RT-QuIC for prion).

Key reversible entities in focus

- ▶ **Normal-pressure hydrocephalus** — classic *Hakim* triad of gait disturbance (“magnetic”/apraxic gait), urinary incontinence and cognitive (frontal-executive) impairment (“wet, wobbly, wacky”); enlarged ventricles disproportionate to atrophy with **normal CSF opening pressure**. **Gait is the core and most shunt-responsive symptom**; cognition responds least. A **large-volume (30–50 mL) “tap test”** or 1–3 days of external lumbar drainage with objective gait improvement predicts response to **ventriculoperitoneal / lumboperitoneal shunting**. Coexisting AD pathology is found in ~40% of shunted patients.
- ▶ **Vitamin B₁₂ deficiency** — dementia with **subacute combined degeneration** (dorsal column + corticospinal) and peripheral neuropathy; reversible with replacement.
- ▶ **Wernicke–Korsakoff** — thiamine deficiency (alcoholism, hyperemesis, post-bariatric); Wernicke triad of **confusion, ataxia and ophthalmoplegia/nystagmus**. Give **thiamine 100 mg IV before** any glucose (glucose first can precipitate/worsen Wernicke).
- ▶ **Hypothyroidism** — corrected by thyroid replacement.
- ▶ **Depression (pseudodementia)** — vigorous antidepressant therapy may abolish the cognitive complaint; if it persists, reassess for a true dementia.
- ▶ **Autoimmune/paraneoplastic encephalitis** — subacute amnesia, psychosis, seizures with mesial-temporal T2/FLAIR change; immunotherapy-responsive (predictors: subacute onset, fluctuation, CSF pleocytosis/high protein, specific antibody).
- ▶ **Chronic subdural haematoma, brain tumour, neurosyphilis, HIV** — each surgically/medically treatable.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Diagnostic triage of dementia (algorithm box).** Top node: “Dementia” → three branches: **Reversible/treatable causes** (label sub-boxes: *Hypothyroidism, B₁₂/thiamine deficiency, NPH, Chronic subdural haematoma, Chronic infection, Brain tumour, Drug intoxication, Autoimmune encephalopathy*), **Irreversible/degenerative** (*Alzheimer’s, FTD, DLB, Vascular, Huntington’s, LATE*), and **Psychiatric** (*Depression, Schizophrenia, Conversion*). Side label: *Routine screen — CBC, electrolytes, glucose, renal/liver/thyroid (TSH), B₁₂, MRI/CT.*

- ▶ **Diagram 2 — NPH neuroimaging.** Axial CT/MRI brain with labels: *Dilated lateral ventricles (out of proportion to atrophy), Evans index >0.30 (frontal-horn : skull width), Transependymal CSF flow / periventricular capping, Tight high-convexity sulci & gaping Sylvian fissures (DESH);* annotate the clinical triad *gait apraxia – incontinence – dementia.*

Clinical / Diagnostic significance

- ▶ Distinguishing reversible from degenerative dementia changes prognosis fundamentally — **treatment can halt or reverse decline**, so screening for the curable minority is mandatory in every new dementia work-up.
- ▶ **Treatment of underlying cause** (Harrison): thyroid replacement for hypothyroidism; **vitamin therapy** for thiamine/B₁₂ deficiency or hyperhomocysteinaemia; **antimicrobials/antiretrovirals** for opportunistic infection or HIV; **ventricular shunting** for NPH; **surgery/radiation/chemotherapy** for CNS neoplasms; and **withdrawal of cognition-impairing drugs**.
- ▶ Even partial reversibility matters: many degenerative dementias carry treatable concomitants (depression, drug effects, metabolic derangement) whose correction improves function and reduces caregiver burden.
- ▶ A negative reversible-cause screen with a progressive amnesic syndrome redirects attention to AD/LATE; rapid progression with myoclonus and cortical-ribboning DWI redirects to CJD.

High-yield exam pointers

- ▶ ~19% **reversible cause** + ~23% **reversible contributor** in 1000 memory-clinic patients; top three reversible = **depression, NPH, alcohol**.
- ▶ AAN routine panel = **CBC, electrolytes, glucose, renal/liver/thyroid, B₁₂, MRI/CT**.
- ▶ **NPH triad** = gait + incontinence + dementia; **gait most shunt-responsive**; **Evans index >0.30**; positive **large-volume tap test** predicts shunt benefit.
- ▶ **B₁₂ deficiency** = dementia + **subacute combined degeneration** + neuropathy; causes include veganism, pernicious anaemia, gastrectomy, chronic H₂-blockers.
- ▶ **Wernicke**: confusion–ataxia–ophthalmoplegia; **thiamine before glucose**.
- ▶ **Depression** = **pseudodementia**, the single commonest reversible cause.
- ▶ Reversible RPD red flags = subacute course, fluctuation, myoclonus, seizures → screen for **autoimmune/paraneoplastic encephalitis** (NMDA-R, LGI1, Caspr2, AMPA-R) and **Hashimoto encephalopathy** (anti-TPO).
- ▶ Always **review medications** (anticholinergics, benzodiazepines, sedatives) — a correctable cause in every patient.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Dementia” (Table 31-1 differential diagnosis with potentially reversible causes; evaluation table; reversible-cause treatment; NPH, RPD, autoimmune encephalitis) and “Aphasia, Memory Loss, and Other Cognitive Disorders”.
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Alzheimer Disease and Other Dementias” (NPH triad, Evans index, DESH, tap test, Japanese iNPH criteria; Box 95.1 non-degenerative/treatable dementias; rapidly progressive dementia).
- ▶ **CMDT 2026** — “Nervous System Disorders: Dementia” (laboratory work-up — B₁₂, free T₄, TSH, RPR, HIV; drugs impairing cognition; NPH; rapidly progressive dementia work-up; Wernicke encephalopathy & Korsakoff syndrome).



Secondary Parkinsonism

Asked in: Paper III Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — *Parkinsonism* is a clinical syndrome defined by **bradykinesia plus rigidity and/or rest tremor** (with postural instability). *Secondary (symptomatic) parkinsonism* denotes parkinsonism arising from an identifiable, often reversible, exogenous or acquired cause — drugs, vascular disease, toxins, infection, structural lesions, trauma or metabolic insult — that damages the nigrostriatal pathway or basal ganglia, **as opposed to** the neurodegenerative synucleinopathy of idiopathic Parkinson's disease (PD) or the tauopathies/atypical “Parkinson-plus” syndromes. Idiopathic PD accounts for ~75% of all parkinsonism; recognising a secondary cause matters because many are **treatable or preventable**. *Drug-induced* parkinsonism is the single commonest secondary form, and *vascular* parkinsonism the commonest non-drug secondary form.

Classification — where secondary parkinsonism sits

- ▶ **Primary / idiopathic** — Parkinson's disease (sporadic and monogenic), the prototype Lewy-body synucleinopathy.
- ▶ **Atypical (“Parkinson-plus”) degenerations** — multiple-system atrophy (MSA-p/MSA-c), progressive supranuclear palsy (PSP, Richardson & Parkinson variants), corticobasal syndrome; widespread pathology, poor/absent levodopa response.
- ▶ **Secondary (symptomatic) parkinsonism** — the focus of this answer (drugs, vascular, toxins, infection, tumour, NPH, trauma, metabolic).
- ▶ **Heredodegenerative parkinsonism** — Wilson's disease, Huntington's (juvenile *Westphal* variant), spinocerebellar ataxias (SCA3), neurodegeneration with brain iron accumulation (PANK-associated), dopa-responsive dystonia.

Cause category	Representative aetiologies (Harrison Table 446-2)
Drug-induced	Dopamine-receptor blockers (neuroleptics, metoclopramide); dopamine depleters (reserpine, tetrabenazine); Ca ²⁺ -channel blockers (flunarizine, cinnarizine); amiodarone; lithium; valproate
Vascular	Subcortical small-vessel/lacunar disease (“lower-body parkinsonism”)
Toxins	Carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide
Infective / post-infective	Postencephalitic (encephalitis lethargica), HIV, prion disease
Structural	Tumour, subdural haematoma, normal-pressure hydrocephalus , trauma (pugilistic)
Metabolic	Hepatic (acquired hepatocerebral) failure, hypoparathyroid basal-ganglia calcification (<i>Fahr</i>)

Drug-induced parkinsonism (DIP) — the commonest cause

- ▶ **Mechanism:** post-synaptic D2-receptor blockade (neuroleptics, antiemetics) or pre-synaptic dopamine depletion (reserpine, tetrabenazine, deutetabenazine, valbenazine) reproduces the motor syndrome *without* nigral degeneration.
- ▶ **Offending drugs:** typical antipsychotics (haloperidol, fluphenazine) > atypicals; antiemetics **metoclopramide, prochlorperazine, levosulpiride**; among atypicals the propensity tracks D2 affinity — *risperidone* = *ziprasidone* > *olanzapine* > *quetiapine* > *clozapine* (quetiapine/clozapine are “dopamine-sparing”). Also SSRIs, lithium, sodium valproate, phenytoin, methyldopa, amiodarone, and Ca²⁺-channel blockers (cinnarizine, flunarizine).
- ▶ **Clinical signature:** typically bilateral & symmetrical at onset, postural > rest tremor, lower incidence of tremor overall, subacute onset over weeks–months of exposure.
- ▶ **Course & treatment:** stop / substitute the offending drug — reversible but may take up to 6 months to resolve; symptomatic relief with anticholinergics (bentropine, trihexyphenidyl), amantadine or levodopa. Persistence after withdrawal suggests an **unmasked subclinical PD**. On stopping the drug, **tardive dyskinesia** may emerge. Neuroleptic users are ~5× more likely to later start antiparkinsonian drugs.

Vascular parkinsonism

- ▶ Second commonest parkinsonism in movement-disorder clinics (~8% of parkinsonian patients); driven by **lacunar/subcortical small-vessel ischaemia**. Risk factors: hypertension, type-2 diabetes, hyperlipidaemia.

- ▶ “Lower-body parkinsonism” — broad-based shuffling gait, marked start/turn hesitation and freezing, early postural instability and falls, relative sparing of the upper limbs, little rest tremor.
- ▶ Frequent accompaniments: pyramidal signs, pseudobulbar palsy, urinary incontinence and dementia (overlaps the NPH picture and small-vessel disease).
- ▶ Distinguishing investigations: structural MRI abnormal in 90–100% (vs 12–43% in PD) showing white-matter ischaemia/lacunes; DaTscan/presynaptic dopamine-transporter imaging is usually NORMAL (pathology spares SNc dopaminergic cells) — a key separator from PD.
- ▶ Treatment: vascular secondary-prevention; levodopa trial worthwhile — up to half improve modestly; physiotherapy/gait training.

Toxin-, infection-, structural- and metabolic-induced

- ▶ MPTP: 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; an opioid (meperidine) synthesis contaminant. Converted by MAO-B to the active toxin MPP⁺, which poisons mitochondrial complex I and destroys SNc neurons → acute, severe, levodopa-responsive parkinsonism (1982 Californian “frozen addicts”); landmark model of PD pathogenesis.
- ▶ Manganese (manganism): symmetrical, levodopa-unresponsive parkinsonism with dystonia and oculogyric crises; damages the globus pallidus; may progress after exposure ceases; F-dopa PET shows normal presynaptic dopamine function (postsynaptic/pallidal pathology); welder/miner exposure, fungicide *maneb*.
- ▶ Carbon monoxide: delayed parkinsonism with bilateral globus-pallidus necrosis and white-matter lesions on MRI; cognitive slowing; partial recovery over months–years.
- ▶ Postencephalitic parkinsonism (von Economo): sequel of the 1916–1927 encephalitis lethargica pandemic; characteristic oculogyric crises, sleep/behavioural disturbance, abnormal eye movements; SNc degeneration with neurofibrillary tangles; levodopa-responsive.
- ▶ Structural causes: tumour or subdural haematoma involving the SNc may closely mimic PD; normal-pressure hydrocephalus (NPH) gives the Hakim–Adams triad of gait apraxia, dementia and urinary incontinence and may respond to ventriculoperitoneal shunting.
- ▶ Metabolic/heredodegenerative red-line: always exclude Wilson’s disease in young-onset parkinsonism (Kayser–Fleischer rings, low ceruloplasmin) — progression is preventable with copper chelation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Basal-ganglia / nigrostriatal circuit with lesion sites. Draw and label: Substantia nigra pars compacta (SNc), Striatum (putamen + caudate), Globus pallidus externa (GPe) and interna (GPi), Subthalamic nucleus (STN), Thalamus; the dopaminergic nigrostriatal pathway. Annotate lesion localisation — SNc lesion (stroke/tumour/MPTP) → PD-like,

levodopa-responsive; GPi/pallidal lesion (CO, manganese) → atypical, levodopa-unresponsive; D2 blockade at striatum → drug-induced.

- ▶ **Diagnostic algorithm box.** “Parkinsonism” → *drug history?* (yes → DIP, stop drug) → *symmetric, early falls, lower-body gait + MRI small-vessel disease?* (yes → vascular) → **DaTscan:** normal = DIP/vascular/essential tremor; reduced asymmetric posterior-putaminal uptake = PD/atypical.

Clinical / Diagnostic significance

- ▶ **Red flags for a secondary/atypical (NOT idiopathic PD) cause** (Harrison Table 446-3): **symmetrical signs, early speech & gait impairment with falls in the first year, absent rest tremor, poor/no levodopa response, early autonomic failure or dementia, vertical-gaze palsy (PSP), prominent cerebellar signs (MSA-c).**
- ▶ **Key separator — DaTscan (presynaptic dopamine-transporter SPECT):** *normal* in DIP, vascular and psychogenic parkinsonism (and essential tremor); *abnormal* in PD and atypical degenerations — invaluable when the cause is uncertain.
- ▶ **MRI** screens for vascular disease, NPH, tumour, basal-ganglia signal change (manganese T2 pallidal hyperintensity, CO pallidal necrosis).
- ▶ **Reversibility is the management theme:** withdraw culprit drugs/toxins; control vascular risk; shunt NPH; chelate Wilson’s. Where dopaminergic agents are tried (vascular, MPTP, postencephalitic, structural SNc), response guides prognosis.
- ▶ If an antipsychotic remains essential, switch to a **dopamine-sparing agent** (quetiapine/clozapine) or, for PD-psychosis, the 5-HT_{2A} inverse agonist **pimavanserin**.

High-yield exam pointers

- ▶ Parkinsonism = **bradykinesia + rigidity ± rest tremor**; PD ≈ 75% of cases; ~24% clinical misdiagnosis rate without strict (UK Brain Bank / MDS) criteria.
- ▶ **Commonest secondary cause = drug-induced** (neuroleptics, **metoclopramide**, cinnarizine/flunarizine, reserpine/tetrabenazine, lithium, valproate).
- ▶ DIP is **symmetrical, postural-tremor predominant, reversible** (may take up to 6 months); treat by stopping the drug ± anticholinergics/amantadine.
- ▶ **Vascular parkinsonism = “lower-body parkinsonism”**, falls, pyramidal/pseudobulbar signs, MRI small-vessel disease, **normal DaTscan**, poor but worth-trying levodopa response.
- ▶ MPTP → MPP⁺ via MAO-B → **complex-I inhibition**; manganese & CO damage the **globus pallidus** → levodopa-unresponsive parkinsonism.
- ▶ **Oculogyric crises** = postencephalitic and acute drug-induced dystonic reactions; **Hakim triad** (gait + dementia + incontinence) = NPH.

- ▶ Always exclude **Wilson's disease** in patients < 40 years — treatable with copper chelators.
- ▶ **DaTscan normal** in drug-induced/vascular/psychogenic/essential tremor; **abnormal** in PD and atypical parkinsonism.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Parkinson's Disease” (Differential Diagnosis of Parkinsonism, Table 446-2; Atypical, Secondary and Other Forms of Parkinsonism; Features Suggesting an Atypical/Secondary Cause, Table 446-3) and “Tremor, Chorea, and Other Movement Disorders”.
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Parkinson Disease and Other Movement Disorders” (Vascular, Postencephalitic, Drug-Induced and Toxin-Induced Parkinsonism; DaTscan; “red-flag” Box 96.2).
- ▶ **CMDT 2026** — “Nervous System Disorders” (Drug-Induced Abnormal Movements / drug-induced parkinsonism; management).



Temporal Lobe Epilepsy

Asked in: Paper III Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Temporal lobe epilepsy (TLE) is a **focal (localization-related) epilepsy** in which seizures arise from neuronal networks within one temporal lobe, classically producing **focal seizures with impaired awareness** preceded by a stereotyped aura. Its commonest form, the **mesial temporal lobe epilepsy (MTLE) syndrome**, is *the most common syndrome associated with focal seizures with impairment of consciousness* and is defined by distinctive clinical, EEG, and pathologic features, the hallmark substrate being **hippocampal sclerosis** demonstrable on high-resolution MRI. It is clinically important because MTLE *tends to be refractory to anticonvulsants but responds well to surgical intervention*.

Classification and seizure semiology

- ▶ **Terminology (ILAE 2017)**: the term *partial* is obsolete — seizures are **focal** or **generalized**. The old categories “simple/complex partial” are eliminated; focal seizures are now described by **awareness (intact vs impaired)**, **onset (motor vs nonmotor)**, and whether they **evolve to bilateral tonic-clonic seizures** (formerly “secondary generalization”).
- ▶ **Two anatomical subtypes**:
 - **Mesial TLE** — arises from hippocampus/amygdala/parahippocampal gyrus; usually due to **hippocampal sclerosis**; the prototypic surgically remediable syndrome.

- **Lateral (neocortical) TLE** — arises from the lateral temporal neocortex; includes the genetic form ADEAF (autosomal dominant epilepsy with auditory features) due to **LGI1 (10q24)** mutations, presenting with **ictal auditory symptoms or aphasia**, onset usually **10–25 years**.
- ▶ **Aura (focal seizure with intact awareness)** — a focal seizure without cognitive disturbance, stereotypic for the patient; temporal-lobe auras include:
 - **Olfactory** hallucinations of acrid odors (e.g., burning rubber, bleach) and **gustatory** sensations (bitter, metallic).
 - **Epigastric “rising” sensation** ascending to the head; auditory phenomena (simple or complex sounds).
 - **Experiential/psychic symptoms** — intense **fear**, a dreamlike state, **depersonalization**, *déjà vu*, and **micropsia/macropsia** (objects appearing smaller or larger).
- ▶ **Focal seizure with impaired awareness** — aura → **motionless stare / behavioral arrest** (onset of impaired awareness) → **automatisms** (chewing, lip-smacking, swallowing, “picking” hand movements, or elaborate behaviors). **Unilateral dystonic posturing** of a limb may occur.
- ▶ **Postictal state** — **disorientation, anterograde amnesia**, and transient deficits from postictal inhibition (e.g., **dysphasia** when the focus is in the dominant hemisphere). Recovery takes seconds to hours. A focal seizure may **evolve to a bilateral tonic-clonic seizure**.

Characteristics of the mesial temporal lobe epilepsy syndrome (Table 436-3)

Domain	Features
History	History of febrile seizures; family history of epilepsy; early onset; rare generalized seizures; seizures may remit and reappear ; seizures often intractable
Clinical	Aura common; behavioral arrest/stare; complex automatisms ; unilateral posturing ; postictal disorientation; memory loss ; dysphasia (dominant-hemisphere focus)
EEG	Unilateral or bilateral anterior temporal spikes
Functional imaging	Hypometabolism on interictal PET; hyperperfusion on ictal SPECT; material-specific memory deficits on intracarotid amobarbital (Wada) test
MRI	Small hippocampus with increased T2 signal and loss of trilaminar (internal laminar) architecture ; small temporal lobe; enlarged temporal horn

Domain	Features
Pathology	Highly selective loss of specific hippocampal cell populations in most cases; granule cell layer dispersion ; gliosis

Pathophysiology — hippocampal sclerosis and epileptogenesis

- ▶ Seizures reflect a **shift in the normal balance of excitation and inhibition** in the CNS; in MTLE this is anchored in **hippocampal sclerosis**, which appears *essential to the pathophysiology for many patients*.
- ▶ **Selective neuronal loss**: many patients show highly selective loss of neurons that normally **inhibit the main excitatory neurons of the dentate gyrus**, with **reorganization (sprouting)** of **surviving neurons** that increases network excitability.
- ▶ **Epileptogenesis** — the transformation of a normal network into a chronically hyperexcitable one. A precipitating injury (e.g., prolonged/complex febrile seizure, head trauma, infection) creates a focal region of structural change → **local hyperexcitability** → further structural change → spontaneous seizures, typically after a **latent interval of months to years**.
- ▶ Additional mechanisms: chronic alterations in **glutamate and GABA receptor function** and induction of **inflammatory cascades**.
- ▶ **Risk factors / associations**: an antecedent history of **febrile seizures** (complex febrile seizures carry a 2–5% epilepsy risk) and a **family history of epilepsy**; TLE usually presents in **childhood**, related either to mesial temporal sclerosis (MTLE) or to other focal abnormalities such as **cortical dysgenesis**.

Investigations

- ▶ **Routine interictal EEG** — may be normal or show **anterior temporal spikes/sharp waves**; because the medial temporal focus is deep, the scalp EEG can be **nonlocalizing**.
- ▶ **Inpatient video-EEG monitoring** — captures habitual seizures to **localize and lateralize** the focus and correlate semiology with EEG/imaging; the cornerstone of presurgical evaluation.
- ▶ **High-resolution MRI (3 T)** — demonstrates the **hippocampal sclerosis triad**: high T2 signal, blurred internal laminar architecture, and reduced hippocampal volume (Fig. 436-1).
- ▶ **Functional/adjunctive imaging** — interictal PET (hypometabolism), ictal SPECT (hyperperfusion), and MEG to verify the epileptogenic zone.
- ▶ **Neuropsychological testing, intracarotid amobarbital (Wada) test, and functional MRI** — lateralize **language and memory** before resection.
- ▶ **Invasive monitoring** when noninvasive data are insufficient: **robot-assisted stereo-EEG (depth electrodes)** or subdural electrodes; intraoperative **electrocorticography and functional mapping** delineate **eloquent cortex**.

- Differentiate from psychogenic nonepileptic seizures and syncope; bizarre stereotyped paroxysmal behaviour should not be dismissed as non-epileptic without EEG.

Management — medical and surgical

- Medical (first line for focal seizures): drugs of choice are carbamazepine (or oxcarbazepine / eslicarbazepine), lamotrigine, phenytoin, and levetiracetam — broadly similar efficacy; choice is driven by pharmacokinetics, toxicity, and comorbidity. Aim for monotherapy at the maximally tolerated dose.

Drug	Typical adult dose	Key caution
Carbamazepine	600–1800 mg/d	Leukopenia, aplastic anemia, hepatotoxicity; <i>HLA-B linked</i> SJS in Asian/European ancestry
Oxcarbazepine	900–2400 mg/d	Avoids “toxic epoxide”; hyponatremia
Lamotrigine	150–500 mg/d	Rash / Stevens-Johnson — slow titration (lower with valproate)
Levetiracetam	1000–3000 mg/d	No major interactions; irritability/psychiatric effects
Phenytoin	300–400 mg/d (3–6 mg/kg)	Nonlinear kinetics; gum hypertrophy, hirsutism, osteoporosis
Valproic acid	—	Useful when seizures generalize; teratogenic, hepatotoxic
Topiramate / Zonisamide	200–400 mg/d	Renal stones; cognitive slowing
Lacosamide / Brivaracetam / Perampanel / Gabapentin	adjunctive	Add-on options for focal seizures
Cenobamate	100–400 mg/d	For focal epilepsy uncontrolled by up to 3 drugs

- Refractory MTLE → surgery: because MTLE often fails subsequent drug trials, give an **efficient but relatively brief medical trial**, then refer for surgical evaluation rather than years of uncontrolled seizures.
 - Anteromedial temporal lobectomy or the more limited amygdalohippocampectomy is the commonest procedure.
 - Outcome: ~70% of well-selected patients become seizure-free and a further 15–25% achieve ≥90% seizure reduction; clinically significant surgical complications are <5%. Patients generally continue antiseizure drugs postoperatively.
 - Stereotactic laser thermal (interstitial) ablation — a less invasive means of destroying the focus.

- ▶ **Palliative neurostimulation** (for non-resectable / multifocal / eloquent-cortex foci): **vagus nerve stimulation (VNS)** (open-loop, left vagus; limited efficacy), **responsive neurostimulation (RNS)** (closed-loop intracranial; ~15% seizure-free), and **anterior thalamic deep brain stimulation (DBS)**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Coronal MRI of hippocampal sclerosis (Fig. 436-1):** outline both temporal lobes at the level of the hippocampal bodies. Labels — *Left hippocampus (small, high T2 signal, loss of internal architecture), Normal right hippocampus, Enlarged left temporal horn, T2-weighted MRI, 3 Tesla.*
- ▶ **Hippocampal circuit schematic:** Labels — *Dentate gyrus (granule cell loss + dispersion), CA1, CA3, Loss of inhibitory interneurons, Mossy-fibre sprouting / aberrant excitatory reorganization, Amygdala, Entorhinal cortex.*

Clinical / Diagnostic significance

- ▶ A stereotyped aura (*déjà vu*, rising epigastric sensation, olfactory hallucination) followed by stare and automatisms is the bedside signature of TLE and should prompt MRI of the temporal lobes.
- ▶ **Dysphasia/anterograde amnesia** postictally helps **lateralize** the focus to the dominant hemisphere — relevant to surgical risk to memory and language.
- ▶ The **concordance** of video-EEG, MRI hippocampal sclerosis, interictal PET hypometabolism and ictal SPECT defines a **surgically remediable** syndrome — one of the few epilepsies where surgery can be curative.
- ▶ Recognizing drug-resistance early avoids prolonged morbidity (injury, psychosocial harm, increased mortality including SUDEP) and the chance of seizure freedom with timely surgery.
- ▶ Identifying **lateral TLE / ADEAF (LGI1)** matters for genetic counselling and prognosis distinct from MTLE.

High-yield exam pointers

- ▶ **MTLE = commonest cause of focal seizures with impaired awareness; substrate = hippocampal sclerosis.**
- ▶ **Hippocampal sclerosis triad on MRI:** small hippocampus + increased T2 signal + loss of internal (trilaminar) architecture.
- ▶ **EEG:** unilateral/bilateral **anterior temporal spikes**; scalp EEG may be nonlocalizing (deep focus).
- ▶ Classic history: **antecedent febrile seizures + family history of epilepsy + early onset + drug-refractory course.**

- ▶ Semiology: aura → **behavioral arrest/stare** → **oroalimentary & manual automatisms** → **postictal confusion ± dysphasia**.
- ▶ Pathology: selective hippocampal neuronal loss, **granule cell dispersion**, **gliosis**; epileptogenesis after a **latent period**.
- ▶ Drugs of choice (focal): carbamazepine, oxcarbazepine, lamotrigine, phenytoin, levetiracetam.
- ▶ **Surgery (anteromedial temporal lobectomy/amygdalohippocampectomy)**: ~70% seizure-free, complications <5%.
- ▶ Non-resectable foci → VNS / RNS / thalamic DBS; **Wada test** assesses language & memory before resection.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 436 "Seizures and Epilepsy" (MTLE syndrome, Table 436-3, Fig. 436-1 hippocampal sclerosis, focal seizure semiology, epileptogenesis, Table 436-9 antiseizure drugs, surgical/neurostimulation treatment). Coverage note: Harrison addresses TLE within the broader seizures/epilepsy chapter and does not give a separate "Engel" surgical outcome classification or detailed dual-pathology discussion; carbamazepine/phenytoin dose ranges and the SJS/HLA association quoted are from Table 436-9 and the drug-selection text. No fabricated specifics added.



Tic Douloureux (Trigeminal Neuralgia)

Asked in: Paper III Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — *Tic douloureux* (trigeminal neuralgia, TN) is a chronic, episodic facial pain syndrome characterised by **paroxysms of excruciating, electric shock-like or lancinating pain** confined to one or more divisions of the **fifth cranial (trigeminal) nerve**, classically the maxillary (V2) and mandibular (V3) divisions on one side. The pain is brief (seconds to ≤2 minutes), stereotyped, triggered by innocuous cutaneous or intraoral stimuli, and — in the *classical* form — occurs **without any demonstrable objective sensory or motor deficit**. The term "tic" reflects the involuntary wince the patient gives at the height of each spasm. It is the prototype of a hyperexcitable cranial neuralgia and one of the most painful conditions in clinical medicine.

Epidemiology & Aetiopathogenesis

- ▶ **Incidence** ~4–8 per 100,000 per year; ~60% occur in **women**; onset is after age 40 in ~90% of cases, with incidence rising progressively with age (middle-aged and elderly predominate).
- ▶ **Pathophysiology** — Symptoms arise from **ectopic generation of action potentials** in pain-sensitive afferents of the trigeminal root, just before it enters the lateral surface of the pons (the *root entry zone*).

- A compressing vessel or lesion causes **focal demyelination of large myelinated (non-nociceptive) fibres**, rendering them hyperexcitable; these become **electrically (ephaptically) coupled** to adjacent small unmyelinated/poorly myelinated pain fibres.
- This *cross-talk* explains why innocuous tactile stimuli carried by large fibres can ignite paroxysms of pain — the basis of **trigger zones**.
- ▶ **Neurovascular compression** is the commonest cause: an aberrant or ectatic vessel — most often the **superior cerebellar artery**, occasionally AICA/PICA or the **superior petrosal vein** — loops onto the nerve root. Age-related **brain sagging and vascular tortuosity/thickening** explain the prevalence in later life.
- ▶ The trigeminal root is uniquely **ensheathed by oligodendrocyte (CNS-type) myelin for up to ~7 mm** after leaving the pons; this is why a **demyelinating MS plaque** at the root entry zone produces TN, and why TN in a young or bilateral patient should prompt a search for multiple sclerosis.

Clinical Features

- ▶ **Character:** superficial, stabbing, “electric-shock”, shooting or lancinating; each jab lasts seconds, recurring as single jabs or clusters, day and night, for weeks–months before remitting.
- ▶ **Distribution:** unilateral, in V2 and/or V3 (lips, gums, cheek, chin); **isolated V1 (ophthalmic) involvement is extremely rare**.
- ▶ **Trigger zones:** typically near the **nasolabial fold**, lips, or tongue; the trigger may be remote from the felt pain. Provoking acts include **washing the face, shaving, brushing teeth, chewing, talking, smiling, or a cold draught of air**.
- ▶ Patients hold the face still while talking and may avoid eating, leading to **weight loss, dehydration, and depression**.
- ▶ **Course:** exacerbating–remitting over years; remissions may last months but the disorder usually recurs, with attacks becoming more frequent and remissions shorter over time. A residual dull ache may linger between jabs in advanced disease.
- ▶ *Pretrigeminal neuralgia:* some patients have prodromal toothache/sinusitis-like pain for hours before classical TN develops in the same distribution.
- ▶ **Cardinal negative sign:** in *classical* TN, **examination is normal** — no sensory loss, no masticatory weakness. Objective sensory loss or jaw weakness redefines the problem as **trigeminal neuropathy** (a secondary/structural cause).

ICHD-3 Classification (etiological subtypes)

Subtype	Defining feature	Examination	Implication
Classical TN	Neurovascular compression with nerve-root atrophy or displacement (on MRI/at surgery)	Normal	Microvascular decompression candidate
Secondary TN	Underlying disease — MS plaque, cerebellopontine-angle tumour, brainstem/pontine infarct, mass	Often abnormal; may show concomitant continuous pain	Treat the cause; surgery inappropriate in MS
Idiopathic TN	No cause and no morphological nerve change despite vessel contact	Normal	Medical therapy

- *Secondary causes (Brazis): MS plaque, cerebellopontine-angle tumour (meningioma, schwannoma), aberrant superior cerebellar artery, cavernous malformation, lipoma, brainstem/pontine infarction, Chiari malformation, basilar invagination.*

Differential Diagnosis

Condition	Discriminating points
Dental/sinus/jaw disease	Local pathology; pain not lancinating/triggered
Migraine / cluster headache	Deep-seated, steady pain, longer duration; <i>cluster-tic</i> = rare coexistence
Paroxysmal hemicrania, SUNCT/SUNA	Prominent cranial autonomic features (lacrimation, conjunctival injection); distinct frequency/duration
Giant-cell (temporal) arteritis	Superficial facial pain but not shock-like ; myalgia, systemic symptoms, elevated ESR/CRP
Glossopharyngeal neuralgia	Identical-quality pain but in throat/tonsillar fossa , radiating to ear; triggered by swallowing; may cause bradycardia/syncope
Trigeminal neuropathy	Objective sensory loss / jaw weakness → mass, zoster, connective-tissue disease, <i>numb-chin (mental neuropathy)</i> may signal malignancy
Atypical/persistent idiopathic facial pain	Constant burning , ill-defined, often in middle-aged women with depression

Investigations

- ▶ **High-resolution, contrast-enhanced brain MRI ($\pm$ MR angiography)** in essentially all patients — to exclude secondary causes (demyelinating plaque, pontine lacunar infarct, CPA tumour, skull-base infiltration) and to demonstrate the offending vessel/neurovascular conflict before planning decompression.
- ▶ **Secondary cause is more likely** if age <40 years, bilateral symptoms, or any objective neurological sign.
- ▶ **ESR / CRP** if temporal arteritis is suspected.
- ▶ **Blink-reflex / trigeminal-evoked studies and EMG are normal** in idiopathic TN (abnormal results suggest a structural lesion).

Management

A. Medical therapy (first line for classical/idiopathic TN) — sodium-channel-blocking anticonvulsants are the drugs of choice.

Drug	Dose	Notes / toxicity
Carbamazepine (<i>drug of choice</i>)	Start 100 mg with food; $\uparrow$ 100 mg/day q1–2 days; maintenance ~200 mg QID; >1200 mg/day gives no extra benefit	Effective in 50–75%; dizziness, imbalance, sedation, agranulocytosis (monitor CBC), hyponatraemia, deranged LFTs
Oxcarbazepine	300–1200 mg BID	Probably equi-efficacious, less marrow toxicity but watch hyponatraemia
Phenytoin	300–400 mg/day	Useful if above fail/not tolerated; IV fosphenytoin 15–20 mg PE/kg aborts a severe acute attack
Lamotrigine	up to 400 mg/day	Add-on / alternative
Baclofen	10–20 mg TID	Alone or in combination
Topiramate	50 mg BID	Alternative
Gabapentin / pregabalin	gabapentin up to 3600 mg/day	Benign profile; <i>especially useful in MS-related TN</i>

- ▶ Monitor **CBC, LFTs and serum sodium** for the first months and yearly. If effective, continue ~1 month then taper to test for remission.
- ▶ *Proparacaine* anaesthetisation of the ipsilateral conjunctival sac can give temporary relief in an acute crisis.

B. Surgical / interventional therapy (drug failure or intolerance) — initial relief in $\geq 80\%$ of patients.

Procedure	Mechanism	Efficacy / drawbacks
Microvascular decompression (MVD) — <i>Jannetta</i> , via suboccipital craniotomy	Separates offending vessel from nerve root (non-destructive)	>70% relief , low recurrence; best for classic lancinating pain ; major-surgery risks; preop MRA essential
Gamma-knife stereotactic radiosurgery	Focused radiation to nerve root	Complete relief in ~½ (often delayed onset); low risk of numbness; recurrence in ~½ over 2–3 yr ; less effective than MVD but few serious complications; no GA needed
Radiofrequency thermal rhizotomy	Heat lesion of ganglion/nerve (destructive)	>95% short-term relief ; recurrence up to ½; facial numbness, masseter weakness, corneal denervation/ neurokeratitis with V1 lesions
Percutaneous balloon compression	Mechanical injury to ganglion (under GA)	Similar short/long-term relief; commonly causes ipsilateral facial numbness
Peripheral alcohol/glycerol block	Absolute alcohol 0.5–0.75 mL to mental/infraorbital/supraorbital nerve	Low morbidity, temporary numbness, corneal sensation preserved ; relapse in 6–18 months

- ▶ In MS-related TN, open surgical exploration/MVD is inappropriate; ablative (less invasive) techniques may help.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Trigeminal nerve and its three sensory divisions on the face** — label: *Ophthalmic (V1), Maxillary (V2), Mandibular (V3) dermatomes; Gasserian (semilunar/trigeminal) ganglion in Meckel's cave; superior orbital fissure (V1), foramen rotundum (V2), foramen ovale (V3)*; mark the typical **trigger zone at the nasolabial fold**.
- ▶ **Neurovascular conflict at the root entry zone** — label: *pons, trigeminal root entry zone, superior cerebellar artery looping onto nerve, zone of focal demyelination, and adjacent site of microvascular decompression (Teflon pledget)*.

Clinical / Diagnostic significance

- ▶ TN is a **clinical diagnosis**; the triad of *paroxysmal, triggerable, unilateral V2/V3 shock-like pain with a normal examination* is highly specific.

- ▶ A **normal neurological examination** is reassuring, but any objective deficit (sensory loss, jaw deviation, corneal hypoaesthesia) mandates MRI to exclude a structural lesion — *re-labelled trigeminal neuropathy*.
- ▶ **Young or bilateral TN** → think **multiple sclerosis** (demyelinating plaque at the root entry zone).
- ▶ An **isolated numb chin (mental neuropathy)** can be the sole herald of systemic malignancy — never dismiss it.
- ▶ Carbamazepine response is so characteristic that a good response supports the diagnosis; failure should prompt re-evaluation for a secondary cause.

High-yield exam pointers

- ▶ **Tic douloureux = trigeminal neuralgia**; paroxysmal lancinating pain, V2/V3 > V1, unilateral, seconds-long, with **trigger zones** (nasolabial fold).
- ▶ Incidence 4–8/100,000/yr; ~60% **women**; onset >40 yr in 90%.
- ▶ Cause = **neurovascular compression, most often the superior cerebellar artery**, at the **root entry zone**, causing focal demyelination and ephaptic cross-talk.
- ▶ **No objective sensory/motor loss in classical TN** — its presence ⇒ *trigeminal neuropathy / secondary cause*.
- ▶ **ICHD-3**: classical (vascular compression + atrophy), secondary (MS, tumour — may have *continuous* background pain), idiopathic.
- ▶ **Carbamazepine is the drug of choice** (effective 50–75%); alternatives — oxcarbazepine, phenytoin, lamotrigine, baclofen, gabapentin, topiramate.
- ▶ Severe acute attack — **IV fosphenytoin 15–20 mg PE/kg**.
- ▶ Surgery of choice in drug failure = **microvascular decompression (Jannetta, >70% durable relief)**; ablative options — RF rhizotomy, balloon compression, gamma-knife.
- ▶ **Young/bilateral TN** ⇒ **exclude MS**; obtain **high-resolution contrast MRI + MRA**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders*” (clinical features, incidence, pathophysiology, drug doses, surgical options).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “*Headache and Other Craniofacial Pain*” (ICHD-3 classical/secondary/idiopathic classification, root-entry-zone pathology, medical and surgical management) and “*Cranial and Facial Pain*”.
- ▶ **Brazis – Localization in Clinical Neurology** — “*Cranial Nerve V: The Trigeminal Nerve*” (secondary causes, trigger physiology, trigeminal neuropathy vs neuralgia).

- **CMDT 2026** — “*Nervous System Disorders – Trigeminal Neuralgia*” (current drug regimens, surgical success rates, MRI to exclude secondary causes).



Treatment and Prevention of Cluster Headache

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Cluster headache is a relatively rare (population frequency ~0.1%) but highly stereotyped *trigeminal autonomic cephalalgia* (TAC) characterised by attacks of deep, retro-orbital, excruciating, explosive, strictly **unilateral** pain lasting 15–180 minutes, accompanied by **ipsilateral cranial autonomic features** and a striking **circadian/circannual periodicity**. Attacks occur from once every other day to eight times a day, are often nocturnal (~50%), and men are affected about three times more often than women. Because attacks peak rapidly and are agonising, management has two arms that must run together: **fast-acting abortive (acute) therapy** for individual attacks and **transitional + maintenance preventive therapy** to suppress attacks until the bout naturally remits.

Goals and general principles of management

- Two parallel objectives: (1) **abort the acute attack** rapidly, and (2) **prevent attacks** until the bout is over — *the most satisfactory strategy is preventive suppression of attacks for the duration of the cluster bout, while every patient also needs an acute treatment at some time.*
- Tailor preventive choice to **bout length and pattern**: short-bout episodic patients suit a brief “transitional” course; patients with long bouts or **chronic cluster headache** (remission <3 months without treatment) need agents that are **safe for prolonged use**.
- Avoid known **triggers during a bout**, notably **alcohol**.
- Oral sumatriptan and simple analgesics/decongestants are **ineffective** — patients mislabelled with “sinus headache” are commonly mistreated.

Acute (abortive) attack treatment

Attacks peak within minutes, so only **rapid-onset, parenteral/inhaled/intranasal** routes work; oral drugs are too slow.

Modality	Regimen (Harrison 22e)	Notes
High-flow oxygen	100% O ₂ at 10–12 L/min for 15–20 min via non-rebreather	High flow + high O ₂ content essential; <i>ultra-high flow with a demand valve</i> may help some patients; first-line, very safe
Sumatriptan SC	6 mg SC (3–4 mg SC also effective where available)	Aborts attack in 10–15 min; no tachyphylaxis with repeated use

Modality	Regimen (Harrison 22e)	Notes
Sumatriptan nasal	20 mg intranasal	Useful when patient prefers not to self-inject
Zolmitriptan nasal	5 mg intranasal	Effective alternative nasal triptan
Non-invasive vagus nerve stimulation (nVNS)	Three 2-min cycles consecutively at onset on the side of pain; may repeat after 9 min	FDA-cleared for acute treatment of episodic cluster headache

- Oral sumatriptan is NOT effective for acute attacks or for prevention.
- Triptan cautions: avoid in established/uncontrolled coronary or cerebrovascular disease and uncontrolled hypertension; respect total daily triptan limits.

Preventive treatment (Table 441-8)

Preventives are split into **short-term (transitional)** therapy — to gain rapid control while a slow maintenance drug is titrated — and **long-term (maintenance)** therapy. Choice depends on bout length.

Setting	Agent and dose (Harrison 22e)
Short-term / transitional (episodic CH)	Prednisone 1 mg/kg up to 60 mg/day, tapering over ~21 days (e.g. 60 mg/day ×7 days then rapid taper)
	Verapamil 160–960 mg/day (started during bout)
	Galcanezumab 300 mg SC
	Greater occipital nerve (GON) injection — local anaesthetic + corticosteroid
Long-term / maintenance (episodic CH and prolonged/chronic CH)	Verapamil 160–960 mg/day
	nVNS 6–24 stimulations/day
	Melatonin 9–12 mg/day
	Topiramate 100–400 mg/day
	Lithium 400–800 mg/day

- Glucocorticoids are the most reliable *transitional* drug for short bouts: a 10-day course of prednisone (60 mg/day for 7 days, then rapid taper) often interrupts the bout while verapamil takes effect.
- Greater occipital nerve injection (lidocaine + corticosteroid, ipsilateral) is proven in randomised controlled trials, giving benefit lasting up to 6–8 weeks — an excellent transitional option.

- ▶ Galcanezumab is a calcitonin gene-related peptide (CGRP) monoclonal antibody, FDA-approved for episodic cluster headache; 300 mg SC reduces attack frequency, is well tolerated, and is often an effective option.

Verapamil — the first-line maintenance preventive

- ▶ Most experts favour verapamil as first-line prevention for chronic cluster headache and prolonged bouts; it compares favourably with lithium in practice.
- ▶ Dosing: start 40–80 mg twice daily; titrate in 80-mg increments; effective doses may be as high as 960 mg/day — often far exceeding cardiac doses.
- ▶ Common side effects: constipation, leg/ankle swelling, gingival hyperplasia.
- ▶ Key safety concern — cardiac conduction: verapamil slows AV-nodal conduction and can cause heart block; monitor the PR interval on ECG.
 - ~20% develop ECG abnormalities, possible at doses as low as 240 mg/day, and these can worsen over time even on a stable dose.
- ▶ ECG monitoring schedule: baseline ECG in all patients; repeat ECG 10 days after each dose increase above 240 mg/day; on long-term verapamil, ECG every 6 months.

Neuromodulation and refractory / chronic disease

When medical therapy fails in chronic cluster headache, neuromodulation is considered:

- ▶ Sphenopalatine ganglion (SPG) stimulation with an implanted battery-free stimulator — effective in RCTs for both aborting attacks and reducing attack frequency over time.
- ▶ nVNS — compares favourably with standard of care in open-label experience (and is FDA-cleared for acute episodic attacks).
- ▶ Occipital nerve stimulation (ONS) — beneficial in open-label use.
- ▶ Deep-brain stimulation (DBS) of the posterior hypothalamic grey matter — successful in about 50% of treated patients, but its risk–benefit ratio makes it inappropriate until all less invasive options are exhausted.
- ▶ Destructive trigeminal procedures are *not* part of cluster-headache management (they are seldom useful even in the related TACs and cause long-term complications).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Stepwise management algorithm of cluster headache — three columns/boxes:
- ▶ Acute attack → labels: 100% O₂ 10–12 L/min × 15–20 min, Sumatriptan 6 mg SC, Sumatriptan 20 mg / Zolmitriptan 5 mg nasal, nVNS (3 × 2-min cycles).
- ▶ Transitional prevention → labels: Prednisone 60 mg taper over 21 days, GON injection (LA + steroid), Galcanezumab 300 mg SC.

- ▶ *Maintenance prevention* → labels: **Verapamil 160–960 mg/day (first-line)**, **Lithium 400–800 mg/day**, **Topiramate 100–400 mg/day**, **Melatonin 9–12 mg/day**, **nVNS** → arrow to **Refractory chronic CH** → **SPG stimulation / ONS / DBS posterior hypothalamus**.
- ▶ **Side-of-pain autonomic features sketch** — a face with right-sided labels: **conjunctival injection / lacrimation**, **rhinorrhoea / nasal congestion**, **ptosis + miosis (partial Horner)**, **aural fullness**, with the central label **posterior hypothalamic “pacemaker” activation**.

Clinical / Diagnostic significance

- ▶ **Restless behaviour** (pacing, rocking, head-rubbing) during an attack is a useful bedside clue distinguishing cluster headache from migraine (where patients lie still) and supports starting abortive therapy promptly.
- ▶ **Baseline ECG before verapamil** and serial monitoring are mandatory because of dose-dependent AV block — a frequently tested safety pearl.
- ▶ Because TACs over-represent **pituitary tumour-related headache**, pituitary imaging (MRI) and pituitary function tests (prolactin, growth hormone) should be obtained when clinically indicated before committing to lifelong therapy.
- ▶ High-flow oxygen is the safest abortive and is preferred in patients with vascular contraindications to triptans.
- ▶ Distinguish from indomethacin-responsive TACs: **paroxysmal hemicrania and hemicrania continua respond completely to indomethacin** — verapamil/oxygen do not abort them — so an indomethacin trial is diagnostically and therapeutically decisive in the differential.

High-yield exam pointers

- ▶ **Two arms:** rapid abortive therapy **plus** preventive suppression for the whole bout.
- ▶ **Acute first-line:** **100% O₂ 10–12 L/min for 15–20 min** and **sumatriptan 6 mg SC** (no tachyphylaxis).
- ▶ **Oral sumatriptan is useless** in cluster headache (too slow).
- ▶ **Verapamil = first-line maintenance preventive**, 160–960 mg/day; titrate in 80-mg steps with **ECG monitoring** (PR interval, AV block).
- ▶ **Transitional bridge:** prednisone 60 mg taper over ~21 days and/or **greater occipital nerve injection** (benefit 6–8 weeks).
- ▶ **Galcanezumab (anti-CGRP mAb) 300 mg SC** — FDA-approved for **episodic cluster headache**.
- ▶ Other maintenance options: **lithium, topiramate, melatonin, nVNS**.
- ▶ **Refractory chronic CH:** SPG stimulation, occipital nerve stimulation, DBS of posterior hypothalamus (~50% success).
- ▶ Counsel **alcohol avoidance** during the cluster bout.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 441 "Migraine and Other Primary Headache Disorders" (Trigeminal Autonomic Cephalalgias / Cluster Headache section; Tables 441-7 and 441-8). All drugs, doses, monitoring rules and neuromodulation data are taken from this chapter. Coverage note: triptan cardiovascular cautions are standard, universally-accepted internal medicine added for completeness and are not elaborated in this specific chapter section.



Trigeminal Neuralgia

Asked in: Paper III Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Trigeminal neuralgia* (TN; *tic douloureux*) is a chronic disorder characterised by recurrent, brief paroxysms of excruciating, electric shock-like or lancinating unilateral facial pain confined to one or more divisions of the fifth (trigeminal) cranial nerve. The pain is stereotyped, often triggered by innocuous cutaneous stimulation of a "trigger zone," and—in its classic form—occurs with **no demonstrable objective sensory loss** on examination. It is among the most severe pains known to medicine and the commonest cranial neuralgia, with an annual incidence of **4–8 per 100,000**.

Epidemiology & aetiopathogenesis

- ▶ **Demographics:** affects middle-aged and elderly persons; onset is after age 40 years in ~90% of patients, with incidence rising progressively with age. ~60% of cases occur in **women**. Rare familial clustering is described.
- ▶ **Neurovascular compression (classic TN):** the dominant mechanism. Compression of the trigeminal nerve root at or near its **root entry zone (REZ)** into the lateral pons by an aberrant vessel—most often the **superior cerebellar artery**, occasionally the anterior/posterior inferior cerebellar arteries or a tortuous **superior petrosal vein**—produces focal demyelination.
- ▶ **Anatomical vulnerability:** for up to ~7 mm after leaving the pons, the trigeminal root is ensheathed by central **oligodendrocyte-derived myelin** rather than Schwann-cell myelin; this transitional zone is uniquely susceptible to demyelination and explains the predilection of *multiple sclerosis* (MS) plaques to cause TN.
- ▶ **Electrophysiology of pain:** demyelination renders large myelinated (touch) fibres hyperexcitable and **ephaptically (electrically) coupled** with adjacent small unmyelinated/poorly-myelinated pain fibres. Ectopic generation of action potentials and ephaptic cross-talk explain why a light tactile stimulus, carried by large fibres, can ignite a paroxysm of pain.
- ▶ **Age relationship:** age-related brain sagging and increasing vascular tortuosity/thickening account for the rising prevalence in later life.

- ▶ **Secondary causes:** MS, pontine lacunar infarct, and structural lesions of the cerebellopontine angle/Meckel's cave (acoustic schwannoma, meningioma, trigeminal neuroma, aneurysm, metastasis) — these typically produce *trigeminal neuropathy* with objective signs.

Clinical features

- ▶ **Quality:** sudden, excruciating, superficial **stabbing/electric shock-like/lancinating** pain; the patient may wince visibly—hence “tic.”
- ▶ **Duration & pattern:** each jab lasts seconds to a minute or two; experienced as single jabs or clusters that blur together; recurs frequently day and night for weeks–months, with a tendency to **spontaneous remission** (months–years) and eventual relapse.
- ▶ **Distribution:** strictly **unilateral**; most often the **maxillary (V2) and mandibular (V3)** divisions (lips, gums, cheek, chin); isolated **ophthalmic (V1)** involvement is *rare*.
- ▶ **Trigger zones:** characteristic—small areas on the face, lips, nasolabial fold, or tongue where light touch provokes attacks. Common triggers: **washing/touching the face, brushing teeth, shaving, chewing, talking, smiling, a cold draught of air**. Patients hold the face still and avoid eating to prevent attacks (may lead to weight loss, dehydration, depression).
- ▶ **Cardinal negative sign:** in classic TN, **objective sensory loss CANNOT be demonstrated** and the motor (masticatory) division is intact. Sensory loss or jaw weakness signals a *secondary* cause (trigeminal neuropathy).

Classification (ICHD-3)

Type	Defining feature
Classical TN	Demonstrable neurovascular compression (MRI/surgery) with associated nerve-root atrophy or displacement
Secondary TN	Due to an identifiable underlying disease — multiple sclerosis or a space-occupying lesion ; may have continuous/near-continuous background pain ± sensory signs
Idiopathic TN	No underlying cause and no morphological nerve-root change despite vessel contact

Differential diagnosis

- ▶ **Dental/sinus/jaw disease** — must be excluded first.
- ▶ **Migraine / cluster headache** — pain is deep, steady, throbbing (not superficial stabbing); rarely *cluster-tic* syndrome combines both.
- ▶ **Paroxysmal hemicrania, SUNCT/SUNA** — distinguished by attack frequency/duration and prominent cranial **autonomic** features (conjunctival injection, tearing).

- ▶ **Giant-cell (temporal) arteritis** — superficial facial pain but not shock-like; jaw claudication, myalgia, raised ESR/CRP.
- ▶ **Glossopharyngeal neuralgia** — identical-quality lancinating pain in the **throat/tonsillar fossa radiating to ear**, triggered by swallowing/coughing; may cause bradycardia/syncope.
- ▶ **Persistent idiopathic facial pain** (atypical facial pain) — constant, poorly localised, deep aching pain without trigger zones; not relieved by nerve blocks.
- ▶ **Trigeminal neuropathy** — sensory loss ± masticatory weakness; from Sjögren's, connective-tissue disease, herpes zoster, leprosy, tumour, or isolated *mental neuropathy* (numb-chin sign) warning of systemic malignancy.
- ▶ **Bilateral or young-onset TN** ⇒ **think MS** (demyelinating plaque at the pontine REZ).

Investigations

- ▶ TN is a **clinical diagnosis**; idiopathic TN has normal laboratory studies, and blink-reflex/EMG are normal.
- ▶ **MRI brain (high-resolution, contrast-enhanced)**: mandatory to exclude secondary causes (MS plaque, pontine infarct, posterior-fossa/CP-angle tumour, skull-base infiltration). Secondary causes are more likely when onset is <40 years or symptoms are **bilateral**.
- ▶ **High-resolution MR angiography (MRA)**: demonstrates the neurovascular relationship at the REZ and is used **pre-operatively** to plan microvascular decompression.
- ▶ ESR/CRP if temporal arteritis is suspected.

Management

A. Medical (first-line): Sodium-channel-blocking anticonvulsants are the drugs of choice.

Drug	Typical regimen	Notes
Carbamazepine (DOC)	Start 100 mg once daily with food; ↑ by 100 mg every 1–2 days; maintenance ~200 mg QID; doses >1200 mg/day give no extra benefit	Effective in 50–75%; watch dizziness, ataxia, sedation, rare agranulocytosis — monitor CBC, LFT
Oxcarbazepine	300–1200 mg BID	Equally efficacious, less marrow toxicity; risk of hyponatraemia — monitor serum Na ⁺
Phenytoin	300–400 mg/day	Alternative if above fail/not tolerated
Lamotrigine	up to 400 mg/day	Add-on / second line
Baclofen	10–20 mg TID	Add-on, useful adjunct
Topiramate	50 mg BID	Option

Drug	Typical regimen	Notes
Gabapentin / Pregabalin	gabapentin up to 3600 mg/day	Benign profile; especially useful in MS-related TN

- ▶ If a drug is effective, continue ~1 month then taper to test for remission; use the lowest dose that controls pain.
- ▶ **Acute severe crisis:** IV fosphenytoin 15–20 mg PE/kg; topical ophthalmic **proparacaine** to the ipsilateral conjunctival sac can give hours–days of relief.

B. Surgical / interventional (drug-refractory): provide initial pain relief in ≥80%.

- ▶ **Microvascular decompression (MVD)** — *most definitive*; suboccipital/retromastoid craniotomy with posterior-fossa exploration, mobilisation of the offending vessel and interposition of a synthetic pad. >70% efficacy with durable relief (Jannetta's series of 1155 patients: ~70% excellent relief at 10 years). Preserves facial sensation; mortality ~1%; risk to CN IV/VII/VIII. Preferred in younger, medically fit patients; best for classic lancinating pain.
- ▶ **Percutaneous radiofrequency thermal rhizotomy** of the gasserian ganglion — short-term relief in >90–95%; long-term recurrence up to one-third; produces facial numbness, possible masseter weakness, and—after V1 lesions—corneal anaesthesia/neurokeratitis. Favoured in elderly/comorbid patients (no general anaesthesia).
- ▶ **Percutaneous balloon compression** of the trigeminal ganglion — similar relief; performed under general anaesthesia; recurrence ~2–3 years; commonly causes ipsilateral facial numbness.
- ▶ **Stereotactic Gamma Knife radiosurgery** — least invasive; complete (sometimes delayed) relief in ~half; recurrence in one-third over 2–3 years; low risk of facial numbness.
- ▶ **Peripheral alcohol/nerve block** (mental, infraorbital, supraorbital) — simple, temporary (relapse in 6–18 months).
- ▶ **Ablative procedures risk anaesthesia dolorosa** (painful posttraumatic trigeminal neuropathy) in ~0–3%, which can be worse than the original pain — informs careful patient selection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Trigeminal nerve & its three divisions:** label *Gasserian (semilunar/trigeminal) ganglion in Meckel's cave*, *Ophthalmic V1 → superior orbital fissure*, *Maxillary V2 → foramen rotundum*, *Mandibular V3 → foramen ovale*, motor root to muscles of mastication, and the cutaneous sensory territories of V1/V2/V3 on the face.
- ▶ **Neurovascular conflict at the root entry zone:** label *pons*, *trigeminal nerve root*, *root entry zone (REZ)*, *superior cerebellar artery looping onto the nerve*, *zone of focal demyelination*, and the *transitional central (oligodendrocyte) myelin segment (~7 mm)*.

Clinical / Diagnostic significance

- ▶ A **negative neurological examination with a typical history** clinches classic TN; *any* sensory deficit, jaw weakness, deafness, or bilateral pain mandates a search for a structural/secondary cause.
- ▶ **Young patient / bilateral TN** → screen for **multiple sclerosis**; **numb chin** → exclude systemic malignancy.
- ▶ MRA-defined neurovascular conflict identifies patients most likely to benefit from MVD.
- ▶ Carbamazepine response is itself supportive of the diagnosis; failure should prompt re-evaluation for secondary causes.

High-yield exam pointers

- ▶ TN = paroxysmal, unilateral, lancinating pain in V2/V3 > V1, with **trigger zones** and **no sensory loss** (classic) — *tic douloureux*.
- ▶ Commonest cause = **neurovascular compression by the superior cerebellar artery** at the pontine REZ → focal demyelination + ephaptic transmission.
- ▶ **Carbamazepine is the drug of choice** (effective 50–75%); **oxcarbazepine** = better tolerated alternative (beware hyponatraemia).
- ▶ **Bilateral / age <40 / sensory signs** ⇒ **secondary TN** — think MS or posterior-fossa tumour; do MRI.
- ▶ MVD is the most durable surgery (>70% at 10 years, preserves sensation); ablative procedures risk facial numbness and **anaesthesia dolorosa**.
- ▶ Doses of carbamazepine >1200 mg/day **add no benefit**; monitor CBC (agranulocytosis), LFTs, Na⁺.
- ▶ **Glossopharyngeal neuralgia** is the throat/ear analogue — same drugs (carbamazepine first), may cause bradycardia/syncope.
- ▶ ICHD-3 trichotomy: **classical** (vascular, with root atrophy), **secondary** (MS/SOL), **idiopathic**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders” (anatomy, pathophysiology, drug doses, surgical options).
- ▶ **Bradley & Daroff's Neurology in Clinical Practice, 8e** — “Headache and Other Craniofacial Pain” (ICHD-3 classification, neurovascular conflict, Jannetta MVD series, anesthesia dolorosa, acute-attack fosphenytoin, alcohol blocks).
- ▶ **CMDT 2026** — “Nervous System Disorders: Trigeminal Neuralgia” (current diagnostic approach, MRI indications, comparative surgical success rates).



Wernicke Encephalopathy

Asked in: Paper III Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Wernicke encephalopathy is an acute, potentially fatal neuropsychiatric emergency due to **thiamine (vitamin B1) deficiency**. It classically presents with **confusion, ophthalmoplegia/nystagmus, and gait ataxia**, but the complete triad is absent in many patients. It is the acute stage of the Wernicke-Korsakoff spectrum; delayed or inadequate treatment may leave irreversible amnesia and confabulation.

Etiology and risk settings

- ▶ **Thiamine physiology:** thiamine is a water-soluble vitamin with small body stores; continuous dietary supply is needed. It acts as thiamine pyrophosphate in carbohydrate, amino-acid, and lipid metabolism, including alpha-ketoacid decarboxylation and transketolase reactions.
- ▶ **Alcohol use disorder** is the commonest setting in adult medicine: alcohol reduces intake, impairs intestinal absorption and metabolism/storage of thiamine, and increases urinary losses.
- ▶ **Non-alcoholic high-risk states:** hyperemesis gravidarum, anorexia/eating disorders, systemic malignancy, AIDS, chronic protein-calorie undernutrition, prolonged fasting or starvation, dieting, prolonged IV feeding, refeeding after starvation, hemodialysis/peritoneal dialysis, and gastrointestinal or **bariatric/metabolic surgery**.
- ▶ **Precipitating event:** IV glucose, carbohydrate loading, enteral/parenteral nutrition, or refeeding in a thiamine-depleted patient may acutely precipitate Wernicke encephalopathy and lactic acidosis.
- ▶ **Associated deficiency syndromes:** wet beriberi causes high-output heart failure with tachycardia, cardiomegaly, edema and warm extremities; dry beriberi causes symmetric sensorimotor polyneuropathy with pain, paresthesia and loss of reflexes, legs more than arms.

Pathogenesis and vulnerable neuroanatomy

- ▶ Thiamine deficiency impairs cerebral energy metabolism, especially in metabolically active periventricular and diencephalic structures; pyruvate may accumulate and transketolase activity falls.
- ▶ Characteristic sites are **periaqueductal gray**, tectal plates, **medial thalami**, **mammillary bodies**, walls of the third and fourth ventricles, cerebellar vermis, pons, medulla, dentate nuclei, cranial nerve nuclei and vestibular nuclei.
- ▶ Eye signs reflect involvement of **cranial nerve III, VI and VIII nuclei**, medial longitudinal fasciculus and periaqueductal/brainstem ocular motor pathways.
- ▶ Gait ataxia reflects combined involvement of the **cerebellar vermis**, vestibular pathways and often peripheral neuropathy; truncal/gait ataxia is more prominent than limb ataxia.
- ▶ Autonomic features such as **hypothermia** and **postural hypotension** reflect hypothalamic and brainstem autonomic pathway involvement.

- ▶ Korsakoff amnesia reflects damage in the **mammillary bodies, mammothalamic tract, medial dorsal/anterior thalamic nuclei, hippocampal-parahippocampal circuits and related limbic memory pathways.**
- ▶ Pathology evolves from congestion and **petechial hemorrhages** to glial proliferation, myelin pallor, shrinkage and discoloration in the same regions seen on MRI.

Clinical features

Component	Exam-ready points
Mental status	Confusion is the commonest feature, developing over days to weeks: inattention, apathy, disorientation, impaired short-term memory and reduced mental control. Stupor or coma is uncommon but possible.
Ocular signs	Horizontal gaze-evoked nystagmus, vertical nystagmus on upgaze, bilateral lateral rectus weakness/sixth nerve palsy, conjugate gaze palsy, ophthalmoplegia; sluggish pupils and light-near dissociation may occur.
Ataxia	Broad-based gait, truncal instability, inability to stand/walk unaided; limb ataxia is less prominent. Vertigo may be absent despite vestibular nuclear involvement.
Peripheral/autonomic	Peripheral neuropathy, pain/paresthesia, reduced reflexes, hypothermia, postural hypotension; look for malnutrition, liver disease and alcohol withdrawal.
Korsakoff syndrome	Usually follows repeated or inadequately treated Wernicke episodes: severe anterograde and retrograde amnesia, impaired learning, disorientation to time/place and early confabulation, with relative preservation of alertness, attention and social behavior.

- ▶ The classic triad is useful but insensitive: Bradley notes all three elements in fewer than half of patients; a Spanish series found the triad in 39% of alcoholic and 29% of non-alcoholic patients.
- ▶ In alcohol use disorder, Wernicke encephalopathy may coexist with withdrawal delirium, hepatic encephalopathy, head injury, subdural hematoma, hypoglycemia, sepsis and electrolyte disturbances.

Diagnosis and investigations

- ▶ **Diagnosis is clinical and urgent.** Do not wait for laboratory confirmation before giving parenteral thiamine.

- ▶ **Caine criteria:** suspect Wernicke encephalopathy when any **two of four** are present: (1) dietary deficiency/malnutrition, (2) oculomotor abnormality, (3) cerebellar dysfunction or impaired gait, (4) altered mental status or memory impairment. These criteria are more sensitive than requiring the full triad.
- ▶ **Therapeutic response** supports the diagnosis: improvement in ocular signs or confusion within 1-2 days is strongly suggestive, but absence of immediate full recovery does not exclude the diagnosis.
- ▶ **Laboratory tests:** draw blood before treatment if feasible, but never delay therapy. Tests include whole-blood/serum thiamine, urinary thiamine excretion, erythrocyte transketolase activity before and after thiamine pyrophosphate, and serum pyruvate. Harrison uses >25% stimulation of transketolase activity after thiamine pyrophosphate as abnormal.
- ▶ **MRI brain** is the best imaging test when available: symmetric T2/FLAIR and diffusion abnormalities in periaqueductal regions, tectal plates, medial thalami and mammillary bodies; cerebellar vermis, pons, medulla, dentate nuclei, basal ganglia and cranial nerve nuclei may be involved. SWI may show petechial hemorrhage in mammillary bodies.
- ▶ **CT brain** is much less sensitive but may be needed to exclude trauma, hemorrhage, hydrocephalus or stroke. CSF is usually normal or shows only mild protein elevation.
- ▶ **Differential diagnosis:** alcohol intoxication or withdrawal delirium, hepatic encephalopathy, uremic encephalopathy, sepsis-associated encephalopathy, hypoglycemia, stroke/posterior circulation disease, encephalitis, sedative/opioid intoxication, electrolyte disorders and Marchiafava-Bignami disease.

Management

Situation	Treatment
Suspected/established Wernicke encephalopathy	Give thiamine immediately before glucose. CMDT recommends empiric thiamine 500 mg IV three times daily for 3-5 days when Caine criteria are met; Bradley gives 500 mg IV acutely followed by 100 mg three times daily during the first week. Harrison recommends 200 mg IV three times daily in acute thiamine deficiency with neurologic signs until no further acute improvement, then oral thiamine.
At-risk coma/intoxication or emergency dextrose	Give IV thiamine first; CMDT coma protocol gives thiamine 100 mg IV , followed by 50% dextrose 25 g and naloxone when indicated.
Alcohol withdrawal prophylaxis	Hydration, electrolyte correction and vitamins; CMDT uses thiamine 100 mg IV daily for 3 days , then oral thiamine for prevention. Harrison advises

Situation	Treatment
	oral multivitamins with 50-100 mg oral thiamine daily for a week or more in withdrawal.
After acute phase	Continue oral thiamine until nutrition is secure; correct diet, protein-calorie malnutrition and coexisting B-vitamin deficiencies.

- ▶ **Magnesium repletion is essential** because magnesium is required for thiamine activation; thiamine response may be poor if magnesium is low.
- ▶ Treat associated alcohol withdrawal with benzodiazepines when indicated, correct hypokalemia/hypomagnesemia/hypophosphatemia, screen for trauma, infection, hypoglycemia and liver disease, and arrange alcohol-use-disorder treatment and nutritional rehabilitation.
- ▶ Oral thiamine alone is inadequate initially in suspected Wernicke encephalopathy because absorption is unreliable in debilitated and alcoholic patients.

Prognosis, complications and prevention

- ▶ Untreated Wernicke encephalopathy is progressive and may cause death, coma or permanent Korsakoff syndrome.
- ▶ Even with treatment, early studies reported mortality of **10-20%**; delayed recognition is common because the full triad is often absent and non-alcoholic cases are overlooked.
- ▶ Ocular signs usually improve rapidly, often within hours to 24 h, although fine horizontal nystagmus may persist in about **60%**. Gait improves slowly and may remain abnormal for months in more than one-third of patients.
- ▶ Korsakoff syndrome is often persistent; treatment is mainly supportive supervision and rehabilitation, as controlled evidence for cholinesterase inhibitors or memantine is not consistent.
- ▶ Prevention is mandatory in all high-risk patients: give thiamine before carbohydrate, during alcohol withdrawal, before/with refeeding, after bariatric surgery, during prolonged vomiting or hyperemesis, and in dialysis patients with unexplained encephalopathy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Triad and lesion-map diagram:** central label “Thiamine deficiency”; arrows to “Confusion”, “Ophthalmoplegia/nystagmus”, “Gait/truncal ataxia”; side labels “mammillary bodies”, “medial thalami”, “periaqueductal gray”, “tectal plate”, “CN III/VI/VIII nuclei”, “cerebellar vermis”, “hypothalamic autonomic pathways”.
- ▶ **Emergency treatment flowchart:** “At-risk delirium/coma/malnutrition/alcohol use” -> “Draw thiamine labs if feasible” -> “Thiamine IV before glucose” -> “High-dose IV

thiamine + Mg/B-complex/electrolytes” -> “MRI if needed; exclude trauma/sepsis/hepatic/uremic causes” -> “Oral thiamine + nutrition + abstinence plan”.

Clinical / Diagnostic significance

- ▶ Wernicke encephalopathy is a **medical emergency**, not a retrospective diagnosis; treatment is safe, inexpensive and should precede imaging and laboratory confirmation.
- ▶ The most important diagnostic trap is waiting for the full triad; use **Caine criteria** in any malnourished, alcoholic, hyperemesis, post-bariatric, refeeding or dialysis patient with delirium, ataxia or ocular signs.
- ▶ Always give **thiamine before dextrose** in at-risk patients; glucose administration increases thiamine requirement and may precipitate or worsen Wernicke-Korsakoff syndrome.
- ▶ MRI helps confirmation but a negative CT or absent MRI lesion does not exclude the diagnosis.
- ▶ Distinguish from delirium tremens: DT has autonomic hyperactivity, tremor, hallucinations and withdrawal timing; Wernicke has nutritional risk plus ocular motor signs and gait ataxia, and both can coexist.
- ▶ Persistent amnesia after the acute delirium clears suggests **Korsakoff syndrome**.

High-yield exam pointers

- ▶ Write the triad: **confusion + ophthalmoplegia/nystagmus + gait ataxia**.
- ▶ Mention that the full triad is absent in many cases; use **two of four Caine criteria**.
- ▶ Never give glucose first in an at-risk patient; **thiamine before dextrose** is a must-write line.
- ▶ High-dose parenteral thiamine is required for suspected disease: **500 mg IV three times daily for 3-5 days** is the current empiric emergency regimen.
- ▶ Add **magnesium correction**, B-complex vitamins, nutrition and alcohol-withdrawal management.
- ▶ MRI lesions: **mammillary bodies, medial thalami, periaqueductal gray/tectal plate**.
- ▶ Korsakoff syndrome: **anterograde and retrograde amnesia with confabulation** after repeated or undertreated episodes.
- ▶ Prevention is needed in alcohol use disorder, hyperemesis, bariatric surgery, starvation/refeeding, prolonged IV feeding and dialysis.

SOURCE & COVERAGE

Harrison 22e — “Vitamin and Trace Mineral Deficiency and Excess”; “Alcohol and Alcohol Use Disorders”; Bradley & Daroff’s Neurology 8e — “Deficiency Diseases of the Nervous System”; “Toxic and Metabolic Encephalopathies”; Brazis Localization — “Cranial Nerve VIII: The Vestibulocochlear Nerve”; “The Localization of Lesions Affecting the Hypothalamus and

Pituitary”; DeJong’s Neurologic Examination — “An Overview of Brainstem and Cranial Nerve Anatomy”; “The Mental Status Examination”; CMDT 2026 — “Nervous System Disorders”; “Nutrition, Nutritional Disorders, & Obesity”; “Substance Use Disorders”; “Liver, Biliary Tract, & Pancreas Disorders”.



Infectious diseases



Management of a Cat Bite — Wound Care, Antimicrobial Therapy and Infection Prophylaxis (Rabies & Tetanus)

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — An animal bite is a breach of the skin’s protective barrier that inoculates the biting animal’s oropharyngeal flora into deeper, susceptible tissues, converting the wound into a contaminated, often deep, polymicrobial injury. Cat bites are clinically deceptive: although the external wound is small, the cat’s *narrow, sharp canine teeth* drive bacteria deep, so that **more than half of all cat bites become infected** — a far higher rate than dog bites — with a strong predilection for **septic arthritis and osteomyelitis** when punctures overlie a joint, especially of the hand. The dominant pathogen is *Pasteurella multocida*, which advances within hours. Management therefore rests on four pillars: structured assessment, aggressive local wound care, appropriate antibiotic therapy, and prophylaxis against rabies and tetanus.

Microbiology — why a cat bite is dangerous

Cat-bite infections are **polymicrobial**, reflecting the feline oropharynx plus skin/soil organisms; cultures yield a mix of aerobes and anaerobes.

Organism	Note
* <i>Pasteurella multocida</i> *	Small gram-negative coccobacillus; normal feline oral flora; the single commonest isolate (~75% of cat-bite infections); causes rapidly advancing cellulitis with purulent drainage and adenitis, often within hours
<i>Staphylococcus aureus</i> (incl. MRSA)	Skin/oral flora; consider empirical MRSA cover in high-risk wounds
β-hemolytic streptococci	Common aerobic co-pathogen
Anaerobes — <i>Bacteroides</i> , <i>Fusobacterium</i> , <i>Prevotella</i> , <i>Porphyromonas</i>	Especially in deep punctures; many produce β-lactamase

Organism	Note
* <i>Capnocytophaga canimorsus</i> *	Fulminant sepsis, DIC, renal failure in asplenic, cirrhotic or immunosuppressed hosts
<i>Bartonella henselae</i>	Cat-scratch disease — late consequence (see below)
<i>Francisella tularensis</i> (tularemia); <i>Sporothrix schenckii</i> (sporotrichosis)	Reported after cat bites/scratches

Approach to the patient — focused assessment

- ▶ **History:** type of animal, *provoked vs unprovoked* attack (unprovoked raises rabies suspicion), **time elapsed** since injury, the animal's vaccination/ownership status and current whereabouts.
- ▶ **Host risk factors:** diabetes mellitus, liver disease/cirrhosis, **splenectomy/asplenia**, immunosuppression (glucocorticoids, SLE, leukaemia), mastectomy or lymphoedema of the involved limb, prosthetic joints/valves — all favour antibiotics and predict severe disease.
- ▶ **Wound examination:** type (puncture/laceration/scratch), depth, and crucially **joint, tendon, nerve or bone involvement** — hand wounds warrant **hand-surgery consultation**. Document with a diagram or photograph. Assess for established infection (redness, exudate, foul odour, lymphangitis, lymphadenopathy).
- ▶ **Investigations:** **radiograph** of penetrating/hand wounds for fracture, retained tooth or foreign body and to baseline for osteomyelitis; **Gram stain and aerobic + anaerobic culture** of all infected wounds (use a small-tipped swab in deep punctures); WBC count and **blood cultures** if systemic infection is suspected. Notify the laboratory if fastidious organisms (e.g. *Capnocytophaga*) are suspected, as they need prolonged incubation.

Wound management (local care) — the most important step

- ▶ **Copious irrigation** with normal saline and **debridement** of devitalised tissue; remove foreign bodies; drain all abscesses. Thorough cleansing/irrigation is the single most important factor in reducing infection.
- ▶ **Wound closure is controversial and generally avoided** in bite wounds. **Cat-bite puncture wounds should be left unsutured** because of their very high infection rate; small uninfected wounds heal by secondary intention, and **delayed primary closure** is used once the risk of infection has passed.
- ▶ **Facial wounds** are an exception — usually sutured after meticulous cleaning, because of excellent blood supply, low infection risk and cosmetic importance.
- ▶ Wounds **>12 h old** (arm/leg) or **>24 h old** (face) and **all hand wounds** should not be closed primarily.
- ▶ **Elevate and immobilise** the part (especially the hand) — a valuable adjunct to antimicrobial therapy.

Antibiotic therapy

Cover must target *S. aureus*, *Pasteurella*, *Capnocytophaga*, streptococci and oral anaerobes. **Avoid monotherapy with dicloxacillin, cephalexin, macrolides or clindamycin** — all lack reliable *Pasteurella* activity; azithromycin and 1st/2nd-generation cephalosporins are inadequate. **TMP-SMX has poor anaerobic activity** and must be paired with an anti-anaerobe.

Scenario	Regimen
Prophylaxis (early uninfected cat bite — <i>usually advised</i> , see below)	Amoxicillin-clavulanate 875/125 mg PO q12h (or 500 mg PO TID) for 3–5 days
Penicillin-allergic	Clindamycin or metronidazole <i>plus</i> (doxycycline 100 mg BD or double-strength TMP-SMX BD or a fluoroquinolone, e.g. ciprofloxacin 500 mg BD); or moxifloxacin 400 mg OD monotherapy
Established infection	Amoxicillin-clavulanate PO; or ampicillin-sulbactam 1.5–3.0 g IV q6–8h; or ceftriaxone + metronidazole; or ertapenem 1 g IV daily
* <i>Serious P. multocida</i> *** (pneumonia/sepsis/meningitis)	IV penicillin G (alternatives: 2nd/3rd-gen cephalosporin, ciprofloxacin)
** <i>C. canimorsus</i> bacteraemia**	2-week course of IV penicillin G or ampicillin-sulbactam, then step-down oral

- **Duration:** established skin/soft-tissue infection generally 5–7 days (up to 2–3 weeks per CMDT); septic arthritis 4 weeks, osteomyelitis 6 weeks.
- **Prophylaxis is recommended for essentially all cat bites**, particularly hand bites, because of their high infection rate; also for severe/crush/deep wounds, possible bone/joint involvement, genital wounds, delayed care (>8 h), and the immunocompromised/comorbid host. A meta-analysis showed prophylaxis halves the infection rate.

Rabies post-exposure prophylaxis (PEP)

Rabies is almost uniformly fatal but **nearly always preventable** by prompt PEP — *more cats than dogs are reported rabid each year* in the USA, so a cat bite mandates a deliberate rabies decision in consultation with public-health authorities.

- **Risk stratification:** a healthy-appearing **dog, cat or ferret** may be **confined and observed for 10 days** — PEP is not needed if the animal stays healthy; if it sickens, euthanise and test the brain by **direct fluorescent antibody (DFA)**. If the animal escaped, is unprovoked, or rabies is endemic, **start PEP without delay**.
- **Local wound care:** wash thoroughly with **soap and water**, debride — must not be delayed.
- **Passive immunisation** (previously unvaccinated only): **Human Rabies Immune Globulin (HRIG)** 20 IU/kg — infiltrate **as much as anatomically possible into and around the wound**, remainder IM at a distant site. If HRIG is unavailable, **equine RIG** 40 IU/kg. RIG must be given

no later than day 7 after the first vaccine dose; never give RIG and vaccine at the same site/syringe.

- ▶ **Active immunisation:** four 1-mL doses of cell-culture rabies vaccine IM in the deltoid (anterolateral thigh in children) on days 0, 3, 7 and 14; a 5th dose on day 28 only in the immunocompromised. Never give in the gluteus (vaccine failures).
- ▶ **Previously vaccinated patient:** two booster doses on days 0 and 3; no RIG.

Tetanus & other prophylaxis

A bite is a contaminated, tetanus-prone wound.

- ▶ **Booster (Td/Tdap):** indicated if primary immunisation is incomplete/unknown or if the last booster was >5 years ago (bite wounds), as opposed to the >10-year rule for clean minor wounds.
- ▶ **Human Tetanus Immune Globulin (TIG):** given (with the vaccine, at a separate site) to patients who have not completed primary immunisation or whose status is unknown.
- ▶ **Hepatitis B:** for human-bite exposure to blood-tinged saliva, give hepatitis B vaccine ± HBIG (not generally required after animal bites).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Rabies PEP decision algorithm** — boxes/labels: “Bite or saliva contaminating wound/mucosa?” → “Rabies endemic in species & area?” → “Animal captured?” → if a normally-behaving dog/cat/ferret → “Observe 10 days” (well → No prophylaxis; ill/DFA-positive → RIG + vaccine); if escaped/wild/abnormal → RIG + vaccine.
- ▶ **Cat-bite hand puncture (cross-section)** — labels: narrow deep puncture, epidermis/dermis, metacarpophalangeal joint, tendon sheath, deep inoculation of *Pasteurella multocida*, small external wound belying deep penetration.

Clinical / Diagnostic significance

- ▶ The small external wound of a cat bite belies deep inoculation — a low threshold for imaging, prophylaxis and hand-surgery referral prevents missed septic arthritis/osteomyelitis.
- ▶ **Asplenic/cirrhotic patients** are at risk of fulminant *Capnocytophaga canimorsus* sepsis with purpura fulminans and DIC — counsel and treat aggressively.
- ▶ **Cat-scratch disease** (*B. henselae*) is a late consequence: subacute, painful regional lymphadenopathy (axillary/epitrochlear) with a primary inoculation papule; usually self-limited. Aspirate (do not incise) suppurative nodes; treat extensive lymphadenopathy with **azithromycin 500 mg day 1 then 250 mg OD ×4 days**. Atypical forms include *Parinaud’s oculoglandular syndrome* and *neuroretinitis* (macular star).

- ▶ Failure to respond to antibiotics should prompt re-evaluation for **retained foreign body**, **abscess**, or **deep-space infection** needing surgical drainage.

High-yield exam pointers

- ▶ **>50% of cat bites become infected**; deep, narrow puncture → joint/bone risk.
- ▶ ****Pasteurella multocida* = commonest pathogen**; infection within hours; treat with **amoxicillin-clavulanate**.*.
- ▶ **Never use clindamycin, macrolides, cephalexin or dicloxacillin alone** (no *Pasteurella* cover).
- ▶ **Do NOT primarily suture cat-bite punctures** — irrigate, debride, leave open / delayed closure.
- ▶ **Rabies PEP**: wound wash + **HRIG 20 IU/kg infiltrated into wound** + vaccine IM deltoid on **days 0, 3, 7, 14** (4 doses); previously vaccinated → days 0 & 3 only, no RIG.
- ▶ **Healthy dog/cat/ferret** → observe **10 days** before committing to vaccine.
- ▶ **Tetanus**: bite = tetanus-prone → booster if last dose >5 yr; TIG if primary course incomplete.
- ▶ Cover MRSA empirically in high-risk wounds; **asplenia** → **Capnocytophaga** sepsis risk.
- ▶ **Cat-scratch disease** = *B. henselae*, tender regional nodes, **azithromycin**, aspirate not incise.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Infectious Complications of Bites” (microbiology, approach, wound management, antibiotic Table 146-1, prophylaxis); “Rabies and Other Rhabdovirus Infections” (post-exposure prophylaxis — HRIG 20 IU/kg, 4-dose vaccine schedule, 10-day observation); “Tetanus” (wound management, HTIG, prevention); “Bartonella Infections, Including Cat-Scratch Disease” (cat-scratch disease, azithromycin).
- ▶ **CMDT 2026** — “Common Problems in Infectious Diseases & Antimicrobial Therapy: Animal & Human Bites” (current prophylaxis/treatment regimens, durations, indications).

Coverage note: The standard tetanus wound-prophylaxis decision (Td/Tdap if last booster >5 years for tetanus-prone wounds; TIG ~250 IU IM if primary immunisation incomplete) is universally accepted internal medicine; Harrison Ch 146/157 explicitly supports the >5-year booster rule for bites and TIG for incomplete primary immunisation, while the exact prophylactic TIG dose is conventional. All organism names, drug regimens and doses above are taken verbatim from the cited chapters.



Scrub Typhus presenting as Acute Undifferentiated Febrile Illness with an Eschar and Multi-Organ Dysfunction

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Scrub typhus is an acute, mite-borne rickettsiosis caused by the obligate intracellular bacterium **Orientia tsutsugamushi*, characterised by fever, an inoculation eschar, regional lymphadenopathy and rash, and a propensity to evolve into life-threatening multi-organ dysfunction. This 34-year-old farmer with 7 days of high-grade fever and headache, a 0.5 cm punched-out black scabbed lesion (eschar) in the warm, moist left axilla, worsening breathlessness (interstitial pneumonitis/ARDS) and the triad of thrombocytopenia + acute kidney injury + transaminitis is a near-textbook presentation of severe scrub typhus with multi-organ involvement*. The disease responds dramatically to tetracyclines, so early empirical recognition is life-saving.

(a) Diagnosis and differential diagnosis

- ▶ **Most probable diagnosis:** Severe scrub typhus (*Orientia tsutsugamushi* infection) complicated by multi-organ dysfunction — pneumonitis/ARDS (breathlessness), AKI (raised creatinine), hepatitis (raised transaminases) and thrombocytopenia.
- ▶ **Clinching clues:** rural/agricultural exposure; week-long undifferentiated fever with headache; eschar in an intertriginous covered site (axilla — chiggers preferentially feed on warm, moist, occluded skin); and the classic laboratory triad of thrombocytopenia, elevated hepatic aminotransferases and azotaemia with (often) hyponatraemia — the shared signature of rickettsioses.
- ▶ **Differential diagnosis of acute febrile illness in this setting (CMDT/Harrison):** leptospirosis, dengue, enteric (typhoid) fever, malaria, Q fever, other rickettsioses (murine/endemic typhus, Indian tick typhus/spotted fever), viral haemorrhagic fevers/hantavirus, viral hepatitis, meningococcaemia and bacterial sepsis. Co-infection with malaria or leptospirosis can coexist.
- ▶ **Differential diagnosis of a black eschar (tâche noire):** other rickettsioses — Mediterranean spotted fever (*R. conorii*), African tick-bite fever (*R. africae*, often multiple eschars), rickettsialpox (*R. akari*); cutaneous anthrax, ecthyma gangrenosum, necrotic spider bite, and tularaemia/cutaneous leishmaniasis. The combination of eschar + lymphocytosis + raised CRP helps separate scrub typhus from dengue.

(b) Organism and vector

Feature	Detail
Organism	<i>*Orientia tsutsugamushi</i> (formerly <i>Rickettsia tsutsugamushi</i>) — small, obligately intracellular gram-negative coccobacillus; genetically and structurally distinct from <i>Rickettsia</i> — it lacks lipopolysaccharide* (and peptidoglycan) in its cell wall
Antigenic behaviour	Marked antigenic diversity; immunity to a homologous strain wanes over 1–3 years and cross-protection can be lost within a month, allowing

Feature	Detail
	reinfection. Related species: <i>O. chuto</i> (SW Asia/Africa), <i>Candidatus O. chiloensis</i> (Chile)
Vector	Larval trombiculid mite (chigger) — * <i>Leptotrombidium deliense</i> and related species; the larva is the only host-feeding stage*
Reservoir/maintenance	The mite is both vector and reservoir — maintained by transovarial (and transstadial) transmission ; humans are incidental hosts. Chiggers abound in heavy scrub vegetation during the wet season
Geography	Endemic across the “ tsutsugamushi triangle ” — eastern/southern Asia (India, China), northern Australia, and western Pacific & Indian Ocean islands; reemerging

(c) How to confirm the diagnosis

- ▶ **Identify the eschar** — clinically pathognomonic when present; deliberately search axillae, groin, genitalia, waistband and skin folds (eschar is recognised in only ~19% in some series, so absence does not exclude). Look for regional lymphadenopathy.
- ▶ **Serology (mainstay/reference standard):** Indirect fluorescent antibody (IFA) and indirect immunoperoxidase assays are the *gold standard*; demonstrate a **four-fold rise in titre** between acute and convalescent sera. ELISA detects *Orientia*-specific IgM/IgG; **rapid lateral-flow chromatographic tests** aid point-of-care diagnosis.
- ▶ **Molecular:** PCR amplification of *Orientia* genes is the **most sensitive test in early illness** and is **higher-yield from the eschar than from blood**; obtain samples **before starting doxycycline**. CMDT recommends combined ELISA + PCR.
- ▶ **Culture:** feasible from early blood but needs a **BSL-3** specialised laboratory; rarely done.
- ▶ **Supportive laboratory findings:** thrombocytopenia, normal/low WBC, elevated transaminases and bilirubin, raised creatinine, hyponatraemia.
- ▶ **Weil–Felix test** (*Proteus* OX-K agglutination): cheap and widely used in resource-limited settings but **insensitive/non-specific** — only supportive (*see Coverage note*).

(d) How would you treat this patient

- ▶ **Drug of choice** — Doxycycline 100 mg twice daily, PO or IV (IV given the vomiting/severe illness), for 7–15 days; continue **at least 3 days after defervescence** — shorter courses risk relapse. Rapid clinical response (defervescence often within ~48 h) supports the diagnosis.
- ▶ **Severe / multi-organ disease (this patient): combination therapy.** Both Harrison and CMDT note that in severe scrub typhus, the combination of IV doxycycline + azithromycin is superior

to either as monotherapy (***INTREST trial**, *Varghese et al*, NEJM* 2023 — lower 28-day mortality, fewer day-7 complications, less persistent fever than monotherapy).

- ▶ **Azithromycin** 500 mg once daily for 3 days — preferred in **pregnancy, children and doxycycline allergy/intolerance**; efficacy similar to doxycycline with fewer adverse effects.
- ▶ **Chloramphenicol** 500 mg four times daily (7–15 days) — alternative, including pregnancy.
- ▶ **Rifampin** — reserved for the doxycycline/chloramphenicol **poorly-responsive strains** described in northern Thailand (responds to azithromycin and rifampin).
- ▶ **Aggressive supportive/organ care**: ICU admission; **lung-protective mechanical ventilation** for ARDS, judicious fluid resuscitation (avoid precipitating non-cardiogenic pulmonary oedema), **renal replacement therapy** for severe AKI, platelet support if bleeding, vasopressors for shock.

(e) Complications to anticipate

- ▶ **Respiratory**: interstitial **pneumonitis** progressing to **ARDS** (this patient's worsening breathlessness) — a leading cause of death.
- ▶ **Renal**: **acute kidney injury** (already present); may need dialysis.
- ▶ **Hepatic**: hepatitis/transaminitis, hyperbilirubinaemia.
- ▶ **Neurological**: **meningoencephalitis / aseptic meningitis**.
- ▶ **Cardiac**: myocarditis.
- ▶ **Haematological/systemic**: DIC, severe thrombocytopenia with bleeding, **septic/toxic shock and multi-organ failure**, and **haemophagocytic lymphohistiocytosis (haemophagocytosis)** — the latter, like ARDS, tends to appear in the **2nd–3rd week**.
- ▶ **Death**: untreated classic case-fatality ~6% (Harrison), reported up to **10–30%** in severe series (CMDT). **Poor-prognostic markers**: hypotension requiring vasopressors, ICU need, **age >60 years**, **absence of an eschar** (delays diagnosis), pregnancy, leukocytosis and hypoalbuminaemia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **The eschar (labelled)**: central **black necrotic scab/crust** → surrounding **erythematous halo** → at a covered intertriginous site (axilla/groin) → with **draining regional lymphadenopathy**. Labels: *Black eschar (tâche noire)*, *Erythematous rim*, *Site = warm moist skin fold*, *Regional lymph node*.
- ▶ **Transmission cycle**: *Leptotrombidium* mite eggs → **larva (chigger)** — **only feeding stage** bites human → inoculates *O. tsutsugamushi* → **transovarial transmission** maintains infection in mite (mite = vector + reservoir); human = incidental host. Labels: *Egg*, *Larva/chigger*, *Nymph*, *Adult mite*, *Transovarial transmission*, *Human (incidental host)*.

Clinical / Diagnostic significance

- ▶ Scrub typhus is a leading, treatable cause of **acute undifferentiated febrile illness** and of **fever of unknown origin** in India and Asia — always sought in a febrile farmer/agricultural worker.
- ▶ The **eschar is the single most useful clinical clue**; a focused search of skin folds changes management instantly.
- ▶ **Empirical doxycycline must not await serology** — acute-phase antibody tests are frequently negative early; treatment is started on clinical-epidemiological suspicion.
- ▶ The classic biochemical triad (**thrombocytopenia + transaminitis + AKI**) in a febrile patient with an eschar should trigger antirickettsial therapy and ICU-level vigilance for ARDS/MODS.

High-yield exam pointers

- ▶ **Organism:** *Orientia tsutsugamushi* — intracellular gram-negative, **lacks LPS**; strains show wide antigenic diversity (no lasting cross-immunity → reinfection).
- ▶ **Vector & reservoir:** larval *trombiculid mite/chigger* (*Leptotrombidium deliense*); *maintained by transovarial transmission* — mite is both* vector and reservoir.
- ▶ **Eschar** = inoculation site; favours warm, moist, covered areas (axilla, groin, waist); often missed → search deliberately. **Relative bradycardia** is a clue.
- ▶ **Geography:** “tsutsugamushi triangle”; endemic and reemerging in India.
- ▶ **Diagnosis:** IFA = gold standard (4-fold titre rise); **PCR from eschar = most sensitive early test**; obtain samples **before doxycycline**; Weil-Felix OX-K only supportive.
- ▶ **Treatment:** **doxycycline 100 mg BD** (drug of choice); **azithromycin** in pregnancy/children; **doxycycline + azithromycin for severe disease** (INTREST trial); treat ≥3 days post-defervescence.
- ▶ **Lethal complications:** ARDS, AKI, myocarditis, meningoencephalitis, DIC, HLH, MODS — many in week 2–3.
- ▶ **Poor prognosis:** vasopressor-dependent shock, age >60, **absent eschar**, pregnancy, hypoalbuminaemia.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Rickettsial Diseases” (Scrub Typhus section: organism, *Leptotrombidium*/chigger vector, transovarial maintenance, clinical features, IFA/PCR diagnosis, doxycycline/azithromycin/chloramphenicol regimens and the severe-disease combination; rickettsial laboratory triad and eschar differential).
- ▶ **CMDT 2026** — “Viral & Rickettsial Infections” (Scrub Typhus: essentials, tsutsugamushi triangle, eschar yield, relative bradycardia, ELISA+PCR strategy, doxycycline/minocycline/azithromycin treatment, INTREST trial [Varghese et al, *NEJM* 2023], poor-prognostic factors, differential diagnosis and complications).

- **Coverage note:** The Weil-Felix (Proteus OX-K) agglutination test and the named antigenic serotypes Karp/Kato/Gilliam are *universally accepted standard rickettsiology* but are **not explicitly described in the corpus chapters consulted**; Harrison/CMDT instead emphasise IFA/immunoperoxidase, ELISA and PCR. The chigger's preference for moist intertriginous skin (axilla/groin) is standard teaching consistent with, though not verbatim in, the corpus.



Pulmonary Nocardiosis in a Diabetic with Non-resolving Pneumonia — CT Thorax Findings and Management

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Nocardiae* are aerobic, Gram-positive, weakly (partially) acid-fast, catalase-positive filamentous bacteria that are ubiquitous saprophytes of soil and water, acquired chiefly by **inhalation**. Pulmonary nocardiosis is a subacute, **non-resolving necrotising pneumonia** that classically arises in hosts with impaired cell-mediated/phagocyte defence and has a strong tendency to **cavitate, cross tissue planes (pleura/chest wall) and disseminate haematogenously to the brain and skin**. A BAL culture growing *Nocardia* in this 45-year-old diabetic with a pneumonia failing to clear is therefore not a contaminant but a call to define disease extent (especially occult brain abscess) and start prolonged, susceptibility-guided combination therapy led by trimethoprim-sulfamethoxazole.

Why suspect *Nocardia* in this patient (microbiology and host risk)

- **Organism:** Gram-positive, beaded, **branching filaments** ~1 µm wide, up to 50 µm long that fragment into cocco-bacillary forms; **weakly/partially acid-fast** on modified Kinyoun, Ziehl-Neelsen or Fite-Faraco stains (weak-acid decolouriser) — hence frequent confusion with *Mycobacterium tuberculosis*. Cell wall contains mycolic acids; grows as chalky, wrinkled, white-yellow/orange colonies.
- **Common pathogenic species:** *N. farcinica*, *N. cyriacigeorgica*, *N. nova* complex, *N. abscessus*, *N. brasiliensis* (mostly cutaneous), *N. otitidiscaviarum*, *N. transvalensis*. *N. farcinica* has a special predilection for CNS spread and is often ceftriaxone-resistant.
- **Host defects predisposing to invasive disease:** defects of **cell-mediated immunity and phagocytes** — solid-organ or haematopoietic stem-cell transplantation, **systemic corticosteroids/Cushing syndrome**, immunosuppressive therapy, HIV, chronic granulomatous disease (CGD), IL-12/IL-12R deficiency, pulmonary alveolar proteinosis with **anti-GM-CSF autoantibodies**.

- ▶ **Structural lung disease / bronchiectasis** predisposes to airway *colonisation*; a positive respiratory culture must be read in clinical context, but in an immunosuppressed host it usually reflects true disease and warrants empirical therapy.
- ▶ *Diabetes mellitus* (this patient) is a widely recognised predisposing condition through impaired neutrophil/phagocyte function — see Coverage note.

Pleuropulmonary clinical picture (the “non-resolving pneumonia”)

- ▶ **Subacute onset** over days to weeks; in the severely immunocompromised it may be acute. **Cough productive of small amounts of thick, purulent, non-malodorous sputum** is prominent.
- ▶ Fever, anorexia and malaise are common; **weight loss, dyspnoea, pleuritic pain and haemoptysis are less common.**
- ▶ Without definitive therapy there are characteristic **remissions and exacerbations over weeks to months** — the classic “non-resolving / relapsing” pneumonia that fails standard antibiotics and mimics TB, fungal infection or malignancy.
- ▶ **Dissemination occurs in up to one-third** of pulmonary cases — CNS (brain abscess) and skin/subcutaneous tissue are the commonest metastatic sites.

CT thorax — what you would find

Finding	Detail
Nodules and masses	Solid pulmonary nodules and mass lesions in one or more lobes (often multifocal/multilobar)
Cavitation	Nodules and masses frequently cavitate — thick-walled cavities are characteristic
Consolidation / infiltrates	Dense lobar or patchy air-space consolidation
Pleural disease	Pleural effusion or empyema in ~one-third of cases (empyema may occur even without parenchymal disease)
Chest-wall extension	Direct invasion through the ribs and chest wall with chest-wall abscess (non-respect of tissue planes)
Pattern	Multifocal, indolent, progressive; radiologically mimics TB, fungal pneumonia, metastases or bronchogenic carcinoma

- ▶ Representative CT (Harrison Fig. 179-3): solid nodules, a cavitated nodule, an ipsilateral pleural effusion and a chest-wall abscess.
- ▶ *Practical pearl*: the combination of **cavitating nodules/masses + effusion/empyema + chest-wall involvement** in an immunocompromised or diabetic host with a non-resolving pneumonia should raise nocardiosis specifically.

Establishing the diagnosis and staging extent

- ▶ **Microbiology is the cornerstone.** Sputum smears are *often negative*, so **BAL fluid or lung biopsy** (as done here) is the higher-yield specimen.
- ▶ **Stains:** Gram stain (beaded branching filaments) plus a **modified acid-fast stain** (weak-acid decolourisation); organisms may take up silver stains.
- ▶ **Culture:** grows on most fungal/mycobacterial and routine media but **slowly** — **colonies in up to 2 weeks, typical morphology by 4 weeks**; alert the laboratory to incubate longer and to **avoid mycobacterial decontamination procedures** (they kill *Nocardia*). Selective media (colistin-nalidixic acid, modified Thayer-Martin, BCYE) improve recovery from mixed flora.
- ▶ **Speciation and susceptibility:** identify at least to complex level by **MALDI-TOF MS or gene sequencing** (16S rRNA, *secA1*, *hsp65*, *gyrB*); perform **susceptibility testing** by CLSI-approved **broth microdilution** (E-tests less reliable) — species-directed therapy matters because susceptibilities differ markedly.
- ▶ **Mandatory search for disseminated disease — image the brain.** Every patient with pulmonary/systemic nocardiosis, **regardless of CNS symptoms**, must have **contrast-enhanced brain imaging** to exclude occult abscess (one-third of CNS cases are asymptomatic). **MRI with gadolinium is preferred** (more sensitive); CT is reserved for when MRI is not possible. Nocardial brain abscesses are typically **multiple, multilobulated, ring-enhancing**.
- ▶ **Identify the immune defect:** test for **HIV**; in the absence of an obvious risk factor consider **CGD** and anti-GM-CSF autoantibodies; optimise/document the diabetic and any iatrogenic immunosuppression.

Management

Principles: susceptibility-guided, **prolonged** (months), **combination therapy** for **severe/disseminated/CNS disease** then de-escalation to a single oral agent, plus **source control** (drainage of empyema/abscess) and **correction of host factors** (glycaemic control, reduce immunosuppression where feasible).

Agent	Dose	Role / caveats
Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 10–20 mg/kg + SMX 50–100 mg/kg per day in 2 divided doses initially; maintenance down to TMP 5 / SMX 25 mg/kg	Drug of choice; sulfa allergy → desensitisation
Linezolid	600 mg PO/IV q12h	Uniformly active against all species; cytopenias/neuropathy limit therapy after 2–3 weeks (tedizolid less toxic)
Amikacin	5–7.5 mg/kg q12h or 15 mg/kg q24h	Active vs nearly all species (except <i>N. transvalensis</i> , some <i>N.</i>

Agent	Dose	Role / caveats
		<i>pseudobrasiliensis</i>); monitor levels/renal function
Imipenem / Meropenem	Imipenem 500 mg IV q6h; meropenem 2 g IV q8h	β-lactam for combination; meropenem preferred if CNS involved (lower seizure risk)
Ceftriaxone	—	Useful but <i>*not active against N. farcinica***</i>
Amoxicillin-clavulanate	875/125 mg bid	Effective in <i>N. brasiliensis</i> , some <i>N. farcinica</i>
Moxifloxacin / Minocycline	Minocycline 100–200 mg bid	Oral options; moxifloxacin most active quinolone

- ▶ **Severe disease (as here, non-resolving pneumonia ± dissemination):** empirical combination of two or three of TMP-SMX, linezolid, amikacin and a carbapenem (imipenem, or meropenem if CNS). Clinical improvement usually appears in 1–2 weeks (may be slower).
- ▶ **De-escalation:** after definite improvement, continue with a single oral drug, usually TMP-SMX.
- ▶ **Duration:** pulmonary/systemic with intact host defences 6–12 months; with deficient host defences 12 months (indefinite in AIDS with CD4 <200/μL or CGD); CNS disease 12 months (6 months if all CNS disease excised); primary cutaneous 2 months.
- ▶ **Surgery:** drain empyema and chest-wall/soft-tissue abscesses; **brain abscesses** aspirated/drained/excised if diagnosis unclear, large, or failing medical therapy; repeat imaging to confirm resolution (radiographic lag is expected).
- ▶ **Diabetes-specific:** tight glycaemic control and treating any concomitant immunosuppression are integral to cure; **do not give topical corticosteroids** if nocardial keratitis coexists.
- ▶ **Prognosis:** mortality <10% for localised pulmonary disease; higher with dissemination, worst with CNS involvement and delayed therapy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **CT thorax (axial) schematic of pulmonary nocardiosis** — labels: *thick-walled cavitating nodule, multiple solid nodules, lobar consolidation, pleural effusion/empyema, chest-wall abscess invading through rib, (absence of significant hilar lymphadenopathy).*
- ▶ **Modified acid-fast (Kinyoun/ZN) smear of BAL** — labels: *beaded, branching, partially acid-fast filaments ~1 μm wide, fragmentation into cocco-bacillary forms, neutrophilic background.*

Clinical / Diagnostic significance

- ▶ Treat *Nocardia* in BAL of an immunosuppressed/diabetic patient with a non-resolving pneumonia as **true infection**, not colonisation, and act on it.
- ▶ The single highest-yield staging step is **brain imaging (MRI preferred)** to catch silent abscesses that change duration and the choice of carbapenem.
- ▶ **Alert the microbiology lab** (slow grower; avoid mycobacterial decontamination) and obtain **species ID + susceptibilities** — they directly dictate the regimen (e.g., ceftriaxone fails *N. farcinica*).
- ▶ Differentiate from TB (both acid-fast, both cavitate) by branching filament morphology and culture/molecular ID — clinically important because mismanagement as TB delays cure.

High-yield exam pointers

- ▶ *Nocardia* = aerobic, **weakly acid-fast, branching beaded Gram-positive filaments**; acquired by **inhalation**; opportunist of impaired cell-mediated immunity.
- ▶ CT hallmark: **multifocal cavitating nodules/masses + pleural effusion/empyema ($\sim\frac{1}{3}$) + chest-wall invasion**.
- ▶ **Sputum often negative** → BAL/biopsy; cultures slow (up to 2–4 weeks) — *tell the lab*.
- ▶ **TMP-SMX is the drug of choice**; severe disease → **2–3 drug combination** (add linezolid/amikacin/carbapenem).
- ▶ **Meropenem over imipenem if CNS**; **ceftriaxone not active against N. farcinica****.
- ▶ **Always image the brain** even if asymptomatic; nocardial brain abscess = **multiple, multilobulated, ring-enhancing**.
- ▶ Prolonged therapy: **6–12 months (intact), 12 months (immunosuppressed/CNS)**.
- ▶ Linezolid is uniformly active but toxicity limits use after **2–3 weeks**; monitor counts.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Nocardiosis” (microbiology, risk factors, pulmonary/CT features incl. Figs 179-2/179-3, diagnosis, drug doses, treatment-duration Table 179-1).
- ▶ **CMDT 2026** — “Nocardiosis” (Bacterial & Chlamydial Infections) and “Pulmonary Disorders” (essentials of diagnosis, chest-wall invasion, TMP-SMX dosing 15 mg/kg/day, imipenem/meropenem/amikacin/linezolid/minocycline doses, brain-imaging rule, 6–12-month duration).

Coverage note: The corpus describes CT findings qualitatively (nodules, masses, cavitation, effusion/empyema, chest-wall invasion) but does not enumerate finer CT signs (e.g., halo sign, ground-glass, tree-in-bud), so these are deliberately omitted. Harrison's explicit major risk-factor list emphasises T-cell/phagocyte immunosuppression (transplant, corticosteroids, HIV, CGD)

rather than diabetes specifically; **diabetes mellitus as a predisposing condition** is included here as universally accepted internal medicine and is supported indirectly by the chapter's "impaired host-defence" framing.



A 45-year-old man from Chhattisgarh with 6 months of intermittent fever, anorexia, weight loss and massive splenomegaly: differential diagnosis, confirmatory investigations, and treatment of rK39-positive visceral leishmaniasis

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — A middle-aged man from a leishmaniasis-endemic part of India presenting with chronic intermittent fever, constitutional symptoms and *massive splenomegaly* most often has **visceral leishmaniasis (VL, kala-azar)**, a systemic protozoal infection of the reticuloendothelial system caused by the **Leishmania donovani complex** and transmitted by phlebotomine sandflies. "Massive splenomegaly" (spleen palpable >8 cm below the left costal margin or weighing ≥1000 g) sharply narrows the differential, and a positive **rK39 rapid diagnostic test** in this setting effectively confirms VL. The answer below addresses (a) the differential diagnosis and confirmatory work-up, and (b) treatment once rK39 is positive.

(a) Differential diagnosis — fever + weight loss + massive splenomegaly

The combination of a chronic febrile illness with constitutional decline and a *huge* spleen narrows a long list considerably. Causes are grouped below.

Category	Conditions to consider	Discriminating features
Chronic infections (tropical)	Visceral leishmaniasis (kala-azar) — top of the list in an endemic Indian patient; chronic/relapsing malaria & hyper-reactive malarial (tropical) splenomegaly syndrome; disseminated/miliary tuberculosis; enteric (typhoid) fever; brucellosis; schistosomiasis; disseminated histoplasmosis; subacute infective endocarditis	VL: progressive <i>massive</i> spleen, pancytopenia, hypergammaglobulinaemia, skin hyperpigmentation

Category	Conditions to consider	Discriminating features
Haematological / neoplastic (classic massive-spleen causes, Table 70-3)	Chronic myeloid leukaemia (CML); myelofibrosis with myeloid metaplasia; non-Hodgkin lymphoma / chronic lymphocytic leukaemia / hairy cell leukaemia; polycythaemia vera; Gaucher disease; autoimmune haemolytic anaemia	Leucocytosis/immature myeloid cells (CML), leucoerythroblastic film + teardrop cells (myelofibrosis), lymphadenopathy/lymphocytosis (lymphoma/CLL)
Congestive / other	Portal hypertension from chronic liver disease (congestive splenomegaly); sarcoidosis; thalassaemia major	Stigmata of chronic liver disease, varices; transfusion-dependent anaemia

- **Why VL is the leading diagnosis here:** an endemic Indian origin, 6-month indolent course, intermittent fever with the characteristic double-rise pattern, progressive *massive* splenomegaly (the single most important sign of VL), and constitutional wasting. Per Harrison, VL is **easily mistaken for malaria**, and the other key mimics it explicitly lists are **typhoid, tuberculosis, brucellosis, schistosomiasis and histoplasmosis**; splenomegaly from **portal hypertension, CML, tropical splenomegaly syndrome and schistosomiasis** can also be confused with VL.
- **Pointers that strongly suggest VL:** *fever with neutropenia or pancytopenia* in a patient from an endemic region; **hypergammaglobulinaemia** (polyclonal) in long-standing illness; moderate hepatomegaly following the splenomegaly; lymphadenopathy is *uncommon on the Indian subcontinent* (helps distinguish from African VL and from lymphoma).

(a) Investigations to confirm the diagnosis

1. **Demonstration of the parasite (gold standard).** Amastigotes (**Leishman–Donovan bodies**, 2–4 µm, each with a nucleus and a kinetoplast) within macrophages on Giemsa-stained tissue aspirate smears:

- **Splenic aspirate** — highest sensitivity >95%, but invasive and potentially dangerous (haemorrhage) in untrained hands; avoid with deranged coagulation/thrombocytopenia.
- **Bone marrow aspirate** — sensitivity 60–85%; safer and most commonly used in practice.
- **Lymph node aspirate** — sensitivity ~50%.
- **Culture** of the aspirate (e.g. NNN medium) raises yield; **PCR / real-time PCR** and **LAMP** are highly sensitive, allow species identification, and outperform microscopy on blood, but are confined to reference laboratories.

2. **Serology / antigen-based tests.**

- **rK39 immunochromatographic rapid diagnostic test** — detects antibody to a 39-amino-acid recombinant antigen from the kinesin region of *L. infantum*; needs only a drop of finger-prick blood, read in **15 min**; in immunocompetent patients sensitivity ~98% and specificity ~90% (both lower in East Africa). It is the field test of choice.

- ▶ ELISA and indirect immunofluorescent antibody test (IFAT) in equipped laboratories.
- ▶ **Caveat:** antibody tests (including rK39) **stay positive for years after cure**, so they *cannot* be used to confirm cure or detect relapse.

3. Supportive laboratory findings. Pancytopenia (early leukopenia and anaemia, later thrombocytopenia from marrow infiltration/hypersplenism); marked **polyclonal hypergammaglobulinaemia** (basis of the classic bedside **aldehyde/formol-gel test**, non-specific); raised aminotransferases $\pm$ bilirubin; hypoalbuminaemia in advanced disease. Always exclude **HIV co-infection**, which alters diagnosis (serology may be negative in up to 50%) and treatment.

(b) Treatment when the rK39 test is positive — VL in India

A positive rK39 in this clinical context confirms VL; institute supportive care plus a specific antileishmanial regimen tailored to **India**, where there is **widespread resistance to pentavalent antimonials** (cure <50% in Bihar) so antimonials are *not* first-line.

Drug / regimen	Dose & schedule	Notes
Liposomal amphotericin B (LAmB) — <i>drug of choice in India</i>	Single dose 10 mg/kg IV (96% cure; used in the national elimination programme). FDA-approved regimen: 3 mg/kg on days 1–5, 14 and 21 (total 21 mg/kg). Asian total-dose requirement only 10–15 mg/kg	Best safety profile; reticuloendothelial uptake; mild infusion reactions, backache, reversible nephrotoxicity
Amphotericin B deoxycholate	0.75–1.0 mg/kg on alternate days $\times$ 15 infusions	Effective but toxic — infusion fever/chills, nephrotoxicity, hypokalaemia; premedicate with chlorpheniramine + paracetamol
Miltefosine (first oral drug)	28 days: 50 mg/day if <25 kg; 50 mg twice daily if $\geq$ 25 kg; 2.5 mg/kg/day for children 2–11 yr	~94% cure (declining); GI upset; teratogenic — contraindicated in pregnancy , contraception $\geq$ 5 months; give as directed observed therapy
Paromomycin (aminosidine)	11 mg/kg base IM daily $\times$ 21 days	Cure ~94.6%; ototoxicity, reversible hepatotoxicity
Pentavalent antimonials (SbV) — <i>not first-line in India</i>	20 mg/kg/day IV/IM $\times$ 28–30 days	Cure >90% in Africa/Americas but <50% in Bihar ; monitor ECG — QTc >0.5 s risks fatal arrhythmia; pancreatitis, arthralgia

- ▶ **Preferred for this patient:** a single 10 mg/kg dose of liposomal amphotericin B, the regimen adopted by the Indian subcontinent VL elimination programme — short, well-tolerated and highly effective.

- ▶ **Multidrug (combination) therapy** is increasingly favoured for shorter courses, lower toxicity and reduced resistance: in India, **single-dose LAmB 5 mg/kg followed by miltefosine for 7 days, or paromomycin for 10 days, or miltefosine + paromomycin together for 10 days** each give cure rates >97%.
- ▶ **Supportive care:** correct severe anaemia with transfusion; treat intercurrent infections (pneumonia, TB, dysentery); nutritional support.
- ▶ **If HIV co-infected:** LAmB is the drug of choice; WHO now recommends **LAmB total 30 mg/kg (5 mg/kg on days 1,3,5,7,9,11) plus oral miltefosine 100 mg/day for 14 days** in the Indian subcontinent, alongside antiretroviral therapy (restoring CD4 >200/ μ L reduces relapse). Relapse within a year is common; prolonged follow-up is essential.
- ▶ **Response & follow-up:** defervescence, regression of splenomegaly, weight gain and haematological recovery occur within ~1 week; **continued improvement over 12 months indicates cure**. rK39 cannot be used to judge cure. Watch for **post-kala-azar dermal leishmaniasis (PKDL)** in 5–15% of Indian patients 6 months–3 years later (hypopigmented macules/nodules) — treated with miltefosine for 12 weeks; PKDL patients are a human reservoir, important for elimination.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Sandfly–human life cycle of *Leishmania donovani*:** label *Phlebotomus argentipes* sandfly, **promastigote** (flagellate, 10–20 μ m, in sandfly midgut), bite/inoculation into skin, uptake by **neutrophils** → **macrophages**, transformation to **amastigote** (2–4 μ m, intracellular), multiplication and rupture of macrophages, reticuloendothelial spread to **spleen, liver, bone marrow, lymph nodes**, and re-uptake by feeding sandfly.
- ▶ **Giemsa-stained splenic/marrow smear:** macrophage containing multiple **amastigotes** (**Leishman–Donovan bodies**), each labelled with **nucleus** and rod-shaped **kinetoplast**; a few extracellular parasites.

Clinical / Diagnostic significance

- ▶ **Massive splenomegaly** + fever + pancytopenia + hypergammaglobulinaemia in an endemic Indian patient is the classic VL pentad; bone marrow aspirate is the practical confirmatory test, rK39 the field test.
- ▶ Untreated VL is fatal in the majority (and historically ~90% mortality); early diagnosis and treatment cut mortality to 2–5%.
- ▶ Antimonial **resistance in Bihar** is the single most important reason LAmB/miltefosine displaced antimonials as first-line in India — a frequent exam discriminator.
- ▶ Always screen for **HIV**: it changes prognosis (atypical sites, seronegative serology, high relapse) and the specific regimen.

- ▶ VL is targeted for **elimination as a public-health problem** in India (reported 98.7% decline); single-dose LAmB and active PKDL detection underpin the programme.

High-yield exam pointers

- ▶ **Massive splenomegaly** = spleen >8 cm below LCM or ≥ 1000 g; classic causes — CML, myelofibrosis, kala-azar, chronic malaria (tropical splenomegaly), lymphoma/CLL, hairy cell leukaemia, Gaucher disease, thalassaemia major.
- ▶ Kala-azar = *L. donovani* complex; vector in India **Phlebotomus argentipes**; transmission **anthroponotic** (humans reservoir); incubation ~2–6 months.
- ▶ **Splenic aspirate sensitivity** >95% > bone marrow 60–85% > lymph node ~50%.
- ▶ **rK39**: 39-aa kinesin antigen, ~98% sensitive/~90% specific; stays positive after cure — *not* for test-of-cure.
- ▶ **First-line in India** = **liposomal amphotericin B**, single dose 10 mg/kg; antimonials fail (<50% cure) due to Bihar resistance.
- ▶ **Miltefosine** = first oral drug, 28 days, **teratogenic** (avoid in pregnancy).
- ▶ **PKDL** follows treated Indian VL in 5–15% (6 months–3 years); reservoir for transmission.
- ▶ Cure judged **clinically over 12 months** (defervescence, shrinking spleen, count recovery), not by serology.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Leishmaniasis” (visceral leishmaniasis: epidemiology, immunopathogenesis, clinical features, rK39 and parasitological diagnosis, differential diagnosis, and full treatment/regimen detail including LAmB, miltefosine, paromomycin, antimonials, combination therapy, HIV co-infection, PKDL); and “Enlargement of Lymph Nodes and Spleen” (Table 70-3, diseases associated with massive splenomegaly).
- ▶ **CMDT 2026** — “Protozoal & Helminthic Infections: Leishmaniasis” (current management: liposomal amphotericin B dosing in India, miltefosine, paromomycin, combination regimens; rK39 and splenic/marrow aspiration diagnosis; mortality figures).

Coverage note: The patient's specific state (Chhattisgarh) is not named in the corpus; the answer is grounded in the corpus's “Indian subcontinent” VL data, which applies. The **aldehyde (formol-gel) test** is included as universally accepted classic Indian bedside teaching for the hypergammaglobulinaemia that Harrison documents; it is non-specific and not a confirmatory test.



Abdominal tuberculosis

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — Abdominal tuberculosis is *Mycobacterium tuberculosis* (and occasionally *M. bovis*) infection involving the gastrointestinal tract, peritoneum, mesenteric/omental lymph nodes and solid abdominal viscera. It is one of the commonest forms of extrapulmonary TB in endemic regions such as India, classically affecting the **ileocaecal region** and the **peritoneum**. Active pulmonary disease is demonstrable in fewer than half of patients, and the indolent, non-specific presentation (chronic pain, fever, weight loss, ascites, subacute obstruction) makes it a notorious mimic of Crohn disease and malignancy — hence a “great diagnostic challenge.”

Epidemiology, pathogenesis & routes of spread

- ▶ In Harrison’s descending order of extrapulmonary frequency, the **peritoneum** ranks among the major sites; **gastrointestinal TB** accounts for ~3.5% of extrapulmonary cases in low-burden settings but is far commoner in endemic India and in untreated AIDS/immigrant groups.
- ▶ **Four mechanisms of seeding:**
 - **Swallowing of infected sputum** with direct mucosal seeding (in active pulmonary TB).
 - **Haematogenous spread** from a pulmonary or miliary focus.
 - **Ingestion of milk** from cattle with bovine TB (*M. bovis*) — historical, now rare.
 - **Contiguous spread** from adjacent organs (e.g., ruptured mesenteric nodes, female genital TB).
- ▶ The **terminal ileum and caecum** are most often involved because of abundant lymphoid (Peyer’s patch) tissue, physiological stasis and greater contact time for bacillary penetration.

Clinical forms of abdominal TB

Form	Site / pathology	Typical features
Intestinal (luminal) TB	Terminal ileum & caecum most common; any segment possible	Chronic abdominal pain (may mimic appendicitis), subacute/recurrent obstruction , palpable abdominal mass , weight loss, diarrhoea, hematochezia ; ulcers/fistulae may simulate Crohn disease
Tuberculous peritonitis	Peritoneum, omentum, mesentery	Non-specific abdominal pain, fever and ascites ; “doughy abdomen”; SAAG <1.1, lymphocytic exudate
Glandular (nodal)	Mesenteric & retroperitoneal lymph nodes	Massive lymphadenopathy, central necrosis on CT; may cause obstruction or fistulae

Form	Site / pathology	Typical features
Visceral	Liver, spleen, pancreas (part of disseminated/miliary disease)	Hepatosplenomegaly, granulomas on biopsy; rare isolated organ involvement

- ▶ **Morphological subtypes of intestinal TB (standard surgical classification):** *ulcerative* (transverse/circumferential “girdle” ulcers, bleeding, perforation-prone), *hypertrophic* (mass-forming, mimics carcinoma), and *ulcero-hypertrophic* (mixed).
- ▶ **Complications:** intestinal obstruction (commonest), perforation, haemorrhage, fistula and stricture formation; **anal/perianal fistulae** should prompt evaluation for rectal TB.

Tuberculous peritonitis — types & ascitic fluid analysis

- ▶ **Three classical morphological types:** **wet (ascitic)** — free fluid; **dry/plastic (fibroadhesive)** — adhesions, mesenteric thickening, “doughy abdomen”; **fibrotic/encysted (loculated)** — omental masses and loculated collections.
- ▶ **Ascitic fluid (paracentesis) — hallmark findings:**
 - **Exudative, high protein** (>2.5 g/dL) fluid.
 - **Low SAAG** (<1.1 g/dL) — a “diseased peritoneum” pattern; *caveat:* coexistent cirrhosis produces **mixed ascites** with a high SAAG, complicating the diagnosis.
 - **Lymphocyte-predominant leukocytosis** (neutrophils occasionally predominate early).
 - **Elevated adenosine deaminase (ADA)** — useful supportive marker for tuberculous peritonitis.
 - **Low smear/culture yield** — direct AFB smear is usually negative; culturing a **large volume** of fluid increases yield.
- ▶ **Peritoneal/omental biopsy — best obtained at laparoscopy** — is often required for definitive diagnosis (caseating granuloma, AFB, culture). Laparoscopy is specifically recommended for low-SAAG/mixed ascites with non-diagnostic CT and cytology.

Diagnostic approach / investigations

- ▶ **Imaging:**
 - **Contrast CT abdomen** — wall thickening of the **caecum and ileocaecal valve**, **massive (necrotic, low-attenuation) lymphadenopathy**, omental/mesenteric thickening, ascites; CT helps interpret questionable plain-film findings and define intra-abdominal disease.
 - **Ultrasound** confirms ascites and guides paracentesis; barium studies may show strictures, “string sign,” and a contracted caecum.
- ▶ **Colonoscopy + biopsy** — ileocaecal ulcers with steep/undermined edges, adjacent sessile pseudopolyps, small ulcers/erosions or pseudodiverticula; obtain multiple biopsies for histology, AFB, culture and PCR.

- ▶ **Microbiological/histological confirmation** (any one is diagnostic):
 - Caseating granuloma on histology.
 - Acid-fast bacilli on smear/stain.
 - Positive mycobacterial culture (gold standard) of biopsy/fluid.
 - Nucleic acid amplification (PCR / Xpert MTB/RIF) — now the *most sensitive* means of detecting bacilli in biopsy specimens and also reports rifampin resistance.
- ▶ **Tuberculin skin test (PPD)** may be **negative**, especially with weight loss or AIDS — a negative test does *not* exclude the diagnosis.
- ▶ Because surgery is needed in many obstructive/complicated cases, the diagnosis is frequently established on **intraoperative histology and culture**.

Differential diagnosis — intestinal TB vs Crohn disease

Feature	Intestinal TB	Crohn disease
Ulcer orientation	Transverse / circumferential (“girdle”)	Longitudinal, cobblestoning, aphthous
Distribution	Ileocaecal, short segment, contracted caecum	Segmental “skip lesions”, longer involvement
Granuloma	Caseating, confluent, larger	Non-caseating, small, discrete
Microbiology	AFB / culture / PCR positive	Negative
Serology / markers	—	ASCA may be positive

- ▶ Other mimics: **carcinoma**, **lymphoma**, **intestinal amoebiasis**, appendiceal mass, and (for peritoneal disease) **peritoneal carcinomatosis** and ovarian malignancy. A therapeutic ATT trial with response assessment is sometimes used when distinction from Crohn disease is impossible.

Management

- ▶ **First-line anti-tubercular therapy (ATT)** — abdominal (extrapulmonary) TB is treated with the **same regimen as drug-susceptible pulmonary TB**: a 2-month intensive phase of isoniazid + rifampin + pyrazinamide + ethambutol followed by a 4-month continuation phase of isoniazid + rifampin — **2HRZE / 4HR (6 months total)**, curative in >90%.
 - Footnote caveat (Harrison Table 183-4): standard 6 months suffices for extrapulmonary TB except CNS, bone or joint disease, which need longer (CMDT: many experts give **9–12 months** for miliary, meningeal, bone/joint TB).

Drug (daily, adult)	Dose	Max
Isoniazid (H)	5 mg/kg	300 mg
Rifampin (R)	10 mg/kg	600 mg

Drug (daily, adult)	Dose	Max
Pyrazinamide (Z)	25 mg/kg	2 g
Ethambutol (E)	15 mg/kg	—

- ▶ **Adjuncts:** pyridoxine with isoniazid to prevent peripheral neuropathy; daily (not intermittent) dosing is preferred; monitor for **drug-induced liver injury**, optic neuritis (ethambutol) and adherence.
- ▶ **Surgery** is reserved for complications — obstruction not relieved by ATT, perforation, uncontrolled haemorrhage, fistula and abscess. Steroids have an established role only in **TB pericarditis and meningitis**, not in routine intestinal/peritoneal disease (corticosteroids are sometimes used to reduce adhesion/obstruction risk in peritoneal TB — see Coverage note).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Ileocaecal tuberculosis** (line diagram of the terminal ileum, ileocaecal valve and caecum). Labels: *Terminal ileum, Thickened/incompetent ileocaecal valve, Contracted/conical caecum, Transverse (circumferential) ulcers, Hypertrophic mass, Stricture causing obstruction, Enlarged caseating mesenteric lymph nodes.*
- ▶ **Tuberculous peritonitis — ascitic fluid analysis flow box.** Labels: *Paracentesis → Exudate, protein >2.5 g/dL, SAAG <1.1 g/dL, Lymphocytic leukocytosis, Raised ADA, Low AFB smear/culture yield, Laparoscopic peritoneal biopsy = confirmatory.*

Clinical / Diagnostic significance

- ▶ **Index of suspicion** in any patient from an endemic area with chronic abdominal pain, fever, weight loss, ascites or subacute obstruction — abdominal TB is treatable and curable but lethal if missed.
- ▶ The low-SAAG, lymphocytic, ADA-rich exudate plus **necrotic mesenteric nodes on CT** is a classic triad pointing to peritoneal TB; remember “mixed ascites” when cirrhosis coexists.
- ▶ **Ileocaecal TB closely mimics Crohn disease** — empirical immunosuppression/biologics for misdiagnosed Crohn can be catastrophic, so excluding TB (caseation, AFB, PCR, culture) before starting anti-TNF therapy is mandatory.
- ▶ **PCR/Xpert MTB/RIF** on biopsy improves yield and simultaneously screens for rifampin resistance, shortening time to appropriate therapy.

High-yield exam pointers

- ▶ Commonest sites: **ileocaecum** (luminal) and **peritoneum**; <50% have active pulmonary TB.
- ▶ Four routes: **swallowed sputum, haematogenous, ingested (M. bovis) milk, contiguous spread**.
- ▶ Intestinal subtypes: **ulcerative, hypertrophic, ulcero-hypertrophic**; commonest complication = **obstruction**.

- ▶ Peritoneal types: wet (ascitic), dry/plastic, fibrotic/encysted; “doughy abdomen.”
- ▶ Ascites: exudate, SAAG <1.1, high protein, lymphocytic, high ADA, low smear yield; laparoscopic biopsy is most reliable.
- ▶ CT clues: ileocaecal/valve thickening + massive necrotic lymphadenopathy.
- ▶ Diagnosis confirmed by caseating granuloma / AFB / culture / PCR; PPD may be negative.
- ▶ Treatment = 2HRZE/4HR (6 months) — same as pulmonary; longer only for CNS/bone/joint; surgery for complications.
- ▶ Key differential = Crohn disease (transverse vs longitudinal ulcers; caseating vs non-caseating granuloma) — exclude TB before biologics.

SOURCE & COVERAGE

- ▶ Harrison’s Principles of Internal Medicine, 22e — “Tuberculosis” (extrapulmonary TB: Gastrointestinal TB and Tuberculous peritonitis; treatment regimens and drug-dose Tables 183-2/183-4).
- ▶ CMDT 2026 — “Gastrointestinal Disorders” (Intestinal Tuberculosis; Ascites — SAAG classification, ascitic-fluid analysis, ADA, laparoscopy) and “Pulmonary Disorders” (extrapulmonary TB treatment duration; pyridoxine).
- ▶ Coverage note: The morphological subclassifications (intestinal: ulcerative/hypertrophic/ulcero-hypertrophic; peritoneal: wet/dry/fibrotic), the Crohn-vs-TB ulcer-orientation/granuloma contrasts, ASCA, and a specific numerical ADA cut-off are universally accepted standard internal-medicine teaching but are not stated verbatim in the cited corpus, which confirms the underlying findings (lymphocytic exudate, raised ADA, ileocaecal site, Crohn mimicry, caseating granuloma) in narrative form. Routine corticosteroid use in peritoneal TB to reduce adhesions is variably practised and is *not* endorsed by the corpus (which supports steroids only for TB pericarditis and meningitis).



Acute pyelonephritis

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Acute pyelonephritis is a symptomatic, **tissue-invasive infection of the renal parenchyma, calyces and pelvis**, and is the prototype of a *complicated urinary tract infection (UTI)* because infection has extended beyond the bladder. It usually develops as an **ascending infection** from the bladder, so its microbiology mirrors that of acute cystitis. Affected patients are often systemically ill, and fever is the cardinal feature distinguishing it from cystitis.

Etiology and microbiology

- ▶ **Escherichia coli is the predominant uropathogen across the whole UTI spectrum; the microbiology of pyelonephritis is similar to that of acute cystitis** since it arises by ascent.
- ▶ Other **Enterobacterales** — *Klebsiella*, *Proteus*, *Enterobacter*, *Citrobacter* — and *Staphylococcus saprophyticus* account for most of the remainder.
- ▶ *Staphylococcus aureus* or *Salmonella* in urine should raise suspicion of **haematogenous seeding** and concomitant bacteraemia.
- ▶ **Rising antimicrobial resistance:** surveillance shows >20% resistance to TMP-SMX, fluoroquinolones and nitrofurantoin in many regions; ~9% of isolates produce **extended-spectrum β -lactamase (ESBL)** and ~6% are resistant to ≥ 3 antibiotic classes — hence the value of *local antibiogram* data.

Pathogenesis

- ▶ The urinary tract is a continuous urine column from kidney to urethra; in most UTIs bacteria **ascend** urethra $\rightarrow$ bladder $\rightarrow$ ureter $\rightarrow$ renal parenchyma. **Haematogenous infection accounts for <2% of UTIs.**
- ▶ The **flushing action of normal voiding** is the key host defence; anything causing stasis or obstruction predisposes to infection.
- ▶ **Vesicoureteral reflux** and **inhibition of ureteral peristalsis / decreased ureteral tone** promote ascent — these are central to pyelonephritis in **pregnancy**.
- ▶ **Microbial virulence factors:** *P fimbriae* (bind the blood-group P antigen on renal epithelium) are important in the pathogenesis of pyelonephritis and subsequent **bloodstream invasion**; *type 1 pili* mediate bladder attachment (bind mannose). Toxins, iron-acquisition systems, biofilm and capsule also contribute.
- ▶ **Host factors:** familial/maternal predisposition; mutations in innate-immune genes (**Toll-like receptors, IL-8 receptor**) linked to recurrent UTI and pyelonephritis; non-expression of certain blood-group antigens (non-secretor) increases uroepithelial adherence of *E. coli*.

Predisposing / risk factors

- ▶ **Obstruction & stasis:** renal/staghorn calculi, benign prostatic hypertrophy, neurogenic bladder, vesicoureteral reflux, urinary-diversion surgery, congenital anomalies, cystocele/pelvic-organ prolapse.
- ▶ **Foreign bodies:** indwelling/intermittent catheters, stents, nephrostomy tubes — provide an inert surface for **biofilm** and act as a nidus.
- ▶ **Diabetes mellitus** (2–3 $\times$ higher UTI/ASB rate; predisposes to emphysematous pyelonephritis); **pregnancy**; female anatomy (**short urethra**); sexual activity and **spermicide** use; immunocompromise.

Clinical features

- ▶ **Acute onset**, with or without preceding cystitis symptoms (dysuria, frequency, urgency).
- ▶ ****Mild** pyelonephritis — **low-grade fever ± lower-back or costovertebral-angle (flank) pain****.
- ▶ ****Severe** pyelonephritis — high fever, rigors, nausea, vomiting and flank pain**; may progress to bacteraemia and sepsis.
- ▶ Fever, rigors and unilateral back/flank pain in a patient with “cystitis” are **inconsistent with simple cystitis** and mandate evaluation for infection beyond the bladder.

Complications

Complication	Key features (per source)
Acute papillary necrosis	Sloughed papillae obstruct the ureter → obstructive uropathy; also seen in sickle cell disease and analgesic nephropathy ; <i>bilateral</i> necrosis → rapid rise in serum creatinine
Emphysematous pyelonephritis	Severe form with gas in renal/perinephric tissue ; occurs almost exclusively in poorly controlled diabetes (often <i>E. coli</i> , a gas-forming facultative anaerobe)
Xanthogranulomatous pyelonephritis (XGP)	Chronic obstruction (often staghorn calculus) + chronic infection → suppurative destruction; residual tissue is yellow with lipid-laden macrophages ; can mimic renal malignancy
Intraparenchymal / perinephric / renal cortical abscess	Suspect with continued fever and/or bacteraemia despite antibiotics

Diagnosis / investigations

- ▶ **Urinalysis**: pyuria (>10 WBC/HPF is the accepted standard for pyuria), **nitrite** (only Enterobacterales convert nitrate→nitrite) and **leukocyte esterase** on dipstick; haematuria in ~30%.
- ▶ **Urine culture** before therapy — provides organism identification and **susceptibilities to guide therapy** (essential in pyelonephritis, men, pregnancy and recurrent/resistant cases).
- ▶ **Blood cultures** in systemically ill / febrile patients.
- ▶ **Imaging (CT or ultrasound)** for febrile UTI and febrile UTI in men — to detect **obstruction, abscess, calculi or anatomic abnormalities**; CT also demonstrates gas in emphysematous pyelonephritis.

Treatment

- ▶ **Principle**: empirical therapy must be reliable and **rapidly reach therapeutic levels in renal parenchyma and blood**; nitrofurantoin, fosfomycin and pivmecillinam achieve poor renal-tissue levels and **must not be used** for pyelonephritis.

Setting	Recommended regimen (per source)
Hospitalised patients	Empirical IV β -lactam, chosen by local antibiogram and avoiding agents to which the patient recently had a resistant isolate
Outpatient (not requiring admission)	Empirical TMP-SMX, ciprofloxacin, or levofloxacin per local antibiogram + urine culture + short-term follow-up; an initial IV/IM β -lactam or aminoglycoside dose can be added where feasible
Susceptible isolate, oral therapy	5–7 days of an oral fluoroquinolone OR 7–14 days of oral TMP-SMX; oral β -lactams are less effective → use with caution and close follow-up
Parenteral options (uncomplicated PN)	Late-generation cephalosporin (ceftriaxone, cefepime), piperacillin-tazobactam, a carbapenem, or fluoroquinolone; alternatives — novel β -lactam/ β -lactamase inhibitors (e.g., meropenem-vaborbactam) and aminoglycosides
Pregnant patients with pyelonephritis	Parenteral β -lactam therapy $\pm$ aminoglycoside (based on limited data)

- ▶ **Admit** ambulatory patients who cannot tolerate oral medication (vomiting) or are unlikely to adhere to follow-up.
- ▶ **Step-down:** once a clinical response is achieved, switch parenteral → **oral**; therapy may be concluded at **7 days** in responders treated with a fluoroquinolone or TMP-SMX (oral β -lactams may need longer).
- ▶ **No clinical response within 72 h** → evaluate for an **uncontrolled source** (obstruction, abscess).
- ▶ **Source control:** papillary necrosis with obstruction needs intervention to relieve obstruction; perinephric/cortical abscess → **percutaneous drainage**; **emphysematous pyelonephritis** → percutaneous drainage initially, then **elective nephrectomy** as needed; **XGP** → usually **nephrectomy** with individualized antibiotic duration, in collaboration with urology.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Ascending pathogenesis of pyelonephritis:** vertical urinary tract with labels — Urethra → Bladder (cystitis) → Vesicoureteral reflux → Ureter → Renal pelvis/calices → Renal parenchyma (pyelonephritis); annotate *P fimbriae* adhesion to renal epithelium, *Type 1 pili* (bladder), and *Haematogenous seeding* (<2%: *S. aureus*, *Salmonella*).
- ▶ **Diagram 2 — Labelled kidney showing complications:** cross-section with labels — Cortical abscess, Perinephric abscess, Papillary necrosis (sloughed papilla obstructing ureter), Gas in parenchyma (emphysematous PN), Staghorn calculus with destruction (XGP).

Clinical / Diagnostic significance

- ▶ **Fever + flank/CVA tenderness** in a UTI patient = pyelonephritis until proven otherwise; reclassify “cystitis with fever” as a complicated UTI.
- ▶ Persistent fever/bacteraemia despite appropriate antibiotics signals **abscess or obstruction** — image and arrange drainage.
- ▶ **Diabetic + severe pyelonephritis + gas on imaging** = emphysematous pyelonephritis, a urological emergency.
- ▶ **Pregnancy**: untreated asymptomatic bacteriuria predisposes to pyelonephritis, **preterm delivery and low birth weight** — justifying routine **ASB screening and treatment** by urine culture in pregnancy.
- ▶ **Avoid** nitrofurantoin/fosfomycin/pivmecillinam for upper-tract disease — they fail to reach renal tissue.

High-yield exam pointers

- ▶ Pyelonephritis = **tissue-invasive complicated UTI**; *E. coli* is the commonest organism; ascent is the usual route (<2% haematogenous).
- ▶ **P fimbriae** = key virulence factor for pyelonephritis and bloodstream invasion; **type 1 pili** for bladder attachment.
- ▶ **Triad of severe disease**: high fever + rigors + flank pain, often with nausea/vomiting.
- ▶ **Emphysematous pyelonephritis** → poorly-controlled diabetes; **XGP** → staghorn calculus + lipid-laden macrophages, mimics tumour; **papillary necrosis** → also sickle cell disease & analgesic nephropathy.
- ▶ Always **send urine culture (± blood cultures)** before empirical antibiotics; image febrile UTI/men with CT or US.
- ▶ Outpatient empirical: **TMP-SMX / ciprofloxacin / levofloxacin** by antibiogram; hospitalised: **IV β-lactam**.
- ▶ Oral course for susceptible isolate: **5–7 days fluoroquinolone or 7–14 days TMP-SMX**; reassess at **72 h** if no response.
- ▶ **Pregnant pyelonephritis** = admit + **parenteral β-lactam ± aminoglycoside**.

SOURCE & COVERAGE

Harrison 22e — Ch 140 “Urinary Tract Infections: Cystitis, Prostatitis, and Pyelonephritis.”

Coverage note: This chapter does not state a specific clean-catch colony-count threshold for diagnosing pyelonephritis (it gives $>10^2$ CFU/mL as a sensitive cystitis cut-off and $\geq 10^3$ CFU/mL for CAUTI); the classic $\geq 10^5$ CFU/mL clean-catch criterion is universally accepted standard textbook medicine. Quantified imaging grading (e.g., Huang–Tseng classes of emphysematous pyelonephritis) is also outside the provided text.



Amoebic Liver Abscess

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Amoebic liver abscess (ALA) is the most common extraintestinal manifestation of infection with *Entamoeba histolytica*, produced by portal venous spread of invasive trophozoites from the colon to the liver. It usually presents as a febrile hepatic space-occupying lesion with right-upper-quadrant pain, often without active dysentery. It is a treatable medical emergency because rupture into the pleura, peritoneum, or pericardium may be fatal.

Etiology and Epidemiology

- ▶ **Agent:** *E. histolytica* is the pathogenic species in the *Entamoeba* complex; *E. dispar*, *E. moshkovskii*, and other species may be morphologically indistinguishable on microscopy but do not explain classic invasive disease.
- ▶ **Transmission:** ingestion of mature cysts from fecally contaminated water, food, hands, or mechanically contaminated food; less commonly via oral-anal sexual practices. Trophozoites are killed by gastric acid and air and do not transmit infection.
- ▶ **Reservoir:** humans are the established host; asymptomatic carriers may shed large numbers of cysts.
- ▶ **Geography:** common in tropical and subtropical areas with poor sanitation, crowding, and poor nutrition; important in the Indian subcontinent, Africa, parts of East Asia, Mexico, Colombia, and other endemic regions.
- ▶ **Risk groups:** residents of endemic areas, returning travelers, recent immigrants, men who have sex with men, institutional inmates, and persons exposed to unsafe water or food.
- ▶ **Sex and age:** invasive colitis and liver abscess are much more common in men; Harrison notes that men aged 30-60 years are affected 10-12 times more often than women of the same age.
- ▶ In travelers who develop ALA after leaving an endemic area, most present within 5 months.

Pathogenesis and Pathology

- ▶ After cyst ingestion, **excystation** occurs in the small intestine; trophozoites colonize the large bowel. In most persons infection remains asymptomatic, but trophozoites may invade the colonic mucosa.
- ▶ Virulence depends on **Gal/GalNAc adherence lectin**, cysteine proteinases, glycosidases, contact-dependent cytotoxicity, trophocytosis, inflammatory-cell lysis, and resistance to oxidative and complement-mediated killing.
- ▶ Intestinal disease produces **flask-shaped ulcers** with trophozoites at the margin of viable and necrotic tissue; glucocorticoid exposure can convert unrecognized amebiasis into severe colitis or toxic megacolon.

- ▶ ALA is **always preceded by intestinal colonization**, often asymptomatic. Trophozoites enter mesenteric venules and reach the liver via the **portal venous system**.
- ▶ In the liver, vessel-wall lysis, thrombosis, neutrophil recruitment, neutrophil lysis, and hepatocyte necrosis produce a cavity of necrotic debris surrounded by a thin rim of congested liver.
- ▶ The aspirate is classically described as “**anchovy paste**”, but color is variable. It is usually **bacteriologically sterile**, granular, and poor in cells; trophozoites are uncommon in the aspirated center and are more often near the abscess capsule.

Clinical Features

- ▶ **Classical triad**: fever, right-upper-quadrant abdominal pain, and tender hepatomegaly.
- ▶ Onset may be acute or gradual. Pain is often dull or pleuritic and may radiate to the right shoulder; point tenderness over the liver and **intercostal tenderness** are useful bedside clues.
- ▶ **Fever** is common; **jaundice is rare** and, if prominent, suggests large abscess, biliary obstruction, cholangitis, or alternative diagnosis.
- ▶ Gastrointestinal symptoms are absent in many patients: fewer than one-third have active diarrhea despite colonic origin of infection. Anorexia, malaise, weight loss, nausea, cough, and hiccups may occur.
- ▶ **Right pleural effusion** or elevated right hemidiaphragm may accompany superior right-lobe abscesses.
- ▶ Older patients from endemic areas may present subacutely over months with weight loss and hepatomegaly; 10-15% may present only as fever of unknown origin.

Pattern	Exam clue	Significance
Acute ALA	Fever, RUQ pleuritic pain, tender liver, leukocytosis	Usually symptomatic for <10 days; multiple lesions are more likely early
Subacute/chronic ALA	Weight loss, hepatomegaly, variable fever	Common diagnostic trap in endemic-area patients
Left-lobe abscess	Epigastric pain, pericardial risk	Needs early drainage consideration
Superior right-lobe large abscess	Pleural pain, effusion, basal lung signs	Risk of pleuropulmonary rupture

Investigations and Diagnosis

- ▶ **CBC/LFT**: leukocytosis is common; Harrison notes leukocytosis >10,000 cells/microliter in about three-fourths of ALA. Eosinophilia is not a feature. Liver enzymes may be normal or minimally raised; **alkaline phosphatase** is most often elevated and may remain high for months.

- ▶ **Stool tests:** often negative in isolated ALA. If intestinal symptoms are present, examine at least **three fresh stool specimens**; hematophagous trophozoites are diagnostic, but routine microscopy cannot distinguish *E. histolytica* from nonpathogenic *Entamoeba* species.
- ▶ **Serology:** anti-amebic antibody testing is positive in **>90%** of invasive amebiasis including liver abscess. Early ALA may be seronegative in up to **10%**, so repeat testing after about a week if suspicion remains high.
- ▶ **Antigen/PCR:** stool or aspirate antigen assays targeting *E. histolytica* improve specificity; PCR-based gastrointestinal panels have very high sensitivity and specificity where available. In hepatic abscess, stool antigen is frequently negative, while aspirate antigen is highly diagnostic if aspiration is done.
- ▶ **Imaging:** ultrasonography, CT, and MRI detect round or oval hypoechoic or low-density nonhomogeneous lesions. More than **80%** of patients symptomatic for **>10 days** have a **single right-lobe abscess**; about **50%** of those symptomatic for **<10 days** may have multiple abscesses.
- ▶ **Important limitation:** imaging cannot reliably distinguish amoebic from pyogenic abscess; use epidemiology, serology, cultures when aspirated, and therapeutic response.
- ▶ **Differential diagnosis:** pyogenic liver abscess, cholangitis, acute cholecystitis, hepatocellular carcinoma with necrosis/infection, hydatid cyst, tuberculosis, malaria, typhoid fever, right lower-lobe pneumonia, subphrenic abscess, and inflammatory bowel disease with hepatic sepsis.

Treatment

- ▶ **Principle:** treat both tissue invasion and intestinal carriage. A tissue amebicide alone improves the abscess but does not eradicate bowel cysts; hence add a **luminal amebicide** after or along with nitroimidazole therapy.

Clinical setting	Preferred regimen
Amoebic hepatic abscess	Metronidazole 750 mg orally three times daily for 10 days; if oral therapy is not possible, metronidazole 500 mg IV every 6 hours for 10 days
Alternative	Tinidazole 2 g orally daily for 5 days
Luminal eradication	Diloxanide furoate 500 mg orally three times daily for 10 days or iodoquinol 650 mg orally three times daily for 21 days or paromomycin 10 mg/kg orally three times daily for 7 days

- ▶ Avoid alcohol with metronidazole/tinidazole because of a disulfiram-like reaction; nausea, metallic taste, vomiting, epigastric discomfort, and headache may occur.
- ▶ More than **90%** respond dramatically to metronidazole, with reduction in pain and fever within **72 hours**. With early diagnosis and treatment, mortality from uncomplicated ALA is **<1%**.

- ▶ **No routine aspiration** is required for typical, uncomplicated ALA responding to therapy; aspiration does not hasten healing even for large abscesses up to about 10 cm.
- ▶ **Aspirate/drain if:** pyogenic abscess must be excluded, especially with multiple lesions; no clinical response in **3-5 days**; very large abscess with threatened rupture; left-lobe abscess at risk of pericardial rupture; frank pleural or peritoneal rupture; or the patient is toxic/very ill.
- ▶ **Surgery:** reserve for bowel perforation and rupture into the pericardium; percutaneous drainage may suffice for many ruptured hepatic abscesses.
- ▶ Abscess cavities resolve slowly. Imaging abnormalities may persist despite clinical cure; complete resolution by 6 months occurs in about two-thirds, and 10% may have abnormalities for a year.

Complications and Prevention

- ▶ **Pleuropulmonary complications** are the commonest, reported in **20-30%**: sterile effusion, contiguous spread, rupture into pleural space, lung abscess, or hepatobronchial fistula with expectoration of necrotic material.
- ▶ **Peritoneal rupture** may present as indolent leak or acute abdomen and needs drainage plus medical therapy.
- ▶ **Pericardial rupture**, usually from left-lobe abscess, has the worst prognosis and requires urgent surgical drainage.
- ▶ Rare extraintestinal sites include lung, brain, genitourinary tract, and painful punched-out genital ulcers due to direct extension or hematogenous spread.
- ▶ **Prevention:** safe water, sanitary disposal of feces, hand hygiene, adequate cooking of food, protection of food from flies, avoidance of unpeeled fruits/vegetables in endemic areas, bottled/boiled/filtered water, and treatment of cyst carriers.
- ▶ Cysts resist standard chlorination; iodine treatment or boiling/filtration is more reliable. There is **no effective chemoprophylaxis**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Life cycle and hepatic spread of *E. histolytica*:** ingestion of cysts, excystation in small intestine, colonization of colon, flask-shaped colonic ulcer, portal venous spread, right-lobe liver abscess; labels: cyst, trophozoite, colon, portal vein, liver abscess, asymptomatic cyst passage.
- ▶ **Anatomical complications of ALA:** right-lobe abscess, pleural effusion/rupture, hepatobronchial fistula, peritoneal rupture, left-lobe abscess, pericardial rupture.

Clinical / Diagnostic significance

- ▶ ALA is a classic cause of **fever with right-upper-quadrant pain** in Indian exams and must also be considered in FUO with epidemiologic risk.

- ▶ Absence of diarrhea does **not** exclude ALA; most patients with hepatic disease have no active intestinal symptoms.
- ▶ Positive serology plus compatible imaging and clinical syndrome is usually sufficient for diagnosis; aspiration is mainly for uncertainty, poor response, or rupture risk.
- ▶ Differentiate from pyogenic abscess: pyogenic abscess patients are often older, have biliary disease, bowel disease, diabetes, recent surgery, polymicrobial cultures, and need antibacterial therapy plus drainage.
- ▶ Rule out amebiasis before giving glucocorticoids for presumed inflammatory bowel disease in endemic settings.
- ▶ Do not chase radiologic resolution too frequently: clinical response is more important early because abscess size can lag behind cure.

High-yield exam pointers

- ▶ Most common extraintestinal site of amebiasis is the **liver**.
- ▶ **Right-lobe, solitary abscess in a young/middle-aged man** with fever and RUQ pain is the prototype.
- ▶ **Jaundice is uncommon** in uncomplicated ALA.
- ▶ Stool examination is often negative in ALA; **serology is the key test**.
- ▶ Aspirate is classically **anchovy-paste**, sterile, and poor in cells; trophozoites are usually not seen in the center.
- ▶ Treat with **metronidazole/tinidazole plus luminal agent**; metronidazole alone risks persistent intestinal carriage.
- ▶ Clinical response should occur within **72 hours**; lack of response by **3-5 days** is an aspiration/drainage indication.
- ▶ Left-lobe abscess is dangerous because of **pericardial rupture**.
- ▶ Standard chlorination is unreliable against cysts; emphasize sanitation, boiling/iodination/filtration, and safe food.

SOURCE & COVERAGE

Harrison 22e — “Amebiasis and Infection with Free-Living Amebae”; CMTD 2026 — “Protozoal & Helminthic Infections” and “Liver, Biliary Tract, & Pancreas Disorders”.



Anaerobic organisms infections

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — **Anaerobic bacteria** are organisms that grow optimally in the absence of oxygen and constitute the predominant class of the normal human microbiota residing on mucous membranes. They cause disease chiefly after **breakdown of a mucosal barrier** allows the microbiota to leak into normally sterile tissue, producing infections that are typically **polymicrobial** (mixed anaerobic + facultative/microaerophilic species). Because they are fastidious and hard to culture, the anaerobic aetiology is frequently *unproven*, so the diagnosis often rests on clinical pattern recognition. Treatment hinges on **appropriate antibiotics plus surgical drainage/debridement**.

Classification of anaerobes by oxygen tolerance and morphology

- ▶ **Obligate (strict) anaerobes** — killed in the presence of $\geq 0.5\%$ oxygen (lack superoxide dismutase/catalase).
- ▶ **Aerotolerant anaerobes** — tolerate oxygen but cannot use it for growth; *most clinically relevant anaerobes* (*Bacteroides fragilis*, *Prevotella melaninogenica*, *Fusobacterium nucleatum*) are relatively aerotolerant.
- ▶ **Facultative anaerobes** — grow with or without oxygen (e.g. *E. coli*); preferentially use oxygen when available.
- ▶ **Microaerophilic organisms** — require low O_2 (2–10%) and are damaged by atmospheric $\sim 21\%$.
- ▶ Oxygen tolerance correlates with expression of **superoxide dismutase and catalase** (detoxify O_2^- and H_2O_2). Energy is generated by less-efficient **anaerobic respiration** (acceptors: sulfate, nitrate, CO_2 , fumarate) or **fermentation** ($\sim 5\%$ of the ATP yield of aerobic respiration).

Microbiological group	Representative pathogens
Gram-negative bacilli	<i>Bacteroides fragilis</i> group (25 species), <i>Prevotella</i> , <i>Porphyromonas</i> , <i>Fusobacterium</i> spp.
Gram-negative cocci	<i>Veillonella</i> spp. (few of the gram-neg cocci causing disease)
Gram-positive cocci	Peptostreptococci (<i>P. micros</i> , <i>P. anaerobius</i>), <i>Finegoldia magna</i> (ex- <i>Peptostreptococcus magnus</i>)
Gram-positive spore-forming bacilli	<i>Clostridium</i> spp. (covered separately)
Gram-positive non-spore-forming bacilli	<i>Cutibacterium acnes</i> (ex- <i>Propionibacterium</i>), <i>Actinomyces</i> spp.

Sites of normal anaerobic microbiota and the organisms they seed

- ▶ The **lower GI tract (colon)** is the major reservoir — anaerobe:aerobe ratio $\sim 1000:1$, $\sim 10^{11}$ – 10^{12} organisms/g; *Bacteroides* group, *Prevotella*, *Clostridium*.
- ▶ **Oral cavity / gingival crevices** — ratio up to 1000:1; *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Peptostreptococcus*, *Actinomyces* → odontogenic, peripharyngeal, sinus and pleuropulmonary infections.

- ▶ **Female genital tract** — ratio ~10:1; *Prevotella bivia*, *P. disiens*, *Bacteroides* → pelvic infections.
- ▶ **Skin** — *Cutibacterium acnes* predominant → foreign-body/prosthetic infections.
- ▶ Infections “reflect the neighbouring microbiota”: e.g. **B. fragilis** + **E. coli** dominate intra-abdominal abscesses; oral flora dominate lung abscess.

Pathogenesis and virulence factors

- ▶ **Prerequisite** = an anaerobic micro-environment with lowered oxidation–reduction (redox) potential — created by ischaemia, trauma, surgery, a perforated viscus, or by facultative organisms consuming oxygen (basis of synergy).
- ▶ **Adhesion** — *P. gingivalis* fimbriae; *F. nucleatum* acts as a “bridge” binding almost all oral bacteria; *B. fragilis* pili/fimbriae/haemagglutinins.
- ▶ **Exoproteins/toxins** — *P. gingivalis* collagenase; clostridial exotoxins are among the most potent in nature.
- ▶ **Endotoxin (lipid A)** of *B. fragilis*/*Prevotella*/*Porphyromonas* is **100–1000× less biologically potent** than aerobic gram-negative LPS → explains the *lower rates of DIC, purpura and septic shock* in anaerobic gram-negative bacteraemia. (Exception: *Fusobacterium* LPS, contributing to severe Lemierre’s syndrome.)
- ▶ *****B. fragilis* capsular polysaccharide complex** — **the best-studied anaerobic virulence factor**; ≥8 **distinct capsules**; PSA and PSB are zwitterionic (**free amino + carboxyl groups**). **PSA induces abscesses by stimulating peritoneal macrophages (via TLR-2) to release IL-8, IL-17 and TNF-α, driving PMN chemotaxis and adhesion to ICAM-1****-expressing mesothelium — the abscess nidus.
- ▶ **Bacterial synergy** — infections characteristically involve **3–6 organisms**; facultatives lower redox potential, supply growth factors (e.g. vitamin K for *P. melaninogenica*) and impair phagocytosis (short-chain/succinic acids).

Clinical syndromes by anatomical site

- ▶ **Mouth, head & neck** — dental caries, periodontitis; **Ludwig’s angina** (submandibular/sublingual/submental space cellulitis from molar abscess, tongue elevation, airway threat); **acute necrotizing ulcerative gingivitis** (*trench mouth* / *Vincent’s stomatitis* — painful bleeding gums, grey pseudomembrane); **noma (cancrum oris)** — gangrenous orofacial destruction in malnourished children (sub-Saharan Africa, 70–90% untreated mortality, driven by *F. necrophorum*/*P. intermedia*); **peritonsillar abscess (quinsy)** and **retropharyngeal abscess**; **chronic sinusitis & suppurative otitis media** (anaerobes spare the *acute* forms).
- ▶ **Lemierre’s syndrome** — *F. necrophorum* oropharyngeal infection → **septic thrombophlebitis of the internal jugular vein** with septic pulmonary emboli.

- ▶ **CNS** — anaerobes recovered in ~30% of **brain abscesses**, ~20% of epidural abscesses, ~10% of subdural empyemas (usually by contiguous spread from oto-/odonto-/sinogenic foci); anaerobic meningitis is rare.
- ▶ **Pleuropulmonary** (from microaspiration of oral flora; indolent course) — **aspiration pneumonia** (dependent segments), **lung abscess** (foul sputum, ~90% yield an anaerobe, 3–6 isolates), **empyema** — distinguish from simple parapneumonic effusion:

Feature	Parapneumonic effusion	Anaerobic empyema
WBC (cells/mL)	~5,000	~55,000
LDH (IU/L)	>200	>1000
pH	~7.4	<7.2
Character	thin exudate	foul, thick pus, loculated, pleural peel

(Contrast with **Mendelson syndrome** — *chemical* aspiration pneumonitis from gastric acid, evolving within 4–6 h, needing no antibiotics unless superinfected.)

- ▶ **Intra-abdominal** — peritonitis/abscess after perforation; *E. coli* + *B. fragilis* group; **neutropenic enterocolitis (typhlitis)** — caecal wall thickening >4 mm post-chemotherapy; *Clostridium septicum* bacteraemia flags occult **colon cancer**.
- ▶ **Pelvic** — PID, tubo-ovarian abscess, septic abortion, endometritis (*P. bivia*, *P. disiens*, *B. fragilis*); **bacterial vaginosis** (loss of lactobacilli, overgrowth of *Gardnerella/Prevotella/Mobiluncus*).
- ▶ **Skin/soft tissue** — **gas gangrene** (clostridial), **progressive bacterial synergistic (Meleney) gangrene**, **synergistic necrotizing cellulitis / Fournier gangrene** (scrotum–perineum–abdominal wall), **necrotizing fasciitis, myositis** — foul odour, crepitus/subcutaneous gas, cutaneous anaesthesia.
- ▶ **Bone & joint** — *Actinomyces* “**lumpy jaw**” (cervicofacial, mandible > maxilla, sinus tracts); contiguous mixed osteomyelitis (diabetic foot, decubitus).
- ▶ **Bacteraemia / endocarditis** — *B. fragilis* is the anaerobe most often isolated from blood; mortality of untreated *B. fragilis* group bacteraemia ~60%; gram-negative anaerobic endocarditis carries 21–43% mortality.

Diagnosis

- ▶ **Clinical clues** — abscess formation, **putrid/foul-smelling** discharge (present in only 30–50%, often late), gas in tissues, septic thrombophlebitis, tissue necrosis, and **failure to respond to antibiotics inactive against anaerobes**.
- ▶ “**Sterile pus**” that yields no growth (or only a single aerobe) yet is **teeming with organisms on Gram stain** strongly implies anaerobes (lost on inadequate transport/culture).

- **Specimens** — sample normally sterile sites (blood, pleural/peritoneal fluid, aspirates/biopsy); avoid mucosal-surface swabs (mouth, vagina, faeces) that contain commensal anaerobes. Use **air-free syringe + anaerobic transport medium** and rapid transport. Prior antibiotics reduce recovery.

Treatment / Antimicrobial therapy

- **Two pillars:** (1) appropriate antibiotics active against *both* aerobes and anaerobes; (2) **surgical debridement of devitalized tissue + drainage** of abscesses, and prompt closure of any mucosal breach.
- **No useful anaerobic activity:** aminoglycosides, monobactams (aztreonam), trimethoprim-sulfamethoxazole.

Agent	Caveat
Metronidazole	First-line for gram-negative anaerobes; <i>unreliable</i> against gram-positive non-spore-formers (<i>Actinomyces</i> , <i>Cutibacterium</i> , <i>Peptostreptococcus</i> , <i>Lactobacillus</i>)
β -lactam/ β -lactamase-inhibitor (ampicillin-sulbactam, piperacillin-tazobactam)	Rising resistance in some gram-negatives; newer ceftolozane/ceftazidime-avibactam have limited anaerobic activity
Clindamycin	<i>B. fragilis</i> group resistance now 30–43% in USA → no longer first-line for intra-abdominal sepsis
Carbapenems (meropenem, imipenem, ertapenem, doripenem)	Very low resistance (<5%); rare carbapenemase-producing strains
Chloramphenicol	Occasional clinical failures despite in-vitro susceptibility

- **Above vs below the diaphragm** governs empirical choice:
 - **Above diaphragm** (orodental flora, *Prevotella*/*Porphyromonas*/*Fusobacterium*; >70% β -lactamase-producing): clindamycin, a β -lactam/ β -lactamase-inhibitor, or **metronidazole + penicillin** (for microaerophilic/aerobic streptococci). Penicillin alone is inadequate.
 - **Below diaphragm** (must cover *B. fragilis* + coliforms): single agent — **cefoxitin**, **moxifloxacin**, a β -lactam/ β -lactamase-inhibitor, or a **carbapenem**; or two-drug **metronidazole + cephalosporin/fluoroquinolone**; add ampicillin/vancomycin if enterococci suspected.
- **Representative CMDT 2026 regimens:** ampicillin-sulbactam 3 g IV q6h (then amoxicillin-clavulanate 875/125 mg PO BID); ceftriaxone + metronidazole 500 mg q6–8h; moxifloxacin 400 mg/day; **brain abscess** — ceftriaxone 2 g IV q12h + metronidazole 500 mg q8h for 6–8 weeks (imaging-guided); anaerobic/microaerophilic streptococcal **endocarditis** — penicillin G 12–18 MU/day for 4–6 weeks.

- ▶ **Failure to respond** → re-image for undrained focus, reculture, request susceptibility testing (reserved for serious/refractory/prolonged-therapy infections).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **“Pathogenesis of an anaerobic abscess” flow diagram** — label: *Mucosal barrier breach (perforation/ischaemia/surgery) → Polymicrobial inoculation → Facultative organisms consume O₂ → lowered redox potential → Outgrowth of obligate anaerobes → B. fragilis PSA → TLR-2 on macrophages → IL-8/IL-17/TNF-α → PMN influx → ICAM-1 adhesion → ABSCESS.*
- ▶ **Lung abscess radiograph schematic** — label: *cavity with air–fluid level, dependent (posterior) segment, right upper-lobe posterior / lower-lobe superior segment, surrounding consolidation.*

Clinical / Diagnostic significance

- ▶ Suspect anaerobes whenever an infection arises **adjacent to a mucosal surface**, forms an abscess, is foul-smelling, contains gas, or fails broad-spectrum antibiotics lacking anaerobic cover.
- ▶ **Source control (drainage/debridement) is as important as antibiotics** — many synergistic infections resolve even if therapy targets only the dominant organisms, because resistant species do not survive without their co-pathogens.
- ▶ *B. fragilis* group **always implies significant underlying pathology** (colonic neoplasm, diverticulitis, perforation) when isolated from blood — investigate the gut.
- ▶ Low DIC/shock incidence is a *hint* (weak lipid A), but does not exclude serious infection.

High-yield exam pointers

- ▶ Three oxygen classes: **obligate** (killed $\geq 0.5\%$ O₂) / **aerotolerant** / **facultative**; tolerance = SOD + catalase.
- ▶ *B. fragilis* = commonest anaerobe in intra-abdominal abscess, bacteraemia and endocarditis; only ~0.5–1% of colonic flora yet dominant in disease — due to its **zwitterionic capsular polysaccharide (PSA)**.
- ▶ **Lemierre’s syndrome** = *F. necrophorum* + IJV septic thrombophlebitis + septic pulmonary emboli.
- ▶ **Ludwig’s angina, ANUG (Vincent’s), noma, quinsy** — classic head-and-neck anaerobic eponyms.
- ▶ **Meleney** (progressive synergistic) gangrene and **Fournier** gangrene are anaerobic synergistic soft-tissue infections.
- ▶ **Empyema** fluid: pH <7.2, LDH >1000, WBC ~55,000 → needs drainage.
- ▶ **Typhlitis** + *Clostridium septicum* bacteraemia → screen for **colon cancer**.

- ▶ Metronidazole fails against gram-positive non-spore-formers (Actinomyces, Cutibacterium, Peptostreptococcus).
- ▶ No anaerobic activity: aminoglycosides, aztreonam, co-trimoxazole.
- ▶ Above- vs below-diaphragm rule directs empirical antibiotics.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Infections Due to Mixed Anaerobic Organisms" (primary); with supporting detail from "Pharyngitis, Sinusitis, Otitis, and Other Upper Respiratory Tract Infections," "Lung Abscess," and "Gas Gangrene and Other Clostridial Infections."
- ▶ CMDT 2026 — "Bacterial & Chlamydial Infections: Anaerobic Infections" (current empirical regimens and doses) and "Actinomycosis."



Aspergillus Infections (Aspergillosis)

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Aspergillosis* is the collective term for the spectrum of disease produced by the ubiquitous, hyaline, septate, branching mould *Aspergillus* (~50 pathogenic/allergenic species). *A. fumigatus* causes most invasive disease, >95% of chronic disease and most allergic syndromes; *A. flavus* predominates in sinus, cutaneous and keratitis disease (and granulomatous sinusitis of the Middle East/India); *A. terreus* and *A. nidulans* are intrinsically amphotericin-resistant. Only species growing at 37°C invade; spectrum runs from harmless saprophytic colonisation through devastating angioinvasive infection to allergic hypersensitivity. The clinical form is dictated by the **host immune state**.

Epidemiology, ecology and pathogenesis

- ▶ **Ecology**: worldwide; grows in decomposing plant matter (compost), hay and bedding, producing vast numbers of airborne **conidia**. Inhalation is the route of entry; daily exposure ranges from a few to millions of conidia. Intense exposure (construction, mouldy bark/hay, composting) can cause acute pulmonary aspergillosis even in the immunocompetent.
- ▶ **Incubation** of invasive disease is highly variable (2–90 days), so community-acquired strains often manifest during hospitalisation; outbreaks relate to contaminated air sources or **hospital construction**. **HEPA filtration** is protective and should guard operating rooms, burn units and high-risk wards.
- ▶ **Burden (global, 2024 estimates)**: invasive ~2.1 million; chronic ~6.1 million; allergic ~11.7 million.

- **Pathogenesis is host-determined:** profound neutropenia/phagocyte dysfunction → **angioinvasion**; an inadequate TH1 response with persistent inflammation → **chronic** cavitory disease; an exaggerated TH2/"allergic" response to *A. fumigatus* → **ABPA/SAFS**.

Risk factors (by disease form)

Form	Principal host setting / risk factors
Invasive	Profound, prolonged neutropenia ; high-dose glucocorticoids ; haematological malignancy/relapsed leukaemia; HSCT; chronic granulomatous disease (esp. <i>A. nidulans</i>); advanced HIV; immunomodulators — infliximab , ibrutinib (ibrutinib → cerebral disease); ICU patients (2–5%), severe influenza (8–25%), severe COVID-19 (~10%, "CAPA"), COPD (1.3–3.9%); severe liver disease
Chronic	Apparently immunocompetent but with prior lung damage — prior/active TB , NTM, sarcoidosis, prior pneumothorax/bullae, COPD, rheumatoid lung; subtle NK/IL-12/IFN- γ defects
Allergic (ABPA/SAFS)	Asthma and cystic fibrosis (incl. heterozygous <i>CFTR</i>); genetic TH2 predisposition; common in the Indian subcontinent
Saprophytic	Pre-existing pulmonary cavity (aspergilloma); maxillary sinus (fungal ball)

Classification and clinical manifestations

- **Invasive (acute ≤ 1 month / subacute 1–3 months):**
 - *Invasive pulmonary aspergillosis* — >80% of invasive disease; fever, cough, pleuritic discomfort, trivial **haemoptysis**, dyspnoea (often asymptomatic). Fever may respond transiently to steroids while disease progresses; a frequent **autopsy-only** diagnosis.
 - *Invasive sinusitis* — 5–10%, leukaemia/HSCT; nasal/facial pain, blocked nose, bloody discharge; endoscopy shows pale/dusky/necrotic mucosa.
 - *Tracheobronchitis* — lung-transplant and ventilated patients; ulcerative/pseudomembranous; mucous-plug obstruction.
 - *Disseminated/cerebral disease* — spread to **brain** (haemorrhagic infarction, abscess; rarely meningitis, mycotic aneurysm, granuloma), skin, thyroid, bone, kidney, GI tract, eye, heart valve; blood cultures almost always negative.
 - *Endocarditis* — usually prosthetic-valve (intra-operative contamination) or in PWID; large vegetations, culture-negative.
 - *Cutaneous* — purplish area → necrotic **eschar**; direct invasion at IV-catheter sites and in burns/trauma (esp. *A. flavus*).

- ▶ **Chronic pulmonary aspergillosis (CPA):**
 - *Chronic cavitary pulmonary aspergillosis (CCPA)* — one/more cavities expanding over months–years; >90% with prior lung disease; weight loss/fatigue may dominate; **life-threatening haemoptysis** is the key complication; untreated → *chronic fibrosing pulmonary aspergillosis* (“destroyed lung”). IgG positive in ~90%.
 - *Aspergilloma (fungal ball)* — fungal mass within a cavity; cough, haemoptysis, wheeze; ~10% resolve spontaneously.
 - *Aspergillus nodule* — 5–50 mm, may cavitate, mimics carcinoma; PET-avid; IgG positive ~65%.
- ▶ **Chronic sinusitis:** fungal ball of (maxillary) sinus — non-invasive, surgically curable; chronic invasive sinusitis — slowly destructive (ethmoid/sphenoid), *orbital apex syndrome* (**blindness + proptosis**), cavernous-sinus/carotid involvement; chronic granulomatous sinusitis — Middle East/India, *A. flavus*.
- ▶ **Allergic / saprophytic-allergic:**
 - *ABPA* — hypersensitivity to *A. fumigatus*; ~2.5% of referred asthmatics, up to 15% of CF teenagers; brown sputum casts, fleeting infiltrates, central **bronchiectasis**.
 - *Severe asthma with fungal sensitisation (SAFS)* — fungal sensitisation without full ABPA criteria; total IgE <1000 IU/mL. ABPA + SAFS = “fungal asthma.”
 - *Allergic fungal rhinosinusitis* — perennial sinusitis, nasal polyps, eosinophilic mucin, **Charcot-Leyden crystals**.
- ▶ **Superficial:** keratitis (sight-threatening; treat with topical **natamycin 5%**), onychomycosis (toenail, diabetes), otitis externa (often *A. niger*).

Diagnosis

- ▶ **Microscopy/histology:** hyaline, narrow, **septate hyphae branching at acute (45°) angles**; tissue shows vascular invasion with infarction (angioinvasion) or necrosis.
- ▶ **Galactomannan antigen** (cell-wall) in serum and especially **BAL** — high sensitivity (>80%); BAL more sensitive than serum and essential in ventilated ICU patients where radiology is nonspecific; serum antigen often precedes clinical/radiological signs by days; sensitivity falls with antifungal therapy; rising levels predict worse outcome.
- ▶ **Serum (1,3)- β -D-glucan** — supportive but non-specific (positive in many fungi).
- ▶ **Real-time PCR** (sputum/serum/BAL) — fast and more sensitive than culture; useful combined with antigen.
- ▶ **Culture** — positive in only **10–30%** of invasive disease; *request fungal media/high-volume culture*; vital for **azole-susceptibility testing** (especially during therapy).
- ▶ **Aspergillus IgG antibody** — cornerstone of **chronic** disease diagnosis with characteristic imaging (positive ~90% CCPA).

- ▶ **ABPA serology:** *Aspergillus*-specific IgE (or positive skin-prick) + elevated **total IgE** (usually >1000 IU/mL) + eosinophilia; hyperattenuated/high-density mucus is highly specific.
- ▶ **Imaging:** CT thorax — **halo sign** (ground-glass of haemorrhagic infarction around a nodule; early, ~7 days, good prognosis in neutropenia), nodules, wedge/pleural-based infarcts, later cavitation/**air-crescent sign** (aspergilloma). Sinus CT/MRI; brain MRI preferred for cerebral disease. *Definitive* diagnosis = positive culture from a sterile site, or positive histology **plus** culture/molecular confirmation from affected tissue.

Treatment

Indication	Primary	Alternatives / notes
Invasive aspergillosis	Voriconazole or isavuconazole (azoles ~20% higher response than AmB)	Posaconazole; lipid AmB; caspofungin/micafungin (2nd line). ID consult; therapy 3 months–years until immune reconstitution
Chronic pulmonary (CCPA)	Voriconazole or itraconazole	Posaconazole; IV AmB/micafungin. ≥12 months; avoid steroids (↑mortality ~240% unless antifungal cover)
ABPA / SAFS	Itraconazole + glucocorticoids (prednisone ~0.5 mg/kg/day, taper)	Voriconazole, posaconazole, inhaled AmB; long-term azole spares steroids
Single aspergilloma	Surgical resection (peri-operative antifungal cover)	Intracavitary AmB; medical Rx for multicavity disease
Sinus fungal ball / allergic sinusitis	Surgical removal ± endoscopic clearance	Local ± systemic steroids (allergic); ethmoidectomy if recurrent

- ▶ **Representative doses:** Voriconazole IV 6 mg/kg q12h ×2 loading then 4 mg/kg q12h (oral 200 mg bid); isavuconazole 200 mg q8h ×6 doses (2 days) then 200 mg daily; posaconazole tablet 300 mg daily; caspofungin 70 mg load → 50 mg/day; micafungin ≥150 mg/day (treatment); AmB deoxycholate 1 mg/kg/day; lipid AmB 3 mg/kg (AmBisome) or 5 mg/kg (Abelcet).
- ▶ **Therapeutic drug monitoring** is recommended for voriconazole, itraconazole, posaconazole and isavuconazole (variable absorption/metabolism, drug interactions).
- ▶ **Resistance:** multi-azole resistance in *A. fumigatus* ~3–20% (rising, esp. Southeast Asia; partly from agricultural azole fungicides); AmB inactive against **A. terreus* and *A. nidulans*; *A. niger** resistant to isavuconazole.
- ▶ **Adjuncts:** **bronchial artery embolisation** for problematic haemoptysis; reverse immunosuppression; surgery for endocarditis, brain abscess, keratitis, endophthalmitis, proximal-lung lesions.

- ▶ **Prophylaxis** (AML induction, GVHD, high-risk HSCT): **posaconazole** (most effective) or voriconazole/itraconazole solution/SUBA-itraconazole; IV micafungin if azole-contraindicated. *Fluconazole has no anti-Aspergillus activity.*

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **CT thorax spectrum of pulmonary aspergillosis** — label: (1) *halo sign* = nodule with surrounding ground-glass (early invasive/neutropenic); (2) *air-crescent sign* = crescent of air around a fungal ball (recovery); (3) *aspergilloma* = mobile fungal ball within an upper-lobe cavity with pleural thickening.
- ▶ **Tissue microscopy of Aspergillus** — label: hyaline **septate hyphae**, dichotomous **branching at 45° (acute) angle**, progressive width; inset of **conidiophore** with radiating chains of **conidia** (culture morphology); contrast note: broad, aseptate, right-angle hyphae = *Mucor* (differential).

Clinical / Diagnostic significance

- ▶ The single most useful discriminator is the **host**: neutropenia → invasive/angioinvasive; structurally damaged lung → chronic/aspergilloma; atopic asthma/CF → allergic.
- ▶ In India, CCPA is a **major mimic of, and sequel to, pulmonary TB** (follows treated TB in ~6–13%) — suspect in “smear-negative TB” or relapsing cavitary disease with weight loss; check **Aspergillus IgG**.
- ▶ In neutropenic/leukaemic and ICU/post-influenza/COVID patients, screen with **serum/BAL galactomannan** and urgent **CT thorax**; a *halo sign* warrants pre-emptive therapy.
- ▶ **ABPA** must be sought in poorly controlled asthma (total IgE >1000 IU/mL, specific IgE, eosinophilia, central bronchiectasis) — treatable, prevents fibrosis.
- ▶ Differentiate angioinvasive aspergillosis from **mucormycosis** (broad, aseptate, right-angle hyphae; AmB- rather than voriconazole-responsive) — management diverges sharply.

High-yield exam pointers

- ▶ *A. fumigatus* = most invasive/chronic/allergic disease; *A. flavus* = sinus/cutaneous/keratitis & granulomatous sinusitis (India/Middle East).
- ▶ **Septate hyphae, acute-angle (45°) dichotomous branching** — the classic histology buzz-phrase.
- ▶ **Galactomannan** (serum/BAL) and **β-D-glucan** are key non-culture markers; culture positive in only 10–30% of invasive disease.
- ▶ Radiology: **halo sign** (early), **air-crescent sign** (recovery/aspergilloma).
- ▶ ABPA hallmark: **total IgE usually >1000 IU/mL + Aspergillus-specific IgE + central bronchiectasis + brown mucus plugs**.

- ▶ First-line invasive therapy: **voriconazole or isavuconazole**; voriconazole IV 6 mg/kg q12h load → 4 mg/kg q12h.
- ▶ *AmB does NOT cover *A. terreus* or *A. nidulans*; *A. niger* is isavuconazole-resistant; fluconazole has NO anti-*Aspergillus* activity.*
- ▶ **Surgery cures** single aspergilloma and sinus fungal ball; **bronchial artery embolisation** for massive haemoptysis.
- ▶ Mortality: invasive 30–70% if treated (**100% if missed**); CCPA ~15–20% at 1 year, ~40% at 5 years, 50–60% at 10 years.
- ▶ Avoid glucocorticoids in CCPA (mortality up ~240%) unless covered by antifungals.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Aspergillosis” (Denning), incl. Tables 223-1/2/3 (disease frequency & diagnostic sensitivity, manifestations, treatment).
- ▶ **CMDT 2026** — “Mycotic Infections” (Aspergillosis: allergic/chronic/invasive forms, diagnosis, prevention and IDSA/ESCMID-ECMM-ERS treatment regimens and doses).
- ▶ *Coverage note:* The *air-crescent sign* and the *Aspergillus-vs-Mucor* hyphal contrast are standard, universally accepted radiology/microbiology added for completeness; Harrison explicitly describes the halo sign, cavitation, 45° septate hyphae and the broad differential rather than naming the “air-crescent sign.” Detailed ISHAM/formal ABPA criteria beyond IgE thresholds are not enumerated in the corpus; the serological criteria given are those stated in Harrison/CMDT.



Brucellosis

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals, predominantly domesticated ruminants and swine. It is known colloquially as *undulant fever* because of the remittent (waxing-and-waning) character of its pyrexia. Although it commonly presents as an acute febrile illness, the clinical manifestations are protean and definitive diagnostic signs may be lacking; thus the clinical impression must usually be confirmed by bacteriologic and/or serologic testing. It remains a major public-health problem in India, the Mediterranean basin, western/central Asia, Africa and Latin America, with an estimated >2 million human cases worldwide annually.

Etiologic agents and microbiology

- ▶ Caused by the genus **Brucella* — *small, gram-negative, unencapsulated, non-sporulating coccobacilli that behave in vivo as facultative intracellular parasites**; they grow aerobically on peptone-based medium at 37°C, with growth of some types enhanced by supplementary CO₂.
- ▶ **Species and animal reservoir** (host preference drives epidemiology):

Species	Main animal source	Clinical note
<i>B. melitensis</i>	Sheep, goats, camels	Commonest cause of symptomatic human disease; most acute/aggressive
<i>B. abortus</i>	Cattle, buffalo	Insidious onset; more likely to become chronic
<i>B. suis</i>	Swine (also reindeer/caribou, rodents)	Tendency to focal abscess formation
<i>B. canis</i>	Dogs	Generally milder, but can cause endocarditis
<i>B. ovis</i>	Sheep (reproductive)	Not clearly implicated in human disease
<i>B. neotomae</i> , <i>B. ceti</i> , <i>B. pinnipedialis</i>	Desert rodents; marine mammals	Rare/emerging human infections

- ▶ **Environmental resistance:** killed by **boiling and pasteurization**, sunlight and moderate heat, but **resistant to freezing and drying** — this aerosol stability facilitates airborne and laboratory transmission. Organisms survive ~2 months in soft cheeses, ≥6 weeks in dry contaminated soil and ≥6 months in damp soil/manure.
- ▶ Now genetically related to (and reclassified to include) *Ochrobactrum* spp., which can cause laboratory misidentification with very different clinical management.

Epidemiology and transmission

- ▶ A zoonosis whose human occurrence mirrors prevalence in domesticated animals; increasingly recognised in **India, Pakistan, Sri Lanka and China**.
- ▶ **Occupational exposure:** farmers, shepherds, goatherds, **veterinarians**, abattoir and meat-processing workers, feral-pig hunters, and **diagnostic laboratory staff** (handling cultures/samples).
- ▶ **Food-borne/urban exposure:** consumption of **unpasteurized milk, soft cheeses and ice cream** is the commonest non-occupational route; raw meat/bone marrow rarely.
- ▶ **Routes of entry:** ingestion, inhalation, or mucosal/percutaneous contact. Accidental injection or ingestion of **live veterinary vaccine strains** (*B. abortus* S19 and RB51; *B. melitensis* Rev 1) can cause disease.

- ▶ **Person-to-person transmission is extremely rare** (occasional reports via tissue/blood). No increased prevalence/severity in HIV or other immunosuppression.
- ▶ *B. melitensis* and *B. suis* are recognised potential **bioterrorism agents** — consider in sudden unexplained outbreaks.

Pathogenesis (the “stealth” intracellular pathogen)

- ▶ Both **humoral and cell-mediated** immunity are elicited, but antibodies alone cannot eradicate infection; **protective immunity is predominantly TH1/cell-mediated**.
- ▶ The **macrophage is the key target cell**. After uptake (smooth strains enter via lipid rafts using smooth LPS), the organism survives intracellularly by:
 - restricting fusion of the **type IV secretion system (VirB)-dependent Brucella-containing vacuole with lysosomes, diverting replication to the endoplasmic reticulum**;
 - inhibiting apoptosis of infected mononuclear cells and blocking dendritic-cell maturation/antigen presentation;
 - producing **Cu-Zn superoxide dismutase** and acid-stable proteins resisting reactive oxygen intermediates and defensins.
- ▶ **Smooth LPS** has an unusual O-chain with low endotoxin activity, aiding evasion of serum killing and pyrogenicity.
- ▶ **TNF- α** (early), **IL-12** $\rightarrow$ **IFN- γ** drive macrophage activation and TH1 responses; IL-4/IL-6/IL-10 downregulate protection.
- ▶ Initial replication occurs in regional lymph nodes; **haematogenous spread** seeds the reticuloendothelial system, musculoskeletal and genitourinary tissues, producing **granulomas** (with/without necrosis) and abscesses.

Clinical features

- ▶ **Fever** is almost invariable, with profuse drenching **night sweats**; untreated, it shows the classic **undulating pattern**, and is accompanied by musculoskeletal symptoms in about **half** of patients. Constitutional features: apathy, fatigue, anorexia, weight loss, myalgia, headache, chills. Incubation 1 week to several months.
- ▶ **Three classic presentation patterns**: (1) typhoid-like febrile illness but less severe; (2) **fever + acute monoarthritis of hip or knee in a young child**; (3) long-standing fever with **low-back or hip pain in an older man**.
- ▶ **Musculoskeletal (~40%, the most common focal disease)**:
 - **Spondylitis/osteomyelitis** — favours **lumbar and low-thoracic vertebrae**; anterosuperior end-plate erosion early, eventual whole-vertebra sclerosis.
 - **Septic arthritis** — knee, hip, **sacroiliac**, shoulder, **sternoclavicular** joints (mono- or poly-arthritis).

► **Other organ involvement:**

- Respiratory: dry cough in ~25% (chest X-ray often normal); rarely pneumonia/empyema/lung abscess.
- **Hepatosplenomegaly** (~25%), lymphadenopathy (10–20%) — mimics glandular-fever syndromes.
- Genitourinary: **epididymo-orchitis in up to 10% of men** (distinguish from mumps/torsion); prostatitis, salpingitis, pyelonephritis; **increased fetal loss** in pregnancy (no teratogenicity).
- **Neurobrucellosis**: depression/lethargy; **lymphocytic meningoencephalitis** mimicking neuro-TB; rarely intracerebral abscess, cranial-nerve palsies, mycotic aneurysm.
- **Endocarditis** (~1%) — most often the **aortic valve** (native or prosthetic); leading cause of death.
- Metastatic abscesses, with a predilection for the **breast and thyroid**.

Diagnosis

- **Routine labs (non-specific)**: WBC usually **normal or low with relative lymphocytosis**; mild anaemia, sometimes thrombocytopenia/DIC; ESR and CRP often normal; mildly raised transaminases/bilirubin. CSF/joint fluid show **lymphocytosis with low glucose**; biopsy may show **non-caseating granulomas without acid-fast bacilli**.
- **Culture (definitive)**: isolation from blood, bone marrow, CSF, joint fluid or tissue is positive in 50–70%; automated systems (e.g., Bactec) usually flag within 7 days. Warn the laboratory — handle under **containment for dangerous pathogens**. May be misidentified as *Agrobacterium*, *Ochrobactrum* or *Psychrobacter (Moraxella) phenylpyruvicus*; MALDI-TOF MS identification has historically been unreliable for the genus.
- **PCR / NAAT**: targets the **rrs-rrl (16S–23S) spacer**, outer-membrane protein genes, insertion sequence IS711 and BCSP31 — sensitive, rapid, biohazard-free; prolonged post-treatment positivity is of uncertain significance.
- **Serology (often the only positive finding)**: IgM appears first, followed by IgG and IgA. The **standard agglutination test (SAT)** is the mainstay.
 - **Diagnostic titres**: in endemic areas, **1:320–1:640 or higher**; in non-endemic areas, **≥1:160** is significant. A rising titre on repeat testing at 2–4 weeks is confirmatory.
 - **Rose Bengal test** used for screening.
 - **Cross-reactions** (false positives) with *Yersinia enterocolitica* O:9, *E. coli* O157, *Francisella tularensis*, *Salmonella* group N, *Stenotrophomonas maltophilia* and *Vibrio cholerae*.
 - **Rough strains (B. canis, B. ovis) and vaccine strain RB51 give false-negative results** in conventional smooth-antigen tests.

Treatment

- **Principles:** prolonged combination therapy (single agents relapse), exclude/cover tuberculosis (shared drugs — never use rifampin alone), and emphasise **adherence** (poor compliance, not resistance, causes most failures).

Indication	Regimen	Notes
Acute non-focal (gold standard)	IM streptomycin 0.75–1 g/day × 14–21 days + doxycycline 100 mg BD × 6 weeks	Relapse 5–10%
WHO alternative (oral)	Rifampin 600–900 mg/day + doxycycline 100 mg BD × 6 weeks	Easier; relapse ~10% (>20% in practice)
Aminoglycoside substitute	Gentamicin 5–6 mg/kg/day × 1–2 weeks in place of streptomycin	US/UK guidelines; avoid short courses
Children / pregnant women	High-dose TMP-SMX (with rifampin) — avoid tetracyclines	Watch rising TMP-SMX resistance
Complicated / focal disease	Triple therapy = doxycycline + rifampin + initial aminoglycoside	≥3 months
Neurobrucellosis	Standard regimen + ceftriaxone, 3–6 months	—
Endocarditis	≥3 drugs (aminoglycoside + tetracycline + rifampin ± ceftriaxone/fluoroquinolone) 4–6 months	Surgery usually needed for prosthetic valves

- **Fluoroquinolones** are not recommended first-line (the *Ioannina Recommendations*); poor intravacuolar activity at low pH.
- **Post-exposure prophylaxis:** rifampin + doxycycline (or doxycycline alone) for 3 weeks; omit rifampin after RB51 exposure (RB51 is rifampin-resistant) — substitute TMP-SMX.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Intracellular pathogenesis of Brucella: Inhaled/ingested coccobacillus → uptake by macrophage (smooth LPS / lipid raft entry) → type IV secretion system (VirB) prevents phagolysosome fusion → replication in endoplasmic-reticulum-derived Brucella-containing vacuole → suppressed apoptosis & antigen presentation → haematogenous spread → granuloma in reticuloendothelial/musculoskeletal tissue. Labels: macrophage, smooth LPS, VirB type IV secretion system, Brucella-containing vacuole, ER, blocked phagolysosome fusion, IFN-γ/TH1, granuloma.**
- **Spinal radiology — Brucella vs TB spondylitis:** two vertebral-column sketches. Labels for *Brucella*: lumbar site, **anterosuperior end-plate erosion**, intact body until late, **whole-body sclerosis on recovery**, small well-localised paravertebral abscess, parrot-beak osteophyte,

canal compression rare. Labels for TB: dorsolumbar, early body destruction, gibbus/anterior wedge, large psoas/paravertebral abscess, early canal compression.

Clinical / Diagnostic significance

- ▶ The single most important **differential is tuberculosis**, especially in spondylitis — radiological discriminators (Table 174-1: site, sequence of disk involvement, body destruction, abscess size, gibbus) guide both therapy and prognosis.
- ▶ Triad of **fever + sweats + back/joint pain** with an exposure history (unpasteurized dairy, animal/abattoir contact, endemic-area travel, similar family illness in ~50%) should prompt brucella serology and prolonged blood cultures.
- ▶ A SAT titre alone never diagnoses disease — interpret with **exposure history, clinical picture and a rising titre**; remember rough-strain (*B. canis*) infection is **serology-negative**.
- ▶ Always alert the microbiology laboratory: brucella is a **biosafety-level-3** pathogen and a frequent cause of laboratory-acquired infection.

High-yield exam pointers

- ▶ **Undulant fever**; zoonosis from **unpasteurized dairy / animal contact**; *B. melitensis* commonest and most severe.
- ▶ **Gram-negative facultative intracellular coccobacillus**; macrophage is the key host cell; survives via **type IV (VirB) secretion** avoiding phagolysosome fusion.
- ▶ Musculoskeletal disease in ~40% — **sacroiliitis, lumbar spondylitis**; child with **monoarthritis of hip/knee**.
- ▶ **Endocarditis** (~1%, aortic valve) is the **leading cause of death**; mortality overall <1%.
- ▶ **Gold-standard therapy: streptomycin + doxycycline × 6 weeks**; WHO oral alternative **rifampin + doxycycline**; TMP-SMX for children/pregnancy.
- ▶ **SAT diagnostic titre** ≥1:160 (non-endemic) or 1:320–1:640 (endemic); cross-reacts with *Yersinia enterocolitica* O:9.
- ▶ **Relapse up to 30%** in poorly compliant patients — follow up to **2 years**; weight/well-being beat serology for monitoring.
- ▶ **Notifiable disease**; prevention = animal test-and-slaughter, vaccination and **milk pasteurization**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Brucellosis” (primary source for definition, etiologic agents, epidemiology, pathogenesis, clinical features, diagnosis, Table 174-1 spine radiology, treatment regimens, prognosis and prevention).

- **CMDT 2026** — *Bacterial & Chlamydial Infections* and the *Anti-infective Treatment* chapter (corroboration of streptomycin/doxycycline combination regimens and differential diagnosis of febrile zoonoses).
- *Coverage note:* No dedicated infectious-disease subspecialty text was listed in the spec for this topic; CMDT covers brucellosis only briefly (mainly cross-references). Harrison Ch 174 is comprehensive and fully supports every specific stated above.



Classify the Causes of Chronic Meningitis and Etiologies to be Considered in Advanced HIV Infection

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — Chronic meningitis is diagnosed when a characteristic neurologic syndrome persists for >4 weeks in association with a **persistent CSF inflammatory response** (white cell count >5/ μ L). Unlike acute meningitis, meningeal signs are often *absent*; the cardinal features are persistent headache, hydrocephalus, cranial neuropathies, radiculopathies, and cognitive/personality change. Correct treatment depends entirely on identifying the etiology, which spans infective, malignant, inflammatory and chemical causes. In *advanced HIV/AIDS*, chronic meningitis is common, may present with minimal symptoms even with a paucicellular CSF, and is dominated worldwide by *Mycobacterium tuberculosis* and *Cryptococcus neoformans*.

Classification of the Causes of Chronic Meningitis

Five major disease categories account for most cases (Harrison), with monogenic autoinflammatory disorders added as an emerging cause of recurrent meningitis.

Category	Representative causes
1. Meningeal infections	Bacterial: partially treated pyogenic meningitis, <i>M. tuberculosis</i> , <i>Treponema pallidum</i> (syphilis), <i>Borrelia burgdorferi</i> (Lyme/Bannwarth), <i>Brucella</i> , <i>Nocardia</i> , <i>Actinomyces</i> , <i>Tropheryma whipplei</i> , leptospira
	Fungal: <i>Cryptococcus neoformans/gattii</i> , <i>Coccidioides immitis</i> , <i>Histoplasma capsulatum</i> , <i>Blastomyces</i> , <i>Candida</i> , <i>Aspergillus</i> , <i>Sporothrix schenckii</i>
	Protozoal: <i>Toxoplasma gondii</i> , trypanosomiasis, <i>Acanthamoeba</i> , <i>Balamuthia</i>
	Helminthic: neurocysticercosis (<i>Taenia solium</i>), <i>Gnathostoma</i> , <i>Angiostrongylus cantonensis</i> , <i>Baylisascaris</i> , schistosomiasis, echinococcus

Category	Representative causes
	Viral: HSV-2 (Mollaret), mumps, LCMV, enteroviruses (in agammaglobulinemia), HIV, EBV, CMV
2. Malignancy (neoplastic)	Carcinomatous/lymphomatous meningitis — metastatic breast, lung, stomach, pancreas; melanoma; lymphoma; leukemia; meningeal gliomatosis
3. Autoimmune / inflammatory	Neurosarcoidosis, Behçet's, SLE, rheumatoid arthritis, granulomatosis with polyangiitis, primary CNS (granulomatous) angiitis, Vogt-Koyanagi-Harada syndrome, IgG4-related hypertrophic pachymeningitis, Sjögren's
4. Chemical meningitis	Leak from epidermoid/dermoid tumour, craniopharyngioma or cholesteatoma; subarachnoid haemorrhage; intrathecal drug/contrast injection; drug hypersensitivity (NSAIDs, sulfonamides, IVIG, isoniazid, carbamazepine, lamotrigine)
5. Parameningeal infection	Brain/epidural/subdural abscess, sinusitis, mastoiditis, otitis media, chronic pleuropulmonary infection with right-to-left shunt
6. Monogenic autoinflammatory (recurrent)	TRAPS (<i>TNFRSF1A</i>), CAPS/NOMID (<i>NLRP3</i> gain-of-function → ↑IL-1β), complement factor I deficiency

Recurrent Meningitis — a Distinct Subset

Two clinical forms exist: a *chronic persistent* form and a *recurrent* form in which all symptoms, signs and CSF abnormalities resolve completely between attacks. Recurrent meningitis suggests:

- ▶ **Mollaret's meningitis** — most often HSV-2 (rarely HSV-1); large endothelial ("Mollaret") cells then mononuclear cells in CSF; confirm by HSV PCR.
- ▶ **Chemical (episodic) meningitis** — recurrent leak from an epidermoid tumour, craniopharyngioma or cholesteatoma; xanthochromia/low glucose.
- ▶ **Autoimmune** — VKH syndrome, Behçet's, SLE, neurosarcoidosis, IgG4-related disease, GPA, primary CNS vasculitis.
- ▶ **Drug hypersensitivity** — recurs with re-exposure to the offending agent.
- ▶ **Inherited autoinflammatory syndromes** — TRAPS, CAPS, complement factor I deficiency (recurrent steroid-responsive neutrophilic meningitis).

CSF Clues that Narrow the Differential

The predominant CSF cell type after the third week is a powerful discriminator.

CSF pattern	Principal considerations
Mononuclear (lymphocytic)	Most chronic meningitides — TB, <i>Cryptococcus</i> , syphilis, Lyme, sarcoidosis, neoplastic
Neutrophilic after 3 weeks	<i>Nocardia</i> , <i>Actinomyces</i> , <i>Brucella</i> , <i>M. tuberculosis</i> (5–10% of early cases), fungi (<i>Blastomyces</i> , <i>Candida</i> , <i>Histoplasma</i> , <i>Aspergillus</i> , <i>Pseudallescheria boydii</i> , <i>Cladophialophora</i>), SLE, chemical meningitis
Eosinophilic	Parasites (<i>A. cantonensis</i> , <i>Gnathostoma</i> , <i>Baylisascaris</i> , cysticercosis, schistosomiasis, echinococcus, toxoplasma), coccidioidomycosis (6–20% eosinophils), lymphoma/leukaemia/carcinoma, sarcoidosis, hypereosinophilic syndrome
Low glucose (hypoglycorrhachia)	TB, fungal (esp. <i>Cryptococcus</i> , <i>Coccidioides</i> , <i>Histoplasma</i>), carcinomatous/lymphomatous, sarcoidosis, mumps, LCMV

Imaging clue: **leptomeningeal** enhancement (following gyri/basal cisterns) typifies infective meningitis, whereas thick linear/nodular **pachymeningeal** (dural) enhancement suggests IgG4-related disease, GPA, lymphoma or neurosarcoidosis.

Etiologies in Advanced HIV Infection (the “discuss” component)

Chronic meningitis is not uncommon in HIV; immunosuppression *attenuates* meningeal signs, so CSF examination is mandatory for any persistent headache or unexplained mental change. The relevant pathogens track with the CD4 count.

Etiology (CD4 threshold)	Key features / CSF–imaging	Treatment (Harrison/CMDT)
Cryptococcal meningitis (CD4 <100)	Commonest fungal CNS infection in AIDS; AIDS-defining in ~2%; subacute meningoencephalitis, markedly raised ICP , often pauci-cellular CSF; India ink + CSF cryptococcal antigen (CrAg) ; up to 12% due to <i>C. gattii</i> ; <i>prozone</i> false negatives	Induction: liposomal amphotericin B 3–4 mg/kg/day (or amphotericin B deoxycholate 0.7–1.0 mg/kg/day) + flucytosine 25 mg/kg qid for ≥2 weeks → consolidation fluconazole (Harrison 800 mg, CMDT 400 mg) daily ×8 weeks → maintenance fluconazole 200 mg/day until CD4 >200 for ≥6 months. Serial LPs for ICP; delay ART 4–6 weeks (IRIS risk)
Tuberculous meningitis (any CD4; commonest cause worldwide)	Basal meningitis, cranial neuropathies, stroke from arteritis; CSF: lymphocytic, low glucose, high protein ; AFB	4-drug ATT (HRZE) + adjunctive glucocorticoids ; anti-TNF/PD-1 therapy can reactivate TB

Etiology (CD4 threshold)	Key features / CSF–imaging	Treatment (Harrison/CMDT)
	smear/culture, CSF PCR (Xpert), IGRA; miliary TB on imaging	
Cerebral toxoplasmosis (CD4 <200)	Reactivation of latent cysts; fever, focal deficit, seizures; MRI multiple ring-enhancing lesions, eccentric target sign ; 10× more likely if <i>Toxoplasma</i> IgG-positive	Sulfadiazine + pyrimethamine + leucovorin ≥4–6 weeks (alt: clindamycin + pyrimethamine); empiric trial, biopsy if no response in 2–4 weeks; primary prophylaxis with TMP-SMX if CD4 <100 and IgG+
Primary CNS lymphoma (CD4 ~50)	EBV-driven (often 100% EBV+); 1–3 deep white-matter lesions, ring-enhancing (less than toxoplasmosis); CSF EBV PCR; brain biopsy	Radiotherapy ± chemotherapy + ART; 2-year survival only 20–30%
Progressive multifocal leukoencephalopathy	JC virus ; multifocal deficits, non-enhancing occipito-parietal white-matter lesions; CSF JCV DNA (sensitivity 76%, specificity ~100%)	No specific therapy — immune reconstitution with ART is the mainstay
Neurosyphilis	Meningovascular stroke, dementia, myelopathy; CSF VDRL (specific, insensitive); aggressive in HIV	IV penicillin G
CMV polyradiculopathy/encephalitis (CD4 <50)	Fulminant cauda-equina syndrome, urinary retention; neutrophilic CSF , CMV PCR	IV ganciclovir / foscarnet
Aseptic (HIV) meningitis	At seroconversion (acute retroviral syndrome) or persisting low-grade; immune-mediated, rare after AIDS develops; lymphocytic CSF, HIV RNA	Supportive; ART
Other fungi / bacteria	<i>Histoplasma</i> (CD4 ~33), <i>Coccidioides</i> , <i>Nocardia</i> , <i>Candida</i> ; basis for empiric antifungal cover	Amphotericin B-based regimens

Diagnostic Approach in the HIV Patient

- Image before LP if raised ICP / mass lesion suspected (herniation risk); obstructive hydrocephalus needs ventricular drainage.

- ▶ Send **opening pressure**, cell count + differential, glucose, protein, Gram/India ink, CrAg, VDRL, AFB smear/culture + TB PCR, fungal culture, cytology/flow cytometry, and broad-range 16S/18S rRNA PCR or metagenomic next-generation sequencing in enigmatic cases.
- ▶ Repeat **large-volume CSF** (≥ 3 samples) for neoplastic/fungal causes; cervical cisternal tap if lumbar CSF unrevealing.
- ▶ **Meningeal biopsy** when CSF is non-diagnostic and the patient is deteriorating — target enhancing meninges (diagnostic in 80% vs 9% for non-enhancing regions).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Classification wheel of chronic meningitis:** central hub “Chronic meningitis (>4 weeks, CSF WBC $>5/\mu\text{L}$)” with six labelled spokes — *Meningeal infection*, *Malignancy*, *Autoimmune/inflammatory*, *Chemical*, *Parameningeal infection*, *Autoinflammatory (recurrent)*; annotate infection spoke with *TB*, *Cryptococcus*, *syphilis*, *Lyme*.
- ▶ **Diagram 2 — CD4 ladder of HIV CNS opportunistic infections:** vertical axis falling CD4 with labelled bands — <200 : *Toxoplasma*, *TB*; <100 : *Cryptococcus*, *Histoplasma*; ~ 50 : *Primary CNS lymphoma*, *CMV*; *late/any*: *PML*, *neurosyphilis*; label MRI signatures (toxoplasmosis = ring-enhancing/eccentric target; lymphoma = deep solitary; PML = non-enhancing white matter).

Clinical / Diagnostic significance

- ▶ A **lymphocytic meningitis with low CSF glucose** in any setting should be treated empirically for **tuberculosis**, as delay is devastating.
- ▶ In AIDS, **cryptococcal meningitis can cause fatal raised ICP without ventricular enlargement** — serial therapeutic LPs are lifesaving.
- ▶ **Ring-enhancing lesions** in HIV = toxoplasmosis vs primary CNS lymphoma; *Toxoplasma* IgG-negativity ($<10\%$ probability) or CSF EBV PCR positivity shifts toward lymphoma and earlier biopsy.
- ▶ **IRIS** complicates ART started too early after cryptococcal/TB meningitis — hence the recommended antifungal/anti-TB lead-in before ART.
- ▶ Empirical therapy when diagnosis fails: **antimycobacterials + amphotericin B ($\pm$ flucytosine) $\pm$ glucocorticoids**; transient steroid responses can mask TB, cysticercosis or lymphoma.

High-yield exam pointers

- ▶ Definition: neurologic syndrome **>4 weeks** + CSF WBC $>5/\mu\text{L}$.
- ▶ **Five-category classification:** infection, malignancy, autoimmune, chemical, parameningeal (+ autoinflammatory for recurrent).
- ▶ **Worldwide commonest cause in HIV = TB, then Cryptococcus.**

- ▶ Mollaret's = recurrent HSV-2 meningitis.
- ▶ Cryptococcal Rx triad: amphotericin B + flucytosine (induction) → fluconazole (consolidation → maintenance); treat raised ICP.
- ▶ Toxoplasmosis Rx = sulfadiazine + pyrimethamine + leucovorin; CD4 <200; ring-enhancing lesions.
- ▶ PCNSL = EBV-positive, CD4 ~50; PML = JC virus, non-enhancing.
- ▶ Empiric anti-TB therapy for low-glucose lymphocytic chronic meningitis; ~one-third of cases remain undiagnosed despite full workup.
- ▶ Biopsy yield highest from contrast-enhancing meninges (80%).

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Chronic and Recurrent Meningitis" (classification, CSF/biopsy clues, empiric therapy, immunosuppressed host) and "Human Immunodeficiency Virus Disease: AIDS and Related Disorders" (CNS opportunistic infections, CD4 thresholds, MRI patterns, treatment regimens).
- ▶ CMDT 2026 — "HIV Infection & AIDS" (current induction–consolidation–maintenance regimens for cryptococcal meningitis and CMV; opportunistic-infection management).



Clinical features, diagnosis and treatment of neurosyphilis

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Neurosyphilis is involvement of the central nervous system by *Treponema pallidum* and can occur at any stage of syphilis, not only in late disease. It is best viewed as a continuum: early CNS invasion within weeks, months to years of asymptomatic CSF involvement, and symptomatic early or late neurologic syndromes. Ocular syphilis and otosyphilis may occur with or without other CNS disease but are treated with the same regimen as neurosyphilis because permanent visual or hearing loss may occur.

Etiopathogenesis and natural history

- ▶ *T. pallidum* disseminates early; CSF abnormalities may be found in up to 40% of untreated primary/secondary syphilis and 25% of untreated latent syphilis.
- ▶ Early neurosyphilis includes asymptomatic neuroinvasion, syphilitic meningitis, and meningovascular syphilis. Late neurosyphilis includes general paresis and tabes dorsalis.
- ▶ Approximate timing is exam-important: meningeal disease usually occurs within <1 year, meningovascular disease up to 10 years, general paresis around 20 years, and tabes dorsalis around 25-30 years after infection.

- ▶ Risk is higher with untreated HIV infection, especially low CD4 counts; Harrison notes association with serum RPR $\geq 1:32$ and, in HIV, CD4 $\leq 350/\text{mL}$.
- ▶ Benzathine penicillin does not reliably achieve treponemicidal CSF levels; therefore proven or suspected neurosyphilis needs **aqueous penicillin-based therapy**, not standard benzathine-only syphilis therapy.

Clinical classification and features

Form	Core clinical features	Typical CSF clue
Asymptomatic neurosyphilis	No neurologic symptoms/signs; detected during evaluation of syphilis, tertiary disease, HIV/high-risk state, or treatment failure	Mononuclear pleocytosis, raised protein, or reactive CSF-VDRL
Meningeal syphilis	Headache, nausea, vomiting, neck stiffness, cranial nerve palsy, seizures, altered mental status; may accompany or follow secondary syphilis	Lymphocytic pleocytosis and raised protein; CSF-VDRL may be positive
Meningovascular syphilis	Meningitis plus vasculitis of small/medium/large vessels; subacute prodrome of headache, vertigo, insomnia, psychological change, then progressive stroke syndrome, classically in a young adult and often MCA territory	Higher lymphocytic pleocytosis may occur; CMTD gives 100-1000 cells/mL with elevated protein
General paresis	Progressive cortical disease: personality change, affective disturbance, hyperreflexia, <i>Argyll Robertson pupil</i> , psychosis, memory loss, impaired orientation/calculation/judgment, dysarthria, tremor	Similar to late parenchymatous neurosyphilis; CSF may resemble tabes
Tabes dorsalis	Posterior column/dorsal root disease: lightning pains, sensory ataxia, positive Romberg, impaired position/vibration sense, areflexia, bladder disturbance, impotence, foot drop, Charcot joint, optic atrophy	Normal or lymphocytic CSF, raised protein, variable serology

Ocular, otic and HIV-associated disease

- ▶ **Ocular syphilis** may present as anterior uveitis, iritis, neuroretinitis, optic neuritis, chorioretinitis, optic atrophy, or panuveitis; failure to respond to topical steroids is a classic diagnostic clue.

- ▶ **Otosyphilis** presents with sensorineural hearing loss, vertigo, or tinnitus; untreated disease may lead to deafness.
- ▶ Ask every patient with syphilis about **vision, hearing, headache, cognitive change, stroke symptoms, gait ataxia, bladder symptoms, lightning pains, and cranial nerve symptoms**.
- ▶ Isolated confirmed ocular disease with reactive syphilis serology and no cranial nerve or other neurologic abnormality does **not** require CSF before treatment; full ocular examination is mandatory.
- ▶ Isolated auditory disease with reactive serology and normal neurologic examination usually has normal CSF and does **not** require CSF before treatment.
- ▶ Ocular syphilis and otosyphilis are treated as **neurosyphilis regardless of CSF findings**.
- ▶ In HIV infection, mild CSF pleocytosis may occur due to HIV itself; routine lumbar puncture in asymptomatic patients is not recommended, but a careful neurologic, ophthalmic, otologic, and cranial nerve examination is essential.

Diagnostic approach

- ▶ Establish syphilis first using both **nontreponemal** and **treponemal** serology; one test alone is insufficient. Nontreponemal tests are **VDRL/RPR** and are useful for titers and follow-up; treponemal tests include **FTA-ABS, TPPA, EIA/CIA**.
- ▶ Consider neurosyphilis when reactive syphilis serology is accompanied by neurologic signs/symptoms or compatible CSF abnormalities.
- ▶ **Indications for lumbar puncture:** clinical neurologic involvement such as meningitis, cranial nerve palsy, stroke, altered mental status, motor/sensory deficit, loss of vibration sense; treatment failure or fourfold rise in titer; active tertiary syphilis; ocular disease with cranial nerve or other neurologic signs.
- ▶ **CSF findings:** mononuclear pleocytosis **>5 WBC/mcL**, protein **>45-46 mg/dL**, and/or reactive CSF-VDRL. Classic CMDT description is protein **>46 mg/dL** with lymphocytic pleocytosis **5-100 cells/mcL**.
- ▶ **CSF-VDRL** is highly specific; a positive result without blood contamination is diagnostic. It is insensitive and may be negative in **30-70%** of cases, so a negative test does not exclude neurosyphilis.
- ▶ **CSF-RPR should not replace CSF-VDRL**. CSF FTA-ABS/TPPA is more sensitive but less specific; a negative result makes neurosyphilis unlikely, especially with nonspecific symptoms.
- ▶ In HIV infection, specificity improves by using a higher CSF WBC cutoff, commonly **>20 WBC/mcL**, because HIV itself may cause mild CSF pleocytosis.
- ▶ Differential diagnoses to exclude according to presentation include viral/tuberculous/fungal/chronic meningitis, autoimmune encephalitis, HIV-associated

neurocognitive disorder, B12 or copper myelopathy, stroke in the young, multiple sclerosis, neuro-ophthalmic disease, and primary psychiatric illness.

Treatment

Situation	Recommended regimen	Key notes
Neurosyphilis, ocular syphilis, otosyphilis	Aqueous crystalline penicillin G 18-24 million units/day IV as 3-4 million units every 4 hours or continuous infusion for 10-14 days	Drug of choice; achieves treponemicidal CSF levels
Alternative when adherence assured	Procaine penicillin G 2.4 million units IM daily + probenecid 500 mg orally four times daily, both for 10-14 days	Avoid if adherence is doubtful
Penicillin allergy	Prefer penicillin desensitization and treatment with penicillin	Especially important in pregnancy and definite neurosyphilis
Limited alternative	Ceftriaxone 1-2 g IM/IV daily for 10-14 days with close follow-up	Evidence is limited; seek infectious disease input
After neurosyphilis regimen	Benzathine penicillin G 2.4 million units IM weekly for 1-3 weeks may be considered to match latent-syphilis duration	Not a substitute for CNS-active therapy

- ▶ Admit or closely supervise patients requiring IV therapy; patients with ocular disease need ophthalmology, and otosyphilis needs ENT/audiology involvement.
- ▶ Do **HIV testing** in all patients with syphilis/neurosyphilis; offer prevention counselling and partner notification where relevant.
- ▶ Treat **Jarisch-Herxheimer reaction** supportively: fever, chills, headache, myalgia, tachycardia, and transient worsening after therapy are not penicillin allergy. Use antipyretics; consider expert input in CNS/cardiac disease and pregnancy.
- ▶ Existing parenchymal damage may only stop progressing after treatment; meningeal symptoms respond more dramatically than tabetic or paretic deficits.

Follow-up, prognosis and complications

- ▶ Monitor clinically and with quantitative RPR or VDRL using the same test method; CMDT recommends nontreponemal titers every 3-6 months after neurosyphilis treatment.
- ▶ Adequate response is suggested by clinical improvement and falling serum nontreponemal titers; a fourfold RPR decline correlates with CSF normalization in many treated patients.

- ▶ Repeat CSF is not routinely needed when symptoms improve and titers fall appropriately, especially in HIV-negative patients or HIV-positive patients on effective ART.
- ▶ Repeat CSF or expert consultation is needed if symptoms persist/return, titers fail to fall or rise fourfold, or treatment failure/reinfection is suspected.
- ▶ CSF WBC count is the most sensitive CSF marker of response and generally normalizes within **3-12 months**; CSF protein falls more slowly and CSF-VDRL may decline over years.
- ▶ Major preventable complications are stroke, blindness, deafness, dementia/psychosis, sensory ataxia, bladder dysfunction, Charcot joints, and irreversible posterior column or cortical damage.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Natural history timeline of neurosyphilis:** primary/secondary syphilis -> early CNS invasion/asymptomatic CSF -> meningeal syphilis (<1 year) -> meningovascular syphilis (years) -> general paresis (~20 years) -> tabes dorsalis (25-30 years).
- ▶ **Diagnostic-treatment flowchart:** reactive serum RPR/VDRL + treponemal test -> neurologic/ocular/otic symptoms? -> ocular/ENT/neurologic examination -> CSF cell count, protein, CSF-VDRL +/- FTA-ABS/TPPA -> IV aqueous penicillin G 10-14 days -> clinical and serologic follow-up.

Clinical / Diagnostic significance

- ▶ Neurosyphilis is a **treatable mimic** of meningitis, stroke in the young, dementia, psychiatric illness, sensory ataxia, and posterior column myelopathy.
- ▶ Always examine pupils: **Argyll Robertson pupil** is small/irregular and accommodates but does not react to light; it is high-yield in tabes dorsalis and paresis.
- ▶ A negative CSF-VDRL does not rule out disease; the diagnosis is a **clinic-serologic-CSF synthesis**, not a single-test diagnosis.
- ▶ Do not delay ocular or otic treatment while waiting for CSF when isolated ocular/otic disease is otherwise clear.
- ▶ Benzathine penicillin is correct for uncomplicated latent syphilis but **wrong as sole therapy** for neurosyphilis because of inadequate CSF penetration.
- ▶ In HIV, interpret mild CSF pleocytosis cautiously; treatment regimen is the same, but follow-up must be meticulous.

High-yield exam pointers

- ▶ Write first: **Neurosyphilis can occur at any stage of syphilis.**
- ▶ Classification: **asymptomatic, meningeal, meningovascular, ocular/otic, tabes dorsalis, general paresis.**

- ▶ Meningovascular syphilis: young patient + subacute encephalitic prodrome + stroke, often MCA territory.
- ▶ Tabes dorsalis: lightning pains, sensory ataxia, Romberg sign, areflexia, bladder dysfunction, Charcot joint.
- ▶ General paresis: personality change, psychosis, memory/judgment impairment, dysarthria, tremor, hyperreflexia.
- ▶ Diagnostic triad: reactive serum serology + neurologic syndrome + CSF pleocytosis/protein/reactive CSF-VDRL.
- ▶ CSF-VDRL positive = diagnostic; negative = does not exclude.
- ▶ Treatment: aqueous crystalline penicillin G 18-24 million units/day IV for 10-14 days.
- ▶ Follow response with clinical status and quantitative RPR/VDRL; repeat CSF only when response is poor or uncertain.

SOURCE & COVERAGE

Harrison 22e — “Syphilis”; CDMT 2026 — “Spirochetal Infections” and “Common Problems in Infectious Diseases & Antimicrobial Therapy”.



Clostridium difficile

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — *Clostridioides difficile* infection (CDI) is an antibiotic-associated colonic infection caused by toxigenic, spore-forming, obligate anaerobic, gram-positive bacilli. It follows disruption of normal colonic microbiota, usually after antimicrobial exposure, and ranges from mild watery diarrhea to **pseudomembranous colitis**, toxic megacolon, sepsis, perforation and death. Although the older exam term is *Clostridium difficile*, the current nomenclature is *Clostridioides difficile*.

Etiology, epidemiology and risk factors

- ▶ **Organism:** spore-forming anaerobic bacillus; spores survive gastric acidity, persist for months on hospital surfaces and spread by contaminated hands, equipment and patient-room environments.
- ▶ **Usual setting:** hospitals, nursing homes and the period after discharge; community-associated CDI is increasingly recognized and may occur without documented antibiotic exposure.
- ▶ **Antibiotic risks:** clindamycin, ampicillin, second- and third-generation cephalosporins and fluoroquinolones are classic high-risk drugs. Almost any antibiotic can predispose, including vancomycin, by disturbing colonization resistance.

- ▶ **Lower-risk but not risk-free agents:** penicillin/beta-lactamase-inhibitor combinations such as piperacillin-tazobactam are less strongly associated than cephalosporins or fluoroquinolones.
- ▶ **Host and care-related risks:** older age, severe underlying illness, prolonged hospitalization, gastrointestinal surgery, enteral tube feeding, antacid/PPI exposure, immunocompromise, IBD, chemotherapy, multiple or prolonged antibiotic courses and chronic-care facility residence.
- ▶ **Colonization:** asymptomatic fecal carriage increases with length of hospital stay and may exceed 20% after more than 2 weeks in hospital; healthy community adult carriage is much lower. Infants commonly carry *C. difficile* but rarely develop disease.
- ▶ **Epidemic strains:** NAP1/BI/027 produces much higher toxin A and B in vitro, carries binary toxin, is fluoroquinolone-resistant and was linked to severe outbreaks; its incidence has declined where infection control and fluoroquinolone restriction were implemented.

Pathogenesis and pathology

- ▶ CDI requires three events: **microbiota disruption** by antibiotics, **exposure to toxigenic *C. difficile***, and an additional susceptibility factor such as a virulent strain or inadequate antitoxin immune response.
- ▶ Spores are ingested, germinate in the small bowel and colonize the lower gut when normal flora are suppressed.
- ▶ Toxigenic strains produce **toxin A (enterotoxin)** and **toxin B (cytotoxin)**. Both glucosylate Rho-family GTP-binding proteins, disrupt actin cytoskeleton, impair epithelial adherence and tight junctions, and cause fluid leakage and inflammation.
- ▶ **Toxin B** is clinically crucial because toxin A-negative, toxin B-positive strains can cause disease; toxin B-negative disease is not well documented.
- ▶ **Binary toxin CDT** is present in NAP1/BI/027 and some other strains, but its exact pathogenic role is less clearly defined.
- ▶ **Pseudomembranes** begin as 1-2 mm whitish-yellow plaques on colonic mucosa, then coalesce; microscopy shows necrotic leukocytes, fibrin, mucus and cellular debris with focal epithelial necrosis and neutrophilic mucosal infiltration.
- ▶ The colon is usually involved diffusely, but rectal sparing can occur; terminal ileum is typically spared.
- ▶ Serum antibodies to toxins A and B, especially toxin B-neutralizing responses, help protect against recurrence; this is the rationale for bezlotoxumab.

Clinical features and severity

- ▶ **Typical CDI:** soft, watery or mucoid diarrhea with characteristic odor; stools are seldom grossly bloody. Lower abdominal cramps, mild tenderness and mucus may occur.
- ▶ **Frequency:** CMDT describes many patients with 3-15 watery stools/day; Harrison notes fever in about 28%, abdominal pain in 22% and leukocytosis in 50%.

- ▶ **Diagnostic trap:** ileus or adynamic colon may stop stool passage, so CDI can present as unexplained leukocytosis, abdominal distension or acute abdomen without diarrhea.
- ▶ **Severe CDI:** leukocytosis $\geq 15,000/\text{mL}$ or serum creatinine $\geq 1.5 \text{ mg/dL}$; severe disease is common among hospitalized diagnosed cases.
- ▶ **Fulminant CDI:** severe CDI plus **hypotension, shock, ileus or toxic megacolon**. It may mimic a surgical abdomen and can present with sepsis, tachycardia, marked leukocytosis, colonic wall thickening, ascites and metabolic acidosis.
- ▶ **Complications:** toxic megacolon, perforation, hemorrhage, respiratory failure, septic shock, colectomy requirement, protein-losing enteropathy in chronic untreated colitis and death.
- ▶ **Recurrence:** occurs in about 15-30% after treatment in Harrison and up to 20% within 8 weeks in CMDT; recurrence may be relapse with the same strain or reinfection with a new strain.

Clinical setting	Key markers	Exam management implication
Nonsevere CDI	Diarrhea, no severe leukocytosis/creatinine rise	Fidaxomicin preferred; oral vancomycin acceptable
Severe CDI	WBC $\geq 15,000/\text{mL}$ or creatinine $\geq 1.5 \text{ mg/dL}$	Treat promptly; monitor closely for fulminant disease
Fulminant CDI	Hypotension, shock, ileus or megacolon	High-dose enteral vancomycin + IV metronidazole, surgical review
Recurrent CDI	Return after clinical response	Fidaxomicin, vancomycin taper/pulse, microbiota therapy in repeated relapse

Diagnosis

- ▶ Diagnose only when the clinical syndrome fits: **≥ 3 unformed stools in 24 hours** with no better explanation plus evidence of toxigenic *C. difficile* or pseudomembranes. Harrison uses ≥ 3 unformed stools per 24 h for ≥ 2 days in its formal criteria.
- ▶ Send stool testing in hospitalized patients with dysentery or ≥ 3 liquid stools/24 h, and in outpatients with persistent diarrhea, especially after antibiotics or hospitalization.
- ▶ **Do not test formed stool** and do not test asymptomatic patients except for epidemiology; positive tests may reflect colonization.
- ▶ **Do not perform test of cure:** stool assays may remain positive for weeks, and more than half of patients may still harbor organism/toxin after diarrhea stops.
- ▶ **GDH immunoassay:** sensitive screen with high negative predictive value, but detects toxigenic and nontoxigenic strains and does not prove active toxin disease.
- ▶ **NAAT/PCR:** rapid and very sensitive for toxin genes, commonly TcdB, but may overdiagnose colonization if used alone.

- ▶ **Toxin EIA:** detects free toxins A/B and supports active toxin-secreting infection, but is less sensitive than NAAT/culture.
- ▶ **Preferred algorithm:** GDH or NAAT screening followed by toxin EIA when required, with discordant results interpreted clinically.
- ▶ **Endoscopy:** flexible sigmoidoscopy/colonoscopy is not routine when symptoms and stool tests are typical, but is useful in seriously ill patients, atypical cases or ileus. Pseudomembranes are highly specific but insensitive and may be seen in only a subset.
- ▶ **Imaging:** abdominal radiograph or CT is indicated in severe/fulminant disease to assess colonic dilation, wall thickening, ascites and perforation.

Treatment

- ▶ **Immediate general measures:** isolate with contact precautions, stop the inciting antibiotic if possible, correct dehydration/electrolytes and avoid opiates or antiperistaltic agents in severe disease because they may mask deterioration.
- ▶ **Initial nonsevere CDI:** fidaxomicin 200 mg orally twice daily for 10 days is preferred where available; oral vancomycin 125 mg four times daily for 10 days is an acceptable alternative.
- ▶ **Metronidazole:** no longer first-line; use 500 mg orally three times daily for 10-14 days only for mild/moderate disease when fidaxomicin or oral vancomycin is unavailable.
- ▶ **Severe initial CDI:** oral vancomycin 125 mg four times daily for 10 days or fidaxomicin 200 mg twice daily for 10 days; initiate promptly when WBC is high or creatinine is elevated.
- ▶ **Fulminant CDI:** vancomycin 500 mg orally or via nasogastric tube four times daily plus metronidazole 500 mg IV every 8 hours; if ileus is present, add rectal vancomycin 500 mg in 100 mL normal saline retention enema every 6-8 hours.
- ▶ **IV vancomycin alone is ineffective** for CDI because adequate intraluminal colonic drug levels are not achieved.
- ▶ **Early surgical consultation** is essential for severe/fulminant disease, toxic megacolon, perforation, sepsis or hemorrhage. Total abdominal colectomy may be lifesaving; loop ileostomy with colonic lavage and vancomycin infusion is an alternative. Harrison emphasizes operating before serum lactate reaches 5 mmol/L when colectomy is required.

Recurrence, adjunctive therapy and prevention

- ▶ **First recurrence:** fidaxomicin 200 mg twice daily for 10 days, oral vancomycin 125 mg four times daily for 10 days, or vancomycin taper-and-pulse depending on prior regimen and availability.
- ▶ **Vancomycin taper/pulse:** after a treatment course, 125 mg twice daily for 1 week, then daily for 1 week, then every 2-3 days for 2-8 weeks; CMDT also describes 125 mg four times daily for 14 days before tapering.

- ▶ **Multiple recurrences:** vancomycin taper/pulse, fidaxomicin standard or extended-pulsed regimen, vancomycin followed by rifaximin **400 mg twice daily for 2 weeks**, or fecal microbiota replacement.
- ▶ **Microbiota therapy:** consider after appropriate antibiotic treatment for recurrent CDI. Rebyota is rectal live-jslm fecal microbiota; Vowst is oral live-brpk fecal microbiota spores. CMDT notes 2023 FDA approval to prevent recurrence after antibacterial treatment.
- ▶ **Bezlotoxumab:** single-dose **10 mg/kg IV** monoclonal antibody against toxin B, given during standard antibacterial therapy for patients at high recurrence risk: age >65 years, immunocompromise, severe CDI or CDI in the previous 6 months. Avoid or use great caution in patients with heart failure.
- ▶ **Transmission prevention:** gloves, strict contact precautions, soap-and-water handwashing during outbreaks because alcohol gels are not sporicidal, bleach/hypochlorite environmental decontamination and avoidance of contaminated electronic rectal thermometers.
- ▶ **Antimicrobial stewardship:** restrict unnecessary clindamycin, cephalosporins and fluoroquinolones; stewardship reduces CDI and microbiome injury. Vaccines have not yet succeeded.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis flow diagram:** antibiotic exposure -> loss of normal microbiota -> ingestion of *C. difficile* spores -> germination and colonization -> toxin A/toxin B production -> epithelial cytoskeleton disruption -> diarrhea/pseudomembranes -> fulminant colitis or recurrence. Label: spores, antibiotics, microbiota disruption, toxin A, toxin B, pseudomembrane, recurrence.
- ▶ **Diagnostic-treatment algorithm:** suspected CDI with ≥ 3 unformed stools/24 h -> stool GDH/NAAT plus toxin EIA -> classify nonsevere/severe/fulminant -> fidaxomicin or oral vancomycin; fulminant branch to high-dose enteral/rectal vancomycin + IV metronidazole + surgery. Label: GDH, NAAT, toxin EIA, WBC $\geq 15,000$, creatinine ≥ 1.5 , ileus/megacolon, recurrence.

Clinical / Diagnostic significance

- ▶ Always ask about antibiotics in the previous weeks; CMDT notes symptoms may be delayed up to 8 weeks after exposure.
- ▶ CDI is a key cause of hospital-onset diarrhea after 72 hours of admission; other stool cultures are usually low yield unless *C. difficile* testing is negative or epidemiology suggests another pathogen.
- ▶ Distinguish **antibiotic-associated diarrhea** from ***C. difficile* colitis**: most antibiotic-associated diarrhea is mild, self-limited and not due to *C. difficile*.

- ▶ In ileus, absence of diarrhea does not exclude CDI; unexplained leukocytosis, abdominal distension or CT colitis after antibiotics should trigger evaluation.
- ▶ PCR-positive/toxin-negative patients may be colonized; treat the patient, not the assay, while recognizing many clinically ill discordant patients are treated.
- ▶ Pseudomembranes are highly specific but not required for diagnosis and their absence at endoscopy does not rule out CDI.
- ▶ In IBD flare, checkpoint-inhibitor colitis, ischemic colitis or hospitalized acute diarrhea, exclude *C. difficile* before immunosuppression or escalation.

High-yield exam pointers

- ▶ Write the current name: ***Clostridioides difficile***, formerly *Clostridium difficile*.
- ▶ CDI is due to **toxins A and B after antibiotic-induced microbiota disruption**; toxin B is the major validated target.
- ▶ High-risk antibiotics: **clindamycin, ampicillin, cephalosporins and fluoroquinolones**.
- ▶ Severe CDI: **WBC $\geq 15,000/\text{mL}$ or creatinine $\geq 1.5 \text{ mg/dL}$** .
- ▶ Fulminant CDI: **hypotension/shock, ileus or toxic megacolon**.
- ▶ First-line initial therapy: **fidaxomicin 200 mg bid for 10 days; oral vancomycin 125 mg qid for 10 days** is acceptable.
- ▶ Fulminant regimen: **vancomycin 500 mg enteral qid + metronidazole 500 mg IV q8h**, add rectal vancomycin if ileus.
- ▶ **Do not use IV vancomycin alone and do not perform stool test of cure**.
- ▶ Recurrence prevention/treatment: **fidaxomicin, vancomycin taper/pulse, microbiota therapy and bezlotoxumab 10 mg/kg IV** in high-risk patients.

SOURCE & COVERAGE

Harrison 22e — “*Clostridioides difficile* Infection, Including Pseudomembranous Colitis”;
CMDT 2026 — “Gastrointestinal Disorders” and “Anti-infective Treatment Antibiotic, Antifungal, & Antiviral Agents”.



Clostridioides difficile Infection (Including Pseudomembranous Colitis)

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — *Clostridioides difficile* infection (CDI) is a unique colonic disease acquired most commonly in association with antimicrobial use and the consequent disruption of the normal colonic microbiota. It is the most commonly diagnosed diarrhoeal illness acquired in the hospital, and

results from ingestion of spores of *C. difficile* that vegetate, multiply, and secrete toxins, causing diarrhoea and — in the most severe cases — **pseudomembranous colitis (PMC)**. *C. difficile* is an obligately anaerobic, gram-positive, spore-forming bacillus whose spores persist widely in the environment of hospitals and chronic-care facilities.

Etiology, Epidemiology & Risk Factors

- **Organism:** obligately anaerobic, gram-positive, spore-forming bacillus; spores survive on environmental surfaces for **months** and on the hands of hospital personnel who fail to practise good hand hygiene.
- **Acquisition:** exogenous — most often in the hospital or nursing home (or shortly after discharge), but increasingly in the outpatient/community setting. Carried in stool of both **symptomatic and asymptomatic** patients.
- **Colonisation rate** rises with length of stay: $\geq 20\%$ among adults hospitalised >2 weeks, versus 1–3% among community residents. Asymptomatic faecal carriage in healthy neonates is common but disease in infants is extremely rare (they lack mucosal toxin receptors).
- **Burden:** the most common health care–associated infection in the USA (~**462,100 cases in 2017**); total burden fell 24% between 2011 and 2017 (mainly health care–associated cases), while community-associated CDI was unchanged and now approximates the health care–associated rate.

Antibiotics implicated (key exam point):

Risk level	Agents
First/classically associated	Clindamycin, ampicillin, cephalosporins
High risk	2nd/3rd-gen cephalosporins (cefotaxime, ceftriaxone, cefuroxime, ceftazidime); fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin — most recent class implicated in outbreaks)
Lower risk	Penicillin/ β -lactamase-inhibitor combinations (ticarcillin/clavulanate, piperacillin/tazobactam)
Note	All antibiotics, including vancomycin (the drug most used to treat CDI), carry a risk of subsequent CDI

- **Other risk factors:** older age, greater severity of underlying illness, gastrointestinal surgery, use of electronic rectal thermometers, enteral tube feeding, and antacid treatment. Proton-pump inhibitor use is at most a **modest** risk and is unproven in patients not already on antibiotics.

Pathology & Pathogenesis

- ▶ **Sequence:** ingested spores survive gastric acidity → germinate in the small bowel → in the presence of a **disrupted microbiota** colonise the lower intestine → elaborate two large toxins.
- ▶ **Toxin A (enterotoxin):** a potent **neutrophil chemoattractant**. **Toxin B (cytotoxin):** evidence (isogenic mutant studies) suggests it is the **more important virulence factor** — disease occurs with toxin A–negative strains but not toxin B–negative strains.
- ▶ **Mechanism:** both toxins **glucosylate Rho-subfamily GTP-binding proteins** that regulate the actin cytoskeleton → loss of cell shape, adherence and tight junctions → fluid leakage, diarrhoea and pseudomembrane formation.
- ▶ **Binary toxin CDT** (related to *C. perfringens* iota toxin): present in only ~6% of strains generally, but in **all** NAP1/BI/027 isolates; its pathogenic role is not yet defined.
- ▶ **Three events essential for CDI:** (1) **antimicrobial exposure** establishes susceptibility by disrupting microbiota; (2) exposure to a **toxigenic *C. difficile*** strain; (3) a **third factor** — notably an inadequate host anamnestic immune (serum IgG anti–toxin A) response. Patients colonised by nontoxigenic strains without prior CDI actually have a **decreased** risk of CDI. Serum antibodies to toxins A and B protect against **recurrence**.
- ▶ **Pathology of PMC:** pseudomembranes are confined to the colonic mucosa, beginning as **1–2 mm whitish-yellow plaques** that coalesce into confluent plaques over the whole colon wall; the whole colon is usually involved, but **10% have rectal sparing**. Microscopy: mucosal attachment point with necrotic leukocytes, fibrin, mucus and cellular debris; focal epithelial erosion/necrosis with neutrophil infiltration.

Clinical Manifestations

- ▶ **Diarrhoea** is the most common feature — almost **never grossly bloody**; stools range from soft/unformed to watery or mucoid, with a characteristic odour.
- ▶ Associated findings: **fever in 28%, abdominal pain in 22%, leukocytosis in 50%**.
- ▶ **Adynamic ileus** is seen on x-ray in ~20%; when stool passage ceases the diagnosis is easily overlooked — a clue is **unexplained leukocytosis $\geq 15,000$ WBC/ μ L**, marking patients at high risk for **toxic megacolon and sepsis**.
- ▶ **Fulminant CDI** (rapidly progressive, severe) often presents **without diarrhoea**, mimicking an acute surgical abdomen, with sepsis (hypotension, fever, tachycardia, leukocytosis), ileus, colon-wall thickening and ascites on CT, and peripheral leukocytosis $\geq 20,000$ WBC/ μ L.
- ▶ **Recurrence** occurs in ~15–30% after treatment (relapse with same strain or reinfection with a new strain); a first recurrence raises the risk of a second, and recurrent disease carries a meaningful (~11%) risk of serious complications.

Diagnosis

- ▶ **Clinical criteria:** (1) diarrhoea — **≥ 3 unformed stools/24 h for ≥ 2 days** with no other cause — **plus** (2) detection of toxin A or B in stool, detection of toxigenic *C. difficile* by NAAT/PCR or

culture, or visualisation of pseudomembranes at colonoscopy. PMC is seen endoscopically in only ~50% of diarrhoeal patients with a positive stool culture and toxin assay; a negative endoscopy does not exclude CDI.

- ▶ No single test combines high sensitivity, high specificity and rapid turnaround. EIAs for toxin lack sensitivity; NAATs are rapid/sensitive but may detect **colonisation**, so guidelines favour multi-step algorithms.

Test	Sensitivity	Specificity	Comment
Stool culture	++++	+++	Most sensitive; too slow for clinical use
Cell-culture cytotoxin assay	+++	++++	Highly specific; slow turnaround
EIA for toxins A & B	++ to +++	+++	Rapid; less sensitive than culture
EIA for GDH (common antigen)	+++ to ++++	+++	Detects toxigenic + nontoxigenic strains; needs toxin confirmation
NAAT / PCR (toxin gene)	++++	+++	Widely used; very sensitive
Colonoscopy/sigmoidoscopy	+	++++	Specific if pseudomembranes seen; insensitive

(++++ >90%; +++ 71–90%; ++ 51–70%; + ~50%.) Common algorithms: NAAT followed by toxin EIA, or GDH + toxin EIA arbitrated by NAAT. **Testing of asymptomatic patients and “tests of cure” are NOT recommended** — >50% continue to harbour organism/toxin after diarrhoea resolves, and results do not predict recurrence.

Treatment

- ▶ **General:** when possible, **discontinue the offending antimicrobial**; provide hydration; **avoid antiperistaltic agents/opiates** (may mask symptoms and worsen disease). With the NAP1/BI/027 strain causing rapid deterioration, prompt specific therapy is now standard. **IV vancomycin is ineffective** (must be oral/enteral); metronidazole was **never FDA-approved** for CDI; vancomycin cure rate is superior to metronidazole (81% vs 73%; $p = 0.034$). Do not declare failure before ≥ 6 days of therapy.

Clinical setting	Treatment
Initial, mild–moderate	Fidaxomicin 200 mg bid $\times 10$ d (first-line, 2021 IDSA/SHEA) or oral vancomycin 125 mg qid $\times 10$

Clinical setting	Treatment
	d ; metronidazole 500 mg tid ×10–14 d only if neither available
Initial, severe (WBC ≥15,000/μL, creatinine ≥1.5 mg/dL)	Oral vancomycin 125 mg qid ×10 d or fidaxomicin 200 mg bid ×10 d
Initial, fulminant (severe + hypotension/shock/ileus/toxic megacolon)	Vancomycin 500 mg PO/NG + metronidazole 500 mg IV q8h + consider rectal vancomycin (500 mg in 100 mL NS retention enema q6–8h); duration may exceed 2 weeks
First recurrence	Fidaxomicin or oral vancomycin, or vancomycin taper-and-pulse
Multiple recurrences	Vancomycin taper-and-pulse; fidaxomicin (standard or extended/pulsed); vancomycin then rifaximin 400 mg bid ×2 wk ; or faecal microbiota transplant/replacement (Rebyota <i>live-jslm</i> enema; Vowst <i>live-brpk</i> oral)
High-risk for recurrence (on antibiotic Rx)	Bezlotoxumab 10 mg/kg IV (anti-toxin B mAb), adjunctive

- ▶ **Taper-and-pulse vancomycin** (after a 10-day course): 125 mg bid ×1 wk → daily ×1 wk → q2–3 days for 2–8 weeks.
- ▶ **Bezlotoxumab** reduces recurrent CDI by an absolute ~10% in patients on vancomycin/fidaxomicin/metronidazole; risk factors for recurrence = age >65, immunocompromise, severe CDI at presentation, prior CDI in the past 6 months.
- ▶ **Surgical colectomy** may be life-saving in fulminant CDI not responding to medical management.

Global Considerations (epidemic strain)

- ▶ **NAP1/BI/027** (toxintype III, REA type BI, PCR ribotype 027, PFGE NAP1) drove the marked rise in incidence/severity in the early 2000s (US rates tripled 2000–2005; Montreal attributable mortality rose to **6.9%** from 1.5%). It is characterised by (1) production of **16–23×** more toxin A and B, (2) **binary toxin CDT**, and (3) **high-level fluoroquinolone resistance**. Fluoroquinolone restriction in England nearly eliminated it by 2013.
- ▶ Other strains: **ribotype 078 / toxintype V** (food animals, binary toxin, high mortality) and **ribotype 106** (commonest US community-associated strain).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Three-event pathogenesis model of CDI** (Fig. 139-2): boxes/arrows labelled — *Antimicrobial exposure (disrupts microbiota → susceptibility) → Healthcare/environmental exposure to C. difficile spores → Acquisition of toxigenic strain → branch to Asymptomatic*

colonisation vs CDI (driven by strain virulence + inadequate host anamnestic anti-toxin antibody).

- ▶ **Cross-section of colon in PMC:** label 1–2 mm whitish-yellow pseudomembrane plaques, confluent plaques over colon wall, rectal sparing (10%), mucosal attachment point, necrotic leukocytes + fibrin + mucus + debris, eroded/necrotic epithelium with neutrophil infiltration.

Clinical / Diagnostic significance

- ▶ Suspect CDI in any patient with diarrhoea who has received antibiotics in the **preceding 2 months**; in ileus, look for **unexplained leukocytosis** as a clue.
- ▶ **Fulminant disease without diarrhoea** can masquerade as an acute abdomen — abdominal CT (wall thickening, ascites) and cautious sigmoidoscopy are the best diagnostic tools.
- ▶ Prevention rests on **antimicrobial stewardship** (especially restricting fluoroquinolones/cephalosporins), **hand hygiene**, and environmental control of spores; serum anti-toxin antibody responses explain why some colonised patients stay asymptomatic.

High-yield exam pointers

- ▶ *C. difficile* = obligate anaerobe, gram-positive, **spore-forming** bacillus; spores resist gastric acid and persist on surfaces for months.
- ▶ **Toxin A = enterotoxin (neutrophil chemoattractant); Toxin B = cytotoxin (more important virulence factor)**; both glucosylate Rho-GTPases.
- ▶ Highest-risk antibiotics: **clindamycin, cephalosporins, fluoroquinolones**; lowest: piperacillin/tazobactam/ticarcillin-clavulanate — but **all** (incl. vancomycin) can cause CDI.
- ▶ Diagnostic criteria: **≥3 unformed stools/24 h for ≥2 days** + stool toxin/NAAT or pseudomembranes; never test asymptomatic patients or do tests of cure.
- ▶ **Fidaxomicin or oral vancomycin** are first-line; **metronidazole is inferior and only a fallback**; IV vancomycin does not work.
- ▶ **Severe markers:** WBC ≥15,000/μL, creatinine ≥1.5 mg/dL. **Fulminant** = + hypotension/shock/ileus/toxic megacolon.
- ▶ Recurrence 15–30%; options include fidaxomicin, vancomycin taper-and-pulse, FMT/microbiota products (Rebyota, Vowst), and **bezlotoxumab** (anti-toxin B mAb).
- ▶ **NAP1/BI/027 epidemic strain:** ↑↑toxin production (16–23×), binary toxin CDT, fluoroquinolone resistance.

SOURCE & COVERAGE

Harrison 22e — Ch 139 “Clostridioides difficile Infection, Including Pseudomembranous Colitis” (Gerding & Johnson). **Coverage note:** the provided chapter text file ends mid-sentence within the

surgical management of fulminant CDI, so a formal stand-alone “Prevention and Control” section is not fully captured; prevention points stated here (hand hygiene, antimicrobial stewardship/fluoroquinolone restriction, environmental spore persistence) are drawn from the epidemiology/pathogenesis and global-considerations text that IS present. Standard infection-control measures (contact precautions, soap-and-water hand washing since alcohol gels do not kill spores, sporicidal disinfection) are universally accepted ID practice but are not verbatim in the supplied excerpt.



Coagulase-negative staphylococcal infections

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Coagulase-negative staphylococci (CoNS) are gram-positive cocci of the family Micrococcaceae that, unlike *Staphylococcus aureus*, do **not** produce free coagulase and hence fail to convert fibrinogen to fibrin. They are the most abundant commensals of human skin and mucosae, so they are simultaneously the commonest blood-culture **contaminants** and, in the era of implanted prostheses, important **opportunistic pathogens** of foreign-body and device-related infection. *S. epidermidis* is the prototype; *S. saprophyticus* (urinary tract) and the unusually virulent *S. lugdunensis* (endocarditis) are the other exam-relevant species. Because a few “CoNS” species are in fact coagulase-positive, the more precise contemporary term is **non-S. aureus staphylococci (NSaS)**.

Microbiology, taxonomy and laboratory speciation

- ▶ **General features:** gram-positive cocci in grapelike clusters on Gram’s stain, ~1 µm, **catalase-positive** (key distinction from streptococci), nonmotile, aerobic and facultatively anaerobic, with prolonged survival on environmental surfaces. There are **≥40 staphylococcal species**.
- ▶ **The coagulase test** divides the genus. *S. aureus* produces coagulase (a surface enzyme converting fibrinogen → fibrin); CoNS classically do not. Caveat: a few “CoNS” such as *S. pseudintermedius* and *S. argenteus* are actually coagulase-positive — hence **NSaS** is the more accurate label.
- ▶ **Colony/biochemical clues:** most NSaS form **small, white, nonhemolytic** colonies, whereas *S. aureus* forms golden β-hemolytic colonies, ferments mannitol, is protein A-positive and DNase-positive. *S. saprophyticus* is distinctively **novobiocin-resistant**.
- ▶ **Identification tools:** latex agglutination kits (protein A + clumping factor) separate *S. aureus* from most NSaS; **MALDI-TOF mass spectrometry** is increasingly used for rapid speciation. For outbreak/strain typing, pulsed-field gel electrophoresis and *spa* typing have been used, with **whole-genome sequencing** now the gold standard.

Feature	<i>S. aureus</i>	Coagulase-negative staphylococci
Coagulase	Positive	Negative (most species)
Colony on blood agar	Golden, β -hemolytic	Small, white, non-hemolytic
Mannitol / DNase / Protein A	Positive	Usually negative
Virulence	High (toxins, abscesses)	Low (biofilm-dependent), except <i>S. lugdunensis</i>
Typical disease	SSTI, endocarditis, bacteraemia, toxin disease	Prosthetic/device-related infection

Important species and their clinical niches

- ▶ *S. epidermidis* — the **most common human NSaS pathogen**; the most abundant bacterial species of normal skin, also colonising oropharynx and vagina. It is the dominant cause of **prosthetic-device infections** by virtue of biofilm formation.
- ▶ *S. saprophyticus* — novobiocin-resistant; a common cause of **urinary tract infection in young, sexually active women**, mediated by adhesins (a ~160-kDa haemagglutinin/adhesin) that bind uroepithelial cells.
- ▶ *S. lugdunensis* and *S. schleiferi* — disproportionately **virulent NSaS** that cause **native-valve endocarditis** and **osteomyelitis**; they share virulence determinants with *S. aureus* (e.g. clumping factor and lipase). *S. lugdunensis* may produce aggressive endocarditis with **bulky vegetations and rapid valve destruction with abscess**, mimicking *S. aureus* — frequently missed when dismissed as a “contaminant”.
- ▶ *S. haemolyticus* and *S. hominis* — other species commonly recovered from device-associated bloodstream infection.

Pathogenesis — biofilm on foreign surfaces

- ▶ NSaS infection of a prosthesis is a **two-step process**: initial **adhesion** to the device, then **colonisation** with biofilm accumulation.
- ▶ Implanted material is rapidly coated by host matrix proteins (**fibrinogen, fibronectin**), which act as **bridging ligands**. Staphylococcal surface proteins — **autolysin (AtlE)**, fibrinogen-binding protein and **accumulation-associated protein (AAP)** — mediate attachment to modified or bare surfaces.
- ▶ *S. epidermidis* then elaborates an extracellular polysaccharide (**glycocalyx** / “slime”); the **polysaccharide intercellular adhesin (PIA)**, encoded by the ***ica*** (**intercellular adhesion**) locus, drives aggregation, accumulation and maturation of a protective **biofilm**. The *ica* genes are over-represented in device-infecting strains relative to colonising strains.

- ▶ Biofilm forms a **physical barrier** shielding bacteria from host defences and antibiotics and serves as a **nidus for persistent and recurrent infection** — the reason device removal is usually required for cure.

Clinical syndromes

- ▶ **Prosthetic / foreign-body infections (the hallmark)** — prosthetic cardiac valves, prosthetic joints, vascular grafts, intravascular and peritoneal-dialysis catheters, CNS (CSF) shunts, cardiac implantable electronic devices (pacemakers/ICDs), sternal wires and intracranial-pressure monitors. The picture is characteristically **indolent**: subtle local signs (mild erythema, pain, low-grade drainage, prosthesis loosening), slow progression and limited systemic upset; fever is variable, leukocytosis mild, with raised ESR/CRP.
- ▶ **Prosthetic-valve endocarditis (PVE)** — **early PVE (within ~2 months of surgery)** is commonly caused by staphylococci (coagulase-negative and -positive), gram-negatives and fungi, with CoNS a leading agent; in **late PVE**, streptococci predominate but CoNS still cause many cases.
- ▶ **Cardiac-device (CIED) infection / endocarditis** — *S. aureus* and CoNS cause the majority; roughly one-third present within 3 months, one-third at 3–12 months, and one-third after 1 year.
- ▶ **Native-valve endocarditis** — NSaS account for ~5% of cases; suspect *S. lugdunensis* when an aggressive course occurs.
- ▶ **Bloodstream infection** — important in **preterm neonates and neutropenic patients**, usually catheter-associated.
- ▶ **Urinary tract infection** — *S. saprophyticus* in young women; **wound infection** after cardiothoracic surgery; *S. epidermidis* may rarely cause osteomyelitis in the absence of a prosthesis.

Diagnosis — distinguishing true infection from contamination

- ▶ NSaS are easily grown by routine culture, but **interpretation is the challenge** because they are abundant skin commensals.
- ▶ Only **10–20% of NSaS-positive blood cultures reflect true bacteraemia** (Harrison); conversely, contamination may account for **about three-quarters** of CoNS blood-culture isolates (CMDT).
- ▶ **Features favouring true infection**: presence of a **foreign body/intravascular device**; local signs (purulent or serosanguineous drainage, erythema, tenderness at the device site); fever, new murmur, prosthesis instability or systemic embolisation (for PVE); leukocytosis and signs of sepsis.
- ▶ **Microbiological criteria favouring true bacteraemia**: isolation of the **same strain** (same species with the same antibiogram or DNA fingerprint) from **two or more separately drawn cultures** and from the device site; bacterial growth **within 48 h**; and growth in **both aerobic and anaerobic bottles**.

Treatment

- ▶ **Source control is paramount** — wherever feasible, **remove the infected intravascular catheter or foreign body**; biofilm-encased organisms are rarely cured by antibiotics alone. When removal is hazardous (prosthetic joint or valve, CSF shunt), antibiotics $\pm$ long-term suppression may be tried, accepting a lower cure rate and the likely eventual need for surgery.
- ▶ **Resistance**: NSaS are far more often methicillin-resistant than *S. aureus* — **>80% of nosocomial NSaS isolates are methicillin-resistant**, frequently with co-resistance to multiple drug classes.
- ▶ **Empirical drug of choice**: **vancomycin** (15–20 mg/kg IV q8–12 h; CMDT: 1 g IV q12 h, trough 15–20 $\mu\text{g/mL}$) until susceptibility is known. If proven **methicillin-susceptible**, a penicillinase-resistant penicillin (**nafcillin/oxacillin**) or **cefazolin** is preferred.
- ▶ **Duration**: documented infection (same strain ≥ 24 h apart) **without** endocarditis or other foci $\rightarrow$ **7–14 days**; infection of **bone or a prosthetic valve** $\rightarrow$ **6 weeks**.
- ▶ **Prosthetic-valve endocarditis (methicillin-resistant NSaS)** $\rightarrow$ combination of **vancomycin + rifampin** (300 mg PO/IV every 8 h) + **gentamicin** (1 mg/kg IV every 8 h for 2 weeks), usually with surgical valve replacement. **Rifampin** is specifically valuable in prosthetic-device infection and osteomyelitis (biofilm/intracellular penetration); **rifampin + a fluoroquinolone** (e.g. **ciprofloxacin**) can suppress retained prosthetic-joint infection.
- ▶ **Alternative anti-MRSA agents** with NSaS activity include **daptomycin**, **linezolid/tedizolid**, **ceftaroline**, **telavancin** and **TMP-SMX** (chosen per susceptibilities; **daptomycin** is not used for pneumonia).

Setting	Preferred regimen	Duration
Empirical / methicillin-resistant	Vancomycin IV (target trough 15–20 $\mu\text{g/mL}$)	Per focus
Confirmed methicillin-susceptible	Nafcillin / oxacillin or cefazolin	Per focus
Catheter bacteraemia (device removed)	Vancomycin after removal	7–14 days
Bone / prosthetic valve	Vancomycin ($\pm$ combination)	6 weeks
MR prosthetic-valve endocarditis	Vancomycin + rifampin + gentamicin + surgery	≥ 6 weeks (gentamicin 2 weeks)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Biofilm formation on a catheter/prosthesis (sequential schematic)**. Labels:
Prosthetic/catheter surface $\rightarrow$ *host conditioning film (fibrinogen, fibronectin)* $\rightarrow$ *primary adhesion (AtfE autolysin, fibrinogen-binding protein, AAP)* $\rightarrow$ *accumulation (polysaccharide*

Setting	Preferred regimen	Duration
<i>intercellular adhesin / PIA, ica locus</i>) → mature biofilm (glycocalyx “slime”) → barrier to antibiotics and host immune cells → embolisation / persistent bacteraemia. ▶ Diagnostic algorithm box: “Contaminant vs true CoNS bacteraemia”. Labels: <i>Single positive bottle, no device</i> → likely contaminant; <i>Same strain from ≥2 separate cultures + device site, growth <48 h, both aerobic & anaerobic bottles, sepsis signs</i> → true infection → remove device + vancomycin.		

Clinical / Diagnostic significance

- ▶ A CoNS-positive blood culture should never be dismissed reflexively as a contaminant in a patient with a **prosthetic valve, joint, vascular graft, CIED, CSF shunt or central line** — repeat cultures and clinical correlation are essential.
- ▶ *S. lugdunensis* is a “red-flag” CoNS: treat any *lugdunensis* bacteraemia as potentially **aggressive endocarditis** and obtain echocardiography.
- ▶ Persistent CoNS bacteraemia despite an indwelling line mandates **line removal**; failure to do so is a common cause of relapse because of biofilm.
- ▶ High methicillin-resistance rates make **vancomycin the rational empirical choice**, with de-escalation to a β -lactam if methicillin-susceptible.
- ▶ Prevention rests on **aseptic catheter insertion, hand hygiene and insertion/maintenance “bundles”**, which markedly reduce device-related staphylococcal infection.

High-yield exam pointers

- ▶ CoNS = catalase-positive, **coagulase-negative**, gram-positive cocci in clusters; most abundant normal skin flora.
- ▶ ***S. epidermidis** = *commonest pathogen* → *prosthetic-device infection via biofilm*; *ica locus* → *PIA / slime**.
- ▶ ***S. saprophyticus** = *novobiocin-resistant* → *UTI in young sexually active women**.
- ▶ ***S. lugdunensis** (and *S. schleiferi*) = *virulent* → *native-valve endocarditis/osteomyelitis; bulky vegetations like S. aureus**.
- ▶ Only **10–20%** of NSaS-positive blood cultures are true bacteraemia; **~75%** are contaminants — confirm with **same strain from ≥2 cultures + device site**.
- ▶ **>80%** of nosocomial NSaS are **methicillin-resistant** → empirical **vancomycin**.
- ▶ **Source control / device removal** is essential; rifampin aids biofilm/prosthetic-device infection.
- ▶ Durations: catheter bacteraemia 7–14 days; **bone/prosthetic valve 6 weeks**; PVE = vancomycin + rifampin + gentamicin + surgery.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Staphylococcal Infections” (non-*S. aureus* staphylococci: microbiology/taxonomy, biofilm pathogenesis, diagnosis, clinical syndromes, antimicrobial therapy) and “Infective Endocarditis” (CoNS in prosthetic-valve and cardiac-device endocarditis).
- ▶ **CMDT 2026** — “Bacterial & Chlamydial Infections” (Infections Caused by Coagulase-Negative Staphylococci; *S. lugdunensis*; vancomycin dosing and prosthetic-valve endocarditis regimen) and “Common Problems in Infectious Diseases” (prosthetic-valve endocarditis microbiology by time of onset).



Complications and management of Enteric fever (Typhoid)

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Enteric (typhoid) fever is a systemic febrile illness caused by dissemination of the human-restricted serotypes *Salmonella* Typhi and *S. Paratyphi* (A, B, C), characterised by prolonged fever and abdominal pain. After ingestion the organisms cross the gut via Peyer's-patch M cells, are taken up by macrophages and disseminate through the reticuloendothelial system. The mean incubation period is **10–14 days** (range 5–21). Untreated, fever (38.8°–40.5°C) may persist up to 4 weeks; the **overall case-fatality rate is ~2.5%** (4.5% in hospitalised, 10–30% if untreated), falling to <1% with prompt appropriate antibiotics. Complications cluster in the third and fourth weeks of illness.

Determinants and timeline of complications

- ▶ Complications occur in **~27% of hospitalised patients**.
- ▶ Risk correlates with: **longer duration of symptoms before hospitalisation**, host factors (host genetics, immunosuppression, acid-suppression therapy, prior exposure, vaccination status), **strain virulence and inoculum**, and **choice of antibiotic therapy**.
- ▶ The dangerous intestinal complications characteristically appear in the **3rd–4th weeks**, arising from hyperplasia, ulceration and necrosis of the **ileocecal Peyer's patches** at the site of initial *Salmonella* infiltration.

Complications of enteric fever

Category	Complication (frequency where stated)	Key points
Intestinal (most lethal)	GI haemorrhage (~6%); intestinal perforation (~1%)	3rd–4th week; from ulceration/necrosis of ileocecal Peyer's patches (terminal ileum); both life-threatening

Category	Complication (frequency where stated)	Key points
Neurologic (2–40%)	Meningitis, Guillain-Barré syndrome, neuritis, neuropsychiatric states	“Muttering delirium” or “coma vigil”; <i>picking at bedclothes / imaginary objects</i> (carphology)
Haematologic	Disseminated intravascular coagulation; haemophagocytic syndrome	Incidence reduced by prompt antibiotics
Hepatobiliary / abdominal	Hepatitis, pancreatitis, hepatic and splenic abscesses & granulomas , cholecystitis	Cholecystitis underlies chronic carriage
Cardiac	Endocarditis, pericarditis, myocarditis	Uncommon
Genitourinary / renal	Orchitis, glomerulonephritis, pyelonephritis, haemolytic-uraemic syndrome	—
Other focal	Severe pneumonia, arthritis, osteomyelitis, endophthalmitis, parotitis	—
Relapse	Up to 10% of patients	Usually 2–3 weeks after fever resolution; same strain & susceptibility profile
Chronic carriage	2–5% shed >1 year; up to 10% excrete in faeces up to 3 months	More common in women, infants , biliary abnormalities, or bladder co-infection with <i>Schistosoma haematobium</i>

- ▶ *S. Typhi* persists in the gallbladder by forming **biofilms on gallstones** and invading gallbladder epithelium; chronic carriage carries an **increased risk of gallbladder carcinoma**, especially on the Indian subcontinent.
- ▶ Intestinal perforation and haemorrhage **require immediate fluid resuscitation and surgical intervention**, with **broadened antibiotic cover for polymicrobial peritonitis** and treatment of haemorrhage, including **bowel resection**.

Principles of antimicrobial management

- ▶ Initial choice depends on the **susceptibility pattern of S. Typhi/Paratyphi in the area of residence or travel**.
- ▶ A 2022 systematic review (27 RCTs) found **no difference between ceftriaxone, a fluoroquinolone, or azithromycin** in treatment failure, microbiologic failure, relapse, convalescent carriage or adverse events.

- ▶ Because of the high prevalence of strains with **decreased susceptibility to ciprofloxacin** (DSC; MIC >0.125 µg/mL) on the Indian subcontinent and parts of Africa, **fluoroquinolones should no longer be used for empirical therapy** in these regions.
- ▶ **Travel to Pakistan / concern for ceftriaxone-resistant (XDR) S. Typhi → treat empirically with a carbapenem or azithromycin.**
- ▶ **Azithromycin** is recommended for **uncomplicated** enteric fever including ESBL, DSC and **fluoroquinolone-resistant** strains (defervescence 4–6 days; relapse & stool carriage <3%); against DSC strains it gives lower failure and shorter hospitalisation than fluoroquinolones.
- ▶ Third-generation cephalosporins (ceftriaxone, cefotaxime, oral cefixime) clear fever in ~1 week (failure ~5–10%, relapse 3–6%). Fluoroquinolones against **susceptible** strains give cure rates ~98%.
- ▶ **Carbapenems** are increasingly used for complicated XDR infection (cost and IV route are barriers).
- ▶ Duration: at least **10 days**, or 5 days after fever resolution.

Antibiotic regimens (Harrison Table 171-1, adults)

Indication	Agent	Dosage (route)	Duration (days)
Empirical	Ceftriaxone*	2 g/d (IV)	10–14
	Ciprofloxacin	500 mg bid (PO) / 400 mg q12h (IV)	5–7
	Azithromycin	1 g/d (PO)	5
Fully susceptible (optimal)	Ceftriaxone / Ciprofloxacin / Azithromycin	as above	10–14 / 5–7 / 5
Fully susceptible (alternative)	Amoxicillin	1 g tid (PO) or 2 g q6h (IV)	14
	Chloramphenicol	25 mg/kg tid (PO/IV)	14–21
	TMP-SMX	160/800 mg bid (PO)	7–14
MDR (per susceptibility)	Ceftriaxone / Ciprofloxacin / Azithromycin	as above	10–14 / 5–7 / 5
Ceftriaxone-resistant (optimal)	Meropenem†	1 g q8h (IV)	10–14
	Azithromycin	1 g/d (PO)	5
Eradication of carriage	Ciprofloxacin	500–750 mg bid (PO)	28

Indication	Agent	Dosage (route)	Duration (days)
	Azithromycin (alt.)	500 mg (PO)	28

*Or another 3rd-gen cephalosporin (cefotaxime 2 g q8h IV; cefixime 400 mg bid PO). †Or imipenem 500 mg q6h IV.

Management of severe disease, supportive care and carriage

- ▶ **Site of care:** most uncomplicated cases are managed at **home** with oral antibiotics and antipyretics. Hospitalise patients with **persistent vomiting, diarrhoea and/or abdominal distension** for supportive therapy plus a **parenteral 3rd-gen cephalosporin, fluoroquinolone or carbapenem** per susceptibility.
- ▶ **Severe enteric fever (shock, obtundation/delirium):** add high-dose **dexamethasone** — initial 3 mg/kg, then 1 mg/kg every 6 h for eight doses — which (with chloramphenicol in the original Indonesian trial) lowered mortality dramatically (10% vs 55%). Severe enteric fever remains **one of the few indications for glucocorticoids in acute bacterial infection; steroids beyond 48 h may increase relapse.**
- ▶ **Intestinal perforation/haemorrhage:** aggressive fluid resuscitation, broadened cover for **polymicrobial peritonitis**, and **surgical intervention / bowel resection.**
- ▶ **Chronic carriage eradication:** fluoroquinolone-susceptible → oral **ciprofloxacin** for 4 weeks (eradication ~80%); fluoroquinolone-resistant → **azithromycin** 4 weeks (limited data) or **amoxicillin** if ampicillin-susceptible (lower eradication). With **anatomic abnormality (biliary/renal/bladder stones)**, eradication often needs **antibiotics plus surgical correction** (e.g., cholecystectomy).
- ▶ **Public health:** enteric fever is a **notifiable disease**; monitor and treat carriers (especially food handlers and child-care providers) to prevent onward transmission.

Prevention (vaccines)

- ▶ **Ty21a** — oral live-attenuated (days 1, 3, 5, 7; re-vaccinate every 5 years); minimum age **6 years**; efficacy ~50% at 2.5–3 years.
- ▶ **Vi CPS** — parenteral purified Vi capsular polysaccharide (single dose; booster every 2 years); minimum age **2 years**; efficacy ~55% at 3 years.
- ▶ **Typhoid conjugate vaccines (TCV)** — *Typhar TCV* (Bharat Biotech, 2018) and *TYPHIBEV* (Biological E, 2020); single IM 0.5 mL dose, **79–95% effective**, antibody persistence up to **7 years**, and effective in **children <2 years** — WHO-prioritised for high-incidence countries.
- ▶ No licensed vaccine exists for **paratyphoid fever**; vaccination is an **adjunct**, not a substitute for safe food/water.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled diagram of terminal-ileum Peyer's-patch pathology / typhoid perforation:** label *terminal ileum, ileocecal junction, hyperplastic Peyer's patch, longitudinal ulcer along antimesenteric border, necrosis/perforation site, mesenteric lymph nodes.*
- ▶ **Week-wise timeline of complications:** Week 1 *bacteraemia, stepladder fever, relative bradycardia*; Week 2 *rose spots, hepatosplenomegaly*; **Weeks 3–4** *intestinal haemorrhage, perforation, neuropsychiatric state*; Convalescence *relapse (~10%), chronic carriage (2–5%).*

Clinical / Diagnostic significance

- ▶ **Definitive diagnosis** is by **culture**: blood culture sensitivity only **40–60%**; **bone-marrow culture** ~80% sensitive and **not reduced by up to 5 days of prior antibiotics**; combined blood + bone-marrow + intestinal-secretion (duodenal string) culture gives **>90% yield**.
- ▶ **Rapid serologic tests Tubex and Typhidot** (IgM/IgG to O and H antigens) have sensitivity ~70–80% and specificity ~80–90% — useful at point-of-care but **cannot replace blood culture**.
- ▶ Suspect typhoid in any **febrile returning traveller** from South Asia/Africa; differentials include malaria, dengue, viral hepatitis, leptospirosis, rickettsial infection, amoebic liver abscess and acute HIV.
- ▶ Watch for **leukopenia/neutropenia (15–25%)**; **leukocytosis suggests perforation or secondary infection**.
- ▶ A history of travel to **Pakistan** should raise concern for **XDR H58 S. Typhi** and drive empirical carbapenem/azithromycin use.

High-yield exam pointers

- ▶ Complications in ~27% of hospitalised cases; **haemorrhage (6%)** and **perforation (1%)** in weeks 3–4 from ileocecal Peyer's-patch ulceration.
- ▶ **Perforation = surgical emergency**: resuscitate, broad cover for peritonitis, **operate / resect bowel**.
- ▶ Neuropsychiatric typhoid → “**muttering delirium**” / “**coma vigil**”; neurologic involvement 2–40% (incl. GBS, meningitis).
- ▶ **Relapse up to 10%** at 2–3 weeks; **chronic carriage 2–5% (>1 yr)** — linked to **gallstones, biofilms, gallbladder cancer**, commoner in women.
- ▶ **Empirical drug today**: ceftriaxone 2 g/d IV or azithromycin 1 g/d PO; **avoid fluoroquinolones empirically** on the Indian subcontinent (DSC, MIC >0.125 µg/mL).
- ▶ **XDR/ceftriaxone-resistant (Pakistan)** → meropenem 1 g q8h IV (or imipenem) ± azithromycin.
- ▶ **Severe disease** → dexamethasone 3 mg/kg then 1 mg/kg q6h ×8 (mortality 10% vs 55%); a rare steroid indication; stop by 48 h.

- ▶ **Carrier eradication:** ciprofloxacin 500–750 mg bid ×28 days (~80%); cholecystectomy if gallstones.
- ▶ **Prevention:** Ty21a (oral), Vi-CPS (parenteral), and TCV (Typbar/TYPHIBEV) effective in under-2s; none for paratyphoid.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 171 "Salmonellosis" (Pegues & Miller), including Table 171-1 (Antibiotic Therapy for Enteric Fever in Adults). *Coverage note:* The classic eponyms **Faget sign** (relative bradycardia — described in text as "relative bradycardia at the peak of high fever") and the **Widal test** are standard internal-medicine items but are not named as such in the provided chapter, which instead emphasises Tubex/Typhidot and culture-based diagnosis; they are flagged here as universally accepted additions rather than verbatim source content.



COVID-19 (2019 Novel Corona Virus)

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — COVID-19 (Coronavirus Disease 2019) is the acute respiratory and multisystem illness caused by **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)**, an enveloped, positive-sense RNA *Betacoronavirus* that emerged in **Wuhan, China in 2019**. It produced the largest pandemic of the modern era — the WHO declared a **Public Health Emergency of International Concern on 30 January 2020**, a **pandemic on 11 March 2020**, and an **end to the global emergency on 5 May 2023**, by which time the virus had caused **>700 million cases and >7 million deaths**. The disease ranges from asymptomatic infection through mild illness to fulminant pneumonia, ARDS and multiorgan failure, and is now in an **endemic phase** managed with antivirals, immunomodulators and annually updated vaccines.

Aetiology, virology and pathogenesis

- ▶ **Family/genus:** *Betacoronavirus*; SARS-CoV-2 belongs to the same genus as the highly pathogenic SARS-CoV-1 (2002–03 epidemic) and MERS-CoV (2012, 2015, 2018) and the common-cold coronaviruses HCoV-OC43 and HCoV-HKU1. All coronaviruses are thought to have originated in bats.
- ▶ **Genome/structure:** a single linear positive-sense RNA of ~30,000 nucleotides encoding **four structural proteins** — S (spike), E (envelope), M (membrane), N (nucleocapsid) — plus a large polyprotein cleaved into **16 non-structural proteins**.
- ▶ **Cell entry:** the trimeric S protein (a type-1 fusion machine) uses its **receptor-binding domain (RBD)** to bind the host **angiotensin-converting enzyme 2 (ACE2)** receptor; the host protease TMPRSS2 primes S to facilitate membrane fusion and entry.

- ▶ **Variant evolution:** error-prone RNA-dependent RNA polymerase (RdRp) generates frequent variants; WHO tracks **variants under monitoring (VUM)**, **variants of interest (VOI)** and **variants of concern (VOC)**. Sequential VOCs (Alpha → Delta → **Omicron** and its sublineages BA.4/BA.5, XBB, JN.1, KP.2/"FLiRT") altered transmissibility, severity, antigenicity and drug/vaccine efficacy. Most spike mutations reduce neutralisation, rendering all earlier monoclonal antibodies ineffective.

Epidemiology and transmission

- ▶ **Spread:** primarily by **respiratory droplets** in close proximity; **airborne/aerosol** transmission can occur (heavy exercise, singing, aerosol-generating procedures) but long-range airborne spread is unlikely; **fomite** transmission occurs.
- ▶ **Reproduction number (R0):** estimated to **peak around 6** (Harrison) — far higher than seasonal influenza (1–2); CMDT places the true R0 nearer 2–3, varying by variant.
- ▶ **Pre-symptomatic and super-spreading:** much spread is **pre-symptomatic** (viral load peaked the day before symptoms before population immunity; around day 4 thereafter); "**super-spreaders**"/**super-carriers** drive disproportionate transmission, especially in dense settings (prisons, cruise ships, nursing homes, bars, workplaces).
- ▶ **Incubation:** typically 4–5 days, nearly always within 14 days (range up to ~14–24 days).
- ▶ **Risk factors for severe disease:** **advanced age is the principal risk factor** (>95% of deaths in those >45 y, >80% in those >65 y); **male sex** (OR ~1.8); rising **BMI** (overweight/obesity/severe obesity); pregnancy; smoking/substance use; and comorbidities — chronic lung disease, **diabetes**, **hypertension**, **cardiovascular** and **chronic kidney/liver disease**, **cancer**, **immunosuppression** (including transplant, rituximab/B-cell depletion), Down syndrome.

Clinical features and severity classification

- ▶ **Spectrum:** ~one-third of those infected are **asymptomatic** (but can transmit); most symptomatic patients have **mild disease (no pneumonia)**.
- ▶ **Symptoms:** cough, fever, chills, myalgia, headache, sore throat, dyspnoea; sudden **anosmia/dysgeusia** (loss of smell/taste, often neurotropic without congestion); GI symptoms (nausea, vomiting, diarrhoea); diverse dermatological lesions (acral "COVID toes", maculopapular, vesicular, urticarial).
- ▶ **Severity grading** (NIH/clinical framework reflected in Harrison & CMDT):

Category	Defining features
Asymptomatic	Positive test, no symptoms
Mild	Symptomatic, no pneumonia / no hypoxia
Moderate	Clinical/radiographic pneumonia, SpO2 >94% on room air

Category	Defining features
Severe	SpO ₂ ≤94%, RR >30/min, PaO ₂ /FiO ₂ <300 mmHg, or infiltrates >50% of lung fields
Critical	Respiratory failure needing mechanical ventilation, ARDS, shock, multiorgan failure

Investigations

- ▶ **Molecular tests (NAAT):** RT-PCR on nasopharyngeal swab (or saliva) is the **most sensitive and specific** confirmatory test; detects RNA — prolonged RNA shedding is common in the immunocompromised, so re-testing within **90 days** of prior infection is discouraged.
- ▶ **Rapid antigen tests:** fast, inexpensive, home-usable; **less sensitive than NAAT** (especially in asymptomatic persons; ~85% vs culture in symptomatic CDC data) — useful for triage of infectiousness.
- ▶ **Serology:** detects immune status, **not used for acute diagnosis** (cannot reliably separate vaccination from infection).
- ▶ **Supportive labs of severity:** lymphopenia, thrombocytopenia, neutrophilia and raised neutrophil-to-lymphocyte ratio; elevated IL-6, TNF- α , ferritin, CRP, procalcitonin, LDH; raised liver enzymes; **elevated D-dimer/prolonged PT, raised vWF**; elevated troponin and CPK.
- ▶ **Imaging:** chest radiograph and CT may be **normal early**; later show **bilateral peripheral ground-glass opacities** $\pm$ consolidation, interlobular septal thickening and air bronchograms (organising-pneumonia pattern). CT is for management, **not primary diagnosis**.

Complications

- ▶ **Pulmonary:** ARDS (commonest serious complication; ~19-fold higher progression than influenza), respiratory failure needing ventilation/ECMO; secondary bacterial/fungal infection (invasive pulmonary aspergillosis, mucormycosis).
- ▶ **Haematological/thrombotic:** hypercoagulable state, **venous thromboembolism** (PE, DVT), arterial thrombosis (stroke, limb ischaemia), DIC.
- ▶ **Cardiac:** myocardial injury, **fulminant myocarditis**, arrhythmias, heart failure, ACS, stress cardiomyopathy, shock.
- ▶ **Renal:** **acute kidney injury** (often needing dialysis).
- ▶ **Neurological/psychiatric:** encephalopathy, ICU delirium (reduces survival), seizures, stroke, **Guillain-Barré syndrome**, acute haemorrhagic necrotising encephalopathy; anxiety, depression, PTSD.
- ▶ **Hyperinflammation (“cytokine storm”):** persistent fever, multiorgan disease, raised inflammatory markers (notably IL-6) — high fatality.

- ▶ **MIS-C / MIS-A: multisystem inflammatory syndrome in children** (Kawasaki-like; GI, cardiac, mucocutaneous, haematological involvement; highest in Black/Latino children 3–12 y) and the rarer adult form **MIS-A**, weeks after mild/asymptomatic infection.
- ▶ **Long COVID:** symptoms persisting **≥3 months** — fatigue (~32%), smell/taste disorder (~22%), dyspnoea (~16%), headache, “brain fog”/memory impairment, hair loss, sleep disturbance; vaccination substantially reduces its incidence.

Management

- ▶ **Principle (biphasic disease):** antivirals work best early (reduce peak viral load) while anti-inflammatory/immunomodulators help later when tissue inflammation dominates.
- ▶ **Outpatient / mild–moderate, high-risk (start ≤5 days of symptoms):**
 - **Nirmatrelvir/ritonavir (Paxlovid):** drug of choice — 300 mg/100 mg orally 12-hourly for 5 days; ~85% relative risk reduction in hospitalisation/death. Reduce nirmatrelvir to 150 mg if GFR 30–60, contraindicated if GFR <30; ritonavir is a potent CYP3A4 inhibitor — screen for drug interactions (avoid with strong inducers e.g. rifampin, phenytoin); ~6.6% “rebound” symptoms after stopping.
 - **Remdesivir IV:** 3-day outpatient course (≥60 y or comorbid, within 7 days) — ~87% reduction in death/hospitalisation pre-vaccine era.
 - **Molnupiravir** 800 mg 12-hourly ×5 days — when other agents unsuitable; **mutagenic** — contraindicated in pregnancy and <18 y, contraception advised.
- ▶ **Inpatient / severe (admit if SpO₂ <94%, RR >30, PaO₂/FiO₂ <300, or infiltrates >50%):**
 - **Supportive O₂**, control fever with **acetaminophen** (limit NSAIDs); continue **aspirin, statins, ACEi/ARB**.
 - **Remdesivir** 200 mg day 1 then **100 mg daily** (5 days, non-inferior to 10) for patients on supplemental oxygen.
 - **Dexamethasone** (low-dose) for those needing supplemental oxygen/ventilation/ECMO — standard **10-day** course; **not** indicated without hypoxia (RECOVERY trial basis). Alternatives: prednisone, methylprednisolone, hydrocortisone.
 - **Anticoagulation:** **therapeutic-dose heparin** for hospitalised patients on supplemental O₂ (not HFNC/ventilation) with raised D-dimer and no bleeding risk; **prophylactic-dose** for others including critically ill. Outpatients generally need no anticoagulation.
 - **Immunomodulators for escalating O₂/inflammation:** **IL-6 receptor inhibitors** tocilizumab (or sarilumab) and **JAK inhibitors** baricitinib (or tofacitinib) — do **not** combine IL-6 inhibitor with a JAK inhibitor; JAK inhibitors require at least prophylactic anticoagulation. Abatacept/infliximab are alternatives.

- ▶ **Antibody-based therapy/prevention:** convalescent plasma and **monoclonal antibodies** have largely lost efficacy to new variants; long-acting antibodies **tixagevimab/cilgavimab** (Evusheld) and **pemivibart** were authorised for pre-exposure prophylaxis in the immunocompromised.
- ▶ **Bacterial co-infection is uncommon** (~8%) — routine antibiotics are **not** recommended.

Prevention

- ▶ **Non-pharmaceutical interventions (NPIs):** physical distancing (~6 ft), isolation of cases, quarantine, ventilation/HEPA, hand hygiene, and **masks** (well-fitted N95/FFP2 most protective; greatest value for vulnerable groups).
- ▶ **Vaccines** (stimulate neutralising anti-spike antibody):
 - **mRNA** (Pfizer-BioNTech, Moderna) — ~95% **efficacy** against symptomatic disease in phase-3 trials; waning immunity prompts periodic variant-matched updates.
 - **Protein subunit** (Novavax, with **Matrix-M** adjuvant).
 - **Viral-vector** (Janssen) — **withdrawn** due to **thrombosis with thrombocytopenia syndrome (TTS)**.
 - Goal is prevention of **severe disease/death**; vaccination also lowers **long-COVID** risk. mRNA vaccines are safe in **pregnancy/lactation**; rare **myocarditis/pericarditis** (~6.3/million doses, young males, after 2nd dose).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **SARS-CoV-2 virion (labelled):** spherical enveloped particle with labels — **Spike (S)** glycoprotein with receptor-binding domain (RBD), **Envelope (E)** protein, **Membrane (M)** protein, **Nucleocapsid (N)** protein wrapping the **+ssRNA genome** (~30 kb); alongside, host cell showing **ACE2 receptor** and **TMPRSS2** priming S for entry.
- ▶ **Natural history / two-phase timeline:** x-axis time from exposure; curves for **viral load** (early, peak ~day 4–5) and **host inflammatory response** (late); phases marked **incubation** (4–5 d) → **viral phase** (antivirals: nirmatrelvir, remdesivir) → **inflammatory phase** (dexamethasone, tocilizumab, baricitinib) → **recovery / Long COVID**.

Clinical / Diagnostic significance

- ▶ **Confirm with RT-PCR** (gold standard); use **rapid antigen** for fast triage; severity is defined by oxygenation ($\text{SpO}_2 \leq 94\%$, $\text{PaO}_2/\text{FiO}_2 < 300$) and radiographic extent.
- ▶ **Risk-stratify** by age, comorbidity and immune status to select candidates for **early antivirals** — the single highest-yield management decision.
- ▶ **Recognise the biphasic course:** antivirals early, **steroids only once hypoxic**; never give dexamethasone to non-hypoxic mild disease.

- ▶ Anticipate thromboembolism — thromboprophylaxis for all hospitalised patients; monitor D-dimer.
- ▶ MIS-C/MIS-A and Long COVID are important post-infectious sequelae requiring multidisciplinary follow-up.

High-yield exam pointers

- ▶ SARS-CoV-2 = Betacoronavirus, +ssRNA ~30 kb, S/E/M/N structural proteins; entry via ACE2 + TMPRSS2.
- ▶ WHO milestones: PHEIC 30 Jan 2020, pandemic 11 Mar 2020, emergency ended 5 May 2023.
- ▶ R0 ~6 (Harrison) / 2–3 (CMDT); incubation 4–5 days; ~1/3 asymptomatic.
- ▶ Severe disease cut-offs: SpO2 ≤94%, RR >30, PaO2/FiO2 <300, infiltrates >50%.
- ▶ Lab clues: lymphopenia, raised D-dimer, ferritin, CRP, LDH, IL-6, troponin.
- ▶ Early antiviral of choice: nirmatrelvir/ritonavir 300/100 mg BD ×5 d within 5 days (CYP3A4 interactions; avoid GFR <30).
- ▶ Severe/hospitalised: remdesivir + dexamethasone ± tocilizumab/baricitinib; therapeutic-dose heparin if on supplemental O2.
- ▶ Dexamethasone helps only hypoxic patients (RECOVERY); harmful/no benefit without hypoxia.
- ▶ Vaccines: mRNA (Pfizer/Moderna ~95%), Novavax subunit; Janssen withdrawn (TTS).
- ▶ Sequelae: MIS-C/MIS-A (Kawasaki-like) and Long COVID (fatigue, anosmia, dyspnoea, brain fog) ≥3 months.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "SARS-CoV-2 and COVID-19" (virology, ACE2/TMPRSS2 entry, epidemiology, severity, complications, antiviral/immunomodulator regimens, antibody therapy, vaccines).
- ▶ CMDT 2026 — "Severe Acute Respiratory Syndrome — Coronavirus 2019 (SARS-CoV-2)" and Table 37–1 "Agents for viral infections" (diagnostic strategy, drug doses, anticoagulation thresholds, corticosteroid/IL-6/JAK indications, vaccine and Long-COVID data).



Cytokine Storm in Dengue Fever

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Dengue is caused by four antigenically distinct mosquito-borne orthoflaviviruses (DENV-1 to DENV-4, family *Flaviviridae*) transmitted chiefly by *Aedes aegypti*. While

most infections are subclinical or cause a self-limited febrile illness (“break-bone fever”), a minority progress at defervescence to **severe dengue**, dominated by a **plasma-leakage (critical) phase**. The “*cytokine storm*” refers to an exaggerated, dysregulated surge of pro- and anti-inflammatory cytokines and vasoactive mediators—triggered largely by **antibody-dependent enhancement (ADE)** and cross-reactive memory T-cell activation during heterotypic secondary infection—that drives **endothelial dysfunction, increased vascular permeability, plasma leakage, haemorrhage and shock**. It is the immunopathological engine of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Why a cytokine storm develops — immunological triggers

- ▶ **Antibody-dependent enhancement (ADE):** A first (primary) DENV infection gives lifelong homotypic immunity but only transient cross-protection. On heterotypic **secondary infection**, pre-existing **non-neutralising, sub-neutralising “enhancing” antibodies** opsonise the new serotype and, via **Fcγ receptors**, deliver virus into **monocytes/macrophages**, amplifying viral load and the infected-cell pool that releases cytokines. Harrison explicitly centres severe-dengue risk on “immune-mediated enhancement of disease” and “enhancing and non-neutralising antibodies.”
- ▶ **Original antigenic sin (cross-reactive T cells):** Secondary infection preferentially expands **low-avidity cross-reactive memory CD8⁺/CD4⁺ T cells** from the prior serotype rather than high-affinity protective clones; these clear virus poorly but **over-produce TNF-α and IFN-γ**, fuelling the storm.
- ▶ **NS1-driven endothelial injury:** The secreted viral **non-structural protein 1 (NS1)** is highlighted by Harrison as having “a key role in the vascular leak phenomenon”—it engages **TLR4** on monocytes and endothelium to release inflammatory cytokines and directly degrades the **endothelial glycocalyx**.
- ▶ **Complement activation:** Massive C3/C5 activation generates anaphylatoxins (**C3a, C5a**) that increase vascular permeability and amplify inflammation.
- ▶ **Mast-cell and innate activation:** Infected mast cells and dendritic cells release vasoactive mediators (chymase, VEGF, histamine), adding to leak.
- ▶ **Host/viral risk modifiers (Harrison):** Susceptibility falls sharply after age 12; females > males; certain **infection sequences** are worse (DENV-1 → DENV-2 more severe than DENV-4 → DENV-2); Southeast-Asian DENV-2 variants are more virulent; nutritional status and, per CMDT, **type-2 diabetes and obesity** predispose to severe disease.

Key mediators of the storm and their effects

Mediator	Principal source	Pathophysiological effect
TNF-α	Activated T cells, monocytes	Endothelial activation, increased permeability, fever, haemorrhage

Mediator	Principal source	Pathophysiological effect
IFN- γ	Cross-reactive memory T cells	Macrophage activation, amplifies TNF- α effect
IL-6	Monocytes/macrophages, endothelium	Acute-phase response, vascular permeability, coagulation activation
IL-1 β	Monocytes (inflammasome)	Pyrexia, endothelial activation
IL-8 (CXCL8) / MCP-1	Monocytes, endothelium	Neutrophil/monocyte chemotaxis, vascular leak
IL-10	T cells, monocytes	Anti-inflammatory surge; high levels mark severity & immune paralysis
VEGF	Mast cells, platelets, endothelium	Potent direct $\uparrow$ vascular permeability
NS1 (viral)	Infected cells (secreted)	Glycocalyx degradation, TLR4-mediated cytokine release
Complement C3a/C5a	Plasma cascade	Anaphylatoxin-mediated permeability

- ▶ The **net result** is loss of endothelial barrier integrity and **glycocalyx shedding**, producing the hallmark **plasma leak**: haemoconcentration (rising haematocrit), hypoalbuminaemia, serosal effusions (pleural, ascitic) and, ultimately, hypovolaemic **shock with narrowed pulse pressure**.
- ▶ Concurrent cytokine-driven **thrombocytopenia, platelet dysfunction, consumptive coagulopathy/DIC and liver injury** generate the bleeding diathesis.

Phases of dengue and timing of the storm

- ▶ **Febrile phase (days 1–5)**: High viraemia and innate activation—high fever, retro-orbital pain, myalgia (“break-bone”), flushing, transient rash; leukopenia, early thrombocytopenia, mild AST rise.
- ▶ **Critical / plasma-leakage phase (around defervescence, ~days 3–7)**: The cytokine storm peaks as fever falls; capillary leak, effusions, falling platelets ($<100,000/\mu\text{L}$), rising haematocrit and—if uncorrected—shock. **Warning signs** (abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy/restlessness, hepatomegaly >2 cm, rising HCT with rapid platelet fall) flag impending deterioration.
- ▶ **Recovery phase (~days 7–10)**: Cytokines subside, extravascular fluid is reabsorbed (risk of **fluid overload/pulmonary oedema** with over-resuscitation); convalescent confluent pruritic rash with desquamation; bradycardia.

WHO classification (puts the storm in clinical terms)

1997 WHO	2009 WHO (current)	Defining feature
Dengue fever	Dengue without warning signs	Febrile illness, no leak/warning features
Dengue haemorrhagic fever (DHF, grades I–II)	Dengue with warning signs	Plasma-leak markers + warning signs → admit
DHF III–IV / Dengue shock syndrome (DSS)	Severe dengue	(1) plasma leakage → shock or respiratory distress, or (2) severe bleeding, or (3) severe organ dysfunction

- Severe organ involvement: hepatitis/fulminant hepatic failure, **myocarditis**, encephalitis/encephalopathy, acute kidney injury (especially with shock—high mortality). The most extreme expression of the storm overlaps with **haemophagocytic lymphohistiocytosis (HLH)/macrophage-activation syndrome** (cytopenias, hyperferritinaemia, hepatosplenomegaly).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — “Cytokine storm cascade in secondary dengue”**: Boxes/arrows: *Heterotypic secondary DENV* → *Non-neutralising enhancing antibody + Fcγ receptor (ADE)* → *Infected monocyte/macrophage (↑viral load) + Cross-reactive memory T cell (original antigenic sin)* + *Secreted NS1* → *TLR4* → central node “**Cytokine storm: TNF-α, IFN-γ, IL-6, IL-1β, IL-8, IL-10, VEGF, MCP-1; complement C3a/C5a**” → *Endothelial activation + glycocalyx degradation* → three output boxes: (i) ↑Vascular permeability → plasma leak → effusions → shock, (ii) Thrombocytopenia + DIC → haemorrhage, (iii) Organ injury (liver, heart, brain, kidney).
- **Diagram 2 — “Triphasic dengue timeline”**: X-axis days 1–10; overlaid curves for temperature, platelet count (falling to nadir in critical phase), haematocrit (rising in critical phase); shade the three phases (Febrile / Critical–leakage / Recovery) and mark the band “Cytokine storm / warning-signs window” at defervescence.

Clinical / Diagnostic significance

- **Markers of the storm / severity**: rising haematocrit with falling platelets, hypoalbuminaemia, effusions on lateral-decubitus CXR or ultrasound, elevated transaminases; high IL-10, ferritin and AST track severity. The **tourniquet test** (≥10 new petechiae per square inch after 5-min BP-cuff inflation midway between systolic and diastolic) demonstrates microvascular fragility.
- **Diagnosis**: NS1 antigen ELISA/rapid test and RT-PCR in the first ~5 days; IgM/IgG ELISA thereafter. Early, rapidly rising IgG suggests a **secondary** (ADE-prone) infection. Flavivirus serological cross-reactivity (ZIKV, JEV, YFV) can confound.

- ▶ **Management is supportive—fluids are the keystone:** judicious isotonic crystalloid/colloid guided by vitals, urine output and haematocrit, ideally **before shock**, with careful titration to avoid overload during recovery reabsorption. **Acetaminophen/paracetamol** for fever; **avoid NSAIDs and aspirin** (gastritis/bleeding). Platelet transfusion is reserved for **severe thrombocytopenia** ($<10,000/\mu\text{L}$) or active bleeding—prophylactic transfusion is not beneficial and may harm. Treat shock, DIC and organ failure in critical care.
- ▶ **Immunomodulation:** Routine corticosteroids/IVIG are **not** proven to alter outcome in severe dengue; targeted anti-cytokine therapy remains investigational. The cytokine-storm/ADE concept underpins **vaccine caution**.
- ▶ **Vaccine relevance of ADE:** CYD-TDV (Dengvaxia), built on the YFV-17D platform, *increased* severe dengue in **seronegative** recipients (vaccine acting as a “first serological hit”), mandating **pre-vaccination serostatus screening**; TAK-003 (Qdenga), a two-dose vaccine, shows benefit including in some seronegatives but with serotype caveats.

High-yield exam pointers

- ▶ Cytokine storm = **immunopathology**, not direct viral cytopathic lysis—peaks at **defervescence/critical phase**, not at peak fever.
- ▶ **Secondary heterotypic infection + ADE + cross-reactive T cells (original antigenic sin)** = core triggers; NS1 degrades glycocalyx and is the named driver of vascular leak.
- ▶ Dominant mediators to write: **TNF- α , IFN- γ , IL-6, IL-1 β , IL-8, IL-10, VEGF, complement C3a/C5a**.
- ▶ Cardinal consequence = **increased vascular permeability** $\rightarrow$ **plasma leak** $\rightarrow$ **haemoconcentration** $\rightarrow$ **DSS**; plus **thrombocytopenia/DIC** $\rightarrow$ **bleeding**.
- ▶ **Severe dengue (WHO 2009)** = plasma leakage (shock/respiratory distress) **or** severe bleeding **or** severe organ dysfunction.
- ▶ Triad to monitor: **rising HCT + falling platelets + warning signs**; effusions are an early leak sign.
- ▶ Treatment = **fluids + paracetamol**; **avoid NSAIDs/aspirin**; platelets only if $<10,000/\mu\text{L}$ or bleeding; **steroids/IVIG unproven**.
- ▶ **~500,000 severe dengue cases/year, CFR ~2.5%** (falls to ~1% with expert supportive care).
- ▶ **Dengvaxia ADE pitfall:** harm in seronegatives $\rightarrow$ screen serostatus before vaccinating.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Arthropod-Borne and Rodent-Borne Virus Infections” (Dengue, Severe Dengue and Viral Haemorrhagic Fever sections: ADE/immune enhancement, enhancing non-neutralising antibodies, NS1-driven vascular leak, plasma-leak/critical phase, severe-dengue criteria, host/viral risk factors, tourniquet test, vaccine ADE).

- ▶ **Harrison's 22e** — “Mechanisms of Regulation and Dysregulation of the Immune System” (general biology of pro-inflammatory cytokines TNF- α , IL-1, IL-6, IFN- γ and the anti-inflammatory IL-10/TGF- β axis underpinning immune dysregulation).
- ▶ **CMDT 2026** — “Viral & Rickettsial Infections” (Dengue: WHO 1997 vs 2009 classification, severe-dengue definition, laboratory monitoring, supportive treatment, NSAID avoidance, platelet-transfusion threshold, prognosis, comorbidity risk, vaccines).
- ▶ **Coverage note (spec gap = true):** The corpus grounds the *triggers* of the storm (ADE, secondary heterotypic infection, NS1-mediated vascular leak, T-cell dysregulation) and the *general* cytokine biology, but does **not** enumerate the dengue-specific cytokine cascade (TNF- α /IFN- γ /IL-6/IL-8/IL-10/VEGF, complement C3a/C5a, mast-cell/glycocalyx mechanisms) or use the phrase “cytokine storm” verbatim for dengue. Those mediator-level specifics are included as **universally accepted standard internal-medicine/infectious-disease teaching** and are flagged here for transparency.



Define and classify extended spectrum β -lactamases, list the risk factors for acquiring ESBL and its implications on antibiotic choice

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — β -Lactamases are bacterial enzymes that hydrolyse the four-membered β -lactam ring and thereby inactivate β -lactam antibiotics; they are the commonest mechanism of β -lactam resistance in gram-negative bacteria. **Extended-spectrum β -lactamases (ESBLs)** are plasmid-encoded β -lactamases — usually evolved by point mutations from earlier penicillinases — that have an *expanded substrate profile* enabling them to degrade the oxyimino (third-generation) cephalosporins (ceftriaxone, cefotaxime, ceftazidime) and the monobactam aztreonam, while remaining **susceptible to β -lactamase inhibitors** (clavulanate, sulbactam, tazobactam) and (characteristically) **not** hydrolysing carbapenems or the cephamycins (cefoxitin). They are predominantly found in *Enterobacterales*, chiefly *Escherichia coli* and *Klebsiella pneumoniae*, and are a globally disseminated cause of multidrug-resistant infection.

Where ESBLs sit among β -lactamases — classification

Two complementary schemes are used: the **Ambler molecular classification** (based on amino-acid sequence/active site) and the **Bush–Jacoby functional classification** (based on substrate and inhibitor profile). ESBLs are predominantly **Ambler class A**, **Bush–Jacoby group 2be**.

Ambler class (active site)	Bush–Jacoby group	Enzyme examples	Hydrolyses	Inhibited by clavulanate?
A (serine)	2b / 2be (ESBL) / 2f	Early TEM-1, SHV-1 penicillinases → ESBLs: TEM-, SHV-, CTX-M-types; KPC carbapenemase (2f)	Penicillins, oxyimino-cephalosporins, aztreonam (ESBL); + carbapenems (KPC)	Yes (ESBL); KPC variably
B (metallo-, Zn ²⁺)	3	NDM, VIM, IMP (metallo-carbapenemases)	Penicillins, cephalosporins, carbapenems (not aztreonam)	No (and not avibactam)
C (serine)	1	AmpC (chromosomal in <i>Enterobacter</i> ; also plasmid)	Penicillins, cephalosporins including ceftioxin	No
D (serine)	2d	OXA -type (incl. OXA-ESBLs; OXA-48 carbapenemase)	Oxacillin/cloxacillin; some extended cephalosporins; OXA-48 → carbapenems	Variable / poorly

- ▶ **Phenotypic / practical classification** the candidate must also state: ESBLs are distinguished from the two great mimics — **AmpC cephalosporinases** (class C; not inhibited by clavulanate, *do* hydrolyse ceftioxin) and **carbapenemases** (KPC, NDM, OXA-48; hydrolyse carbapenems) — because the treatment differs sharply.
- ▶ **ESBL families**: the earliest were TEM- and SHV-derived; the now globally **predominant family** is CTX-M (e.g. CTX-M-15), which preferentially hydrolyses cefotaxime/ceftriaxone and drives community-onset ESBL *E. coli*.

Defining hydrolytic profile of ESBLs (substrate “fingerprint”)

- ▶ **Degraded (resistant)**: all penicillins; early- and extended-spectrum cephalosporins — ceftriaxone, cefotaxime, **ceftazidime**; and the monobactam **aztreonam**. Some ESBLs additionally degrade the fourth-generation cephalosporin **cefepime**, making cefepime unreliable.
- ▶ **Usually spared (treatment relevant)**: carbapenems (imipenem, meropenem, ertapenem, doripenem) are *not* degraded by ESBLs; cephamycins (ceftioxin) are also stable but are not used clinically for this.
- ▶ **Inhibited by**: clavulanate, sulbactam, tazobactam (and the newer diazabicyclooctanes avibactam, relebactam) — this *clavulanate susceptibility* is the basis of laboratory confirmation.

- ▶ **Co-resistance:** the ESBL plasmid frequently co-carries genes for **fluoroquinolone and aminoglycoside resistance**, so ESBL isolates are often resistant to ciprofloxacin and gentamicin as well — a key reason the carbapenems become indispensable.

Risk factors for acquiring an ESBL-producing organism

- ▶ **Prior antimicrobial exposure** — especially recent **third-generation cephalosporins and fluoroquinolones** (selection pressure favouring resistant strains); prior antibiotic therapy of any kind.
- ▶ **Prior infection or colonisation with a resistant pathogen**, and being part of a population with a large resistance reservoir.
- ▶ **Prior or prolonged hospitalisation**, particularly **ICU stay**; transfer from or residence in **long-term-care / nursing facilities**.
- ▶ **Invasive devices breaching host barriers** — indwelling **urinary catheters**, central venous/IV catheters, surgical drains, nasogastric and endotracheal tubes — a frequent source of health-care-associated gram-negative infection.
- ▶ **Cross-transmission** in health-care settings via the **contaminated hands of health-care workers** when hand hygiene/infection-control is inadequate.
- ▶ **Other widely accepted host factors:** recurrent or complicated urinary tract infection, recent surgery, haemodialysis, diabetes mellitus, immunosuppression, and **travel to / residence in highly endemic regions** (e.g. the Indian subcontinent for community-acquired CTX-M and for NDM carbapenemases).

Implications on antibiotic choice

- ▶ **Carbapenems are the drugs of choice** for serious ESBL infections (bacteraemia, pyelonephritis, intra-abdominal sepsis): they are *the most reliable agents* against ESBL producers. Use **meropenem/imipenem** for severe disease; **ertapenem** is a useful *carbapenem-sparing* once-daily option for stable, non-pseudomonal ESBL infection (preserves antipseudomonal carbapenems).
- ▶ **Do NOT rely on third-generation cephalosporins** even if the disk reports “susceptible” — there is an inoculum effect and high failure rate; ESBLs hydrolyse them *in vivo*.
- ▶ **β -Lactam/ β -lactamase-inhibitor combinations** (e.g. piperacillin-tazobactam) inhibit ESBLs *in vitro*, but their role in serious/bacteraemic ESBL infection is *debated* and they are generally inferior to carbapenems — reserve, if at all, for source-controlled, lower-acuity infection.
- ▶ **If a carbapenem cannot be used** (allergy, stewardship, carbapenemase co-existence): **ceftazidime-avibactam**, or possibly **ceftolozane-tazobactam** or **imipenem-cilastatin-relebactam** can be considered (avibactam/relebactam additionally cover KPC/AmpC, not metallo-enzymes).
- ▶ **Uncomplicated lower UTI (cystitis):** oral **nitrofurantoin** or **fosfomycin** are effective ESBL-active options that spare carbapenems (avoid in pyelonephritis/bacteraemia).

- ▶ **Fluoroquinolones and aminoglycosides are unreliable empirically** because of frequent plasmid-linked co-resistance — use only if susceptibility is confirmed; amikacin or **plazomicin** may remain active where gentamicin/tobramycin are not.
- ▶ **Salvage / extensively-resistant gram-negatives: cefiderocol** (siderophore cephalosporin) and the polymyxins (colistin) are options for carbapenem-resistant organisms.
- ▶ **Stewardship and empirical strategy:** in patients with ESBL risk factors who are septic, start **empirical carbapenem cover**, then **de-escalate** to the narrowest effective agent for the shortest course once cultures/susceptibilities return; restrict cephalosporin/fluoroquinolone over-use, enforce hand hygiene and contact precautions to limit spread.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Gram-negative cell-envelope schematic** showing the resistance site: outer membrane with porin channel, β -lactamase enzyme in the periplasmic space degrading the β -lactam before it reaches its target, and the inner-membrane **penicillin-binding proteins (PBPs/transpeptidases)**. Labels: *Outer membrane, Porin, Periplasmic space, β -lactamase (ESBL), β -lactam antibiotic, PBP/transpeptidase, Peptidoglycan, Inner (cytoplasmic) membrane, Efflux pump.*
- ▶ **Classification tree** of β -lactamases: β -lactamases $\rightarrow$ Ambler A (ESBL: TEM/SHV/CTX-M, KPC) / B (metallo – NDM, VIM, IMP) / C (AmpC) / D (OXA, OXA-48), with a side box: “ESBL = hydrolyses 3rd-gen cephalosporins + aztreonam; inhibited by clavulanate; spares carbapenems & ceftazidime.”

Clinical / Diagnostic significance

- ▶ **Laboratory detection** rests on the *clavulanate effect*: a **phenotypic confirmatory test** shows a ≥ 3 -doubling-dilution fall in the MIC of cefotaxime or ceftazidime when combined with clavulanate; the **double-disk synergy test** shows enhancement of the cephalosporin inhibition zone towards a co-placed amoxicillin-clavulanate disk. Distinguish from AmpC (no clavulanate synergy, ceftazidime-resistant).
- ▶ **Empirical choice is local-data-driven:** know the unit/hospital ESBL prevalence; obtain cultures **before** antibiotics; communicate rapid susceptibility results promptly to guide directed therapy.
- ▶ **Infection control:** ESBL producers are an *escalating, transmissible* threat (CDC “Serious” category — ESBL-producing *Enterobacterales*); contact precautions, hand hygiene, device removal and antimicrobial stewardship reduce acquisition and spread.
- ▶ **Prognostic impact:** ESBL infection independently delays appropriate therapy, prolongs hospital stay and increases mortality — hence the value of risk-stratified empirical carbapenem cover in the septic at-risk patient.

High-yield exam pointers

- ▶ **ESBL** = plasmid-mediated, Ambler class A / Bush–Jacoby 2be, clavulanate-inhibited enzyme that hydrolyses oxyimino-cephalosporins + aztreonam but spares carbapenems and ceftazidime.
- ▶ Commonest hosts: *E. coli* and *K. pneumoniae* (and other *Enterobacteriales*); dominant family now CTX-M (CTX-M-15).
- ▶ **Three mimics to separate**: ESBL (class A, clavulanate-sensitive), **AmpC** (class C, clavulanate-resistant, ceftazidime-resistant), **carbapenemase** (KPC/NDM/OXA-48).
- ▶ **Top risk factors**: prior cephalosporin/fluoroquinolone use, prior hospitalisation/ICU, long-term-care residence, indwelling catheters/devices, prior resistant-organism colonisation, endemic-area exposure.
- ▶ **Treatment of choice** = carbapenem (ertapenem for carbapenem-sparing; meropenem for severe); do not use cephalosporins despite “S” on the report.
- ▶ **Carbapenem-sparing alternatives**: ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam; cystitis → nitrofurantoin/fosfomycin.
- ▶ **Co-resistance** to fluoroquinolones and aminoglycosides is common → narrows empirical options.
- ▶ **Detection**: double-disk synergy / clavulanate MIC reduction test.
- ▶ **Control**: stewardship + de-escalation + hand hygiene/contact precautions.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Bacterial Resistance to Antimicrobial Agents” (β -lactamases, ESBL substrate profile, AmpC vs ESBL, carbapenemases KPC/NDM/OXA-48, β -lactamase inhibitors, ceftazidime; risk factors and epidemiology of resistance; CDC threat categories) and “Treatment and Prophylaxis of Bacterial Infections” (β -lactam mechanism, empirical vs directed therapy, antimicrobial stewardship).
- ▶ **CMDT 2026** — “Common Problems in Infectious Diseases & Antimicrobial Therapy” (ESBL → carbapenem; ceftazidime-avibactam / ceftolozane-tazobactam / imipenem-relebactam alternatives; ESBL *E. coli* co-resistant to cephalosporins, aminoglycosides, fluoroquinolones) and “Anti-infective Treatment: Antibiotic, Antifungal & Antiviral Agents” (carbapenems most reliable for ESBL; extended-spectrum penicillins; fosfomycin for UTI).

Coverage note: The Harrison/CMDT corpus describes ESBLs, AmpC, carbapenemases, the inhibitors and the management hierarchy in full, and supplies the risk-factor set (prior antibiotics, prior hospitalisation, prior resistant infection, invasive devices, cross-transmission). The **formal scheme names** (Ambler classes A–D; Bush–Jacoby group 2be), the **enzyme-family names** (TEM/SHV/CTX-M), and the **phenotypic confirmatory/double-disk synergy test** are universally

accepted standard infectious-disease microbiology added for completeness, though not spelled out verbatim in this Harrison/CMDT corpus; all such points are stated accurately.



Define shock. Discuss the pathophysiology and management of Septic shock

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Shock is the clinical condition of organ dysfunction resulting from an imbalance between cellular oxygen supply and demand, producing cellular and tissue hypoxia; it is a life-threatening state and a common reason for ICU admission. Organ dysfunction in early shock is often reversible with restoration of oxygen delivery, but untreated shock transitions to an irreversible phase with multisystem organ failure and death. **Septic shock** is the commonest cause of distributive shock and is defined (Sepsis-3, 2016) as the subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities increase mortality risk beyond sepsis alone — operationally, a septic patient requiring vasopressors to maintain MAP ≥ 65 mmHg and with serum lactate > 2 mmol/L despite adequate fluid resuscitation.

Determinants of oxygen delivery and classification of shock

- ▶ Oxygen delivery: $DO_2 = CO \times CaO_2$, where $CO = HR \times SV$ and $CaO_2 = (Hb \times 1.34 \times SaO_2) + (PaO_2 \times 0.003)$; stroke volume $SV \propto (Preload \times Contractility) / SVR$.
- ▶ Any disturbance of HR, preload, contractility, SVR, SaO_2 or haemoglobin can reduce DO_2 and cause shock. Shock can also arise from increased consumption or impaired utilisation (e.g., cyanide poisoning uncouples oxidative phosphorylation).
- ▶ Four major physiologic types, each with a distinct haemodynamic profile:

Type	Primary derangement	CVP	PCWP	Cardiac output	SVR	Examples
Distributive	↓ SVR (vasodilation)	↓	↓	↑	↓	Septic shock, pancreatitis, severe burns, anaphylaxis, neurogenic, adrenal crisis
Cardiogenic	↓ CO (pump failure)	↑	↑	↓	↑	MI, myocarditis, arrhythmia, acute valvular failure

Type	Primary derangement	CVP	PCWP	Cardiac output	SVR	Examples
Obstructive	↓ CO (mechanical obstruction)	↑	↓/↑	↓	↑	Tension pneumothorax, tamponade, massive PE, aortic dissection
Hypovolemic	↓ preload	↓	↓	↓	↑	Haemorrhage (trauma, GI bleed), GI/renal/skin fluid losses

- ▶ **Mixed shock** is common: e.g., distributive septic shock with superimposed sepsis-induced cardiomyopathy adds a cardiogenic component. **Sepsis is the most common cause of distributive shock** and predominates in the ICU.

Stages of shock

- ▶ **Compensated (pre-shock)**: physiologic responses (tachycardia, rising CO in early sepsis; ↑SVR and ↑HR in haemorrhage) maintain perfusion; no overt organ dysfunction, perhaps mild lactate or creatinine rise.
- ▶ **Decompensated shock**: compensatory mechanisms overwhelmed → frank organ dysfunction (encephalopathy, oliguria). Still reversible with timely restoration of perfusion.
- ▶ **Irreversible shock**: permanent organ damage progressing to multisystem organ dysfunction and death.

Pathophysiology of septic shock

- ▶ **Trigger**: Pathogen-associated molecular patterns (PAMPs) — bacterial LPS, cell-wall components, pathogen nucleic acids — and host **damage-associated molecular patterns (DAMPs)** — histones, HMGB1, S100 proteins, extracellular DNA, ATP — are sensed by **pattern recognition receptors (PRRs)**: toll-like receptors (TLRs), C-type lectin receptors, RAGE, RIG-I-like and NOD-like receptors.
- ▶ **Dysregulated host response**: PRR activation on neutrophils, monocytes and macrophages triggers release of **pro-inflammatory cytokines/chemokines** (IL-1 β , IL-6, TNF- α), up-regulates vascular adhesion molecules and drives **emergency granulopoiesis**. Neutrophils release **neutrophil extracellular traps (NETs)**. Concurrent lymphoid exhaustion/apoptosis and myeloid-derived suppressor cells cause **immunosuppression**, predisposing survivors to secondary infection.

- ▶ **Endothelial activation:** breakdown of the endothelial **glycocalyx**, ↑ICAM/VCAM-1 expression, loss of VE-cadherin and tight junctions, and endothelial apoptosis cause **capillary leak**, interstitial oedema and increased oxygen-diffusion distance.
- ▶ **Coagulopathy:** ↑tissue factor triggers the extrinsic cascade; vWF and platelet aggregates plus NETs form **fibrin-rich microthrombi**. Anticoagulants (antithrombin, tissue factor pathway inhibitor, activated protein C) are depleted and fibrinolysis is impaired (↑PAI-1) → microvascular thrombosis; consumption of factors and platelets causes **DIC** and bleeding. The complement cascade is activated (C3a, C5a anaphylatoxins; **C5b-9 membrane attack complex**) amplifying injury.
- ▶ **Circulatory failure:** systemic **arteriolar vasodilation** (partly excess **nitric oxide**) lowers SVR; venodilation and capillary leak reduce venous return and preload; hypotension results. Up to half of patients develop **sepsis-induced cardiomyopathy** (↓LVEF, ↑end-diastolic volume index, RV impairment).
- ▶ **Cellular injury:** inadequate oxygen delivery plus direct injury from ROS/reactive nitrogen species and **mitochondrial/metabolic dysfunction** (cytopathic hypoxia) impair ATP generation and ion homeostasis even when oxygen delivery is restored → multiorgan injury. Anaerobic metabolism converts pyruvate to **lactate** (lactic acidosis), the biochemical hallmark.

Recognition and diagnostic criteria

- ▶ **Sepsis-3 (current):** sepsis = **life-threatening organ dysfunction from a dysregulated host response to infection**, operationalised as a rise of ≥ 2 in **SOFA score**. SOFA scores six systems — neurologic (GCS), cardiovascular (MAP/vasopressors), respiratory ($\text{PaO}_2/\text{FiO}_2$), hepatic (bilirubin), renal (creatinine), coagulation (platelets).
- ▶ **Septic shock:** vasopressor requirement to keep **MAP ≥ 65 mmHg** plus **lactate > 2 mmol/L** despite fluid resuscitation; mortality up to **40%**.
- ▶ **qSOFA** (rapid bedside screen): RR $\geq 22/\text{min}$, altered mentation (GCS < 15), SBP ≤ 100 mmHg — score ≥ 2 (with suspected infection) flags high mortality risk; more specific but less sensitive than SIRS.
- ▶ **Historical:** SIRS criteria (temp $< 36/ > 38$ °C, HR > 90 , RR > 20 or $\text{PaCO}_2 < 32$, WBC $< 4000/ > 12000$ or $> 10\%$ bands); Sepsis-1 (1992), Sepsis-2 (2003) preceded Sepsis-3.
- ▶ Initial workup: CBC with differential, basic metabolic panel, LFTs, **serum lactate**, coagulation panel, urinalysis; **cultures of blood and other sites before antibiotics**; targeted imaging (X-ray/CT/USG) for source. Exclude **sepsis mimics** (heart failure, mesenteric ischaemia, adrenal insufficiency, hypovolaemia) — ~25% of presumed sepsis are mimics.

Management of septic shock (Surviving Sepsis Campaign 2021)

- ▶ **Early antibiotics — most important survival lever:** immediate empiric **broad-spectrum antimicrobials within 1 h of shock recognition** (after cultures, but do not delay for them). Every

1-h delay adds an estimated 7–8% **mortality**. De-escalate on culture data; practise stewardship and short courses.

- Site-directed empiric choices: **ceftriaxone/cefotaxime** if *Pseudomonas* unlikely; **cefepime, piperacillin-tazobactam, or a carbapenem (meropenem/imipenem)** if *Pseudomonas* likely; add **vancomycin or linezolid** for MRSA risk; **echinocandin** if fungal risk (recent abdominal surgery, TPN, *Candida* colonisation).
- ▶ **Fluid resuscitation: balanced crystalloid (lactated Ringer's)** preferred over 0.9% saline; initial bolus ~30 mL/kg over 5–10 min. Albumin if large crystalloid volumes already given; **avoid hydroxyethyl/pentastarch** (kidney injury, death). Guide further fluids by **dynamic measures** (capillary refill time, passive leg raise, point-of-care ultrasound/IVC, SV variation) — *not* static CVP-targeted protocols.
- ▶ **Vasopressors: Norepinephrine is first-line** (α_1 vasoconstriction + β_1 inotropy/chronotropy) to target MAP ≥ 65 mmHg; add **vasopressin as second agent**, then **epinephrine third**. Place an arterial line for continuous BP. **Dopamine is not first-line** (arrhythmia; increased mortality in cardiogenic subgroup).
- ▶ **Corticosteroids: IV hydrocortisone 200 mg/day (50 mg q6h)** for ongoing vasopressor requirement.
- ▶ **Inotropy:** for sepsis-induced cardiomyopathy with persistent hypoperfusion after volume, **add dobutamine to norepinephrine or switch to epinephrine**; pulmonary artery catheter only for mixed septic + cardiogenic shock.
- ▶ **Source control:** drain abscesses, debride necrotising soft-tissue infection, decompress obstructed biliary/urinary tract, remove infected catheters — **as rapidly as possible**.
- ▶ **Organ support:** lung-protective ventilation (tidal volume 6–8 mL/kg ideal body weight, plateau pressure <30 cmH₂O, SpO₂ 90–96%; rescue with prone positioning, neuromuscular blockade, VV-ECMO); RRT for standard indications (refractory acidemia, hyperkalemia, uraemia, volume overload); transfuse PRBC for Hb <7 g/dL; insulin for glucose >180 mg/dL; stress-ulcer prophylaxis and early enteral nutrition (within 48 h) once shock is controlled.

Organ-specific complications and supportive targets

System	Frequency	Key management
Neurologic (encephalopathy)	~54%	Treat cause; correct metabolic/electrolyte derangements; limit neurotoxic sedatives (<i>cefepime, opioids, benzodiazepines</i>)
Cardiovascular (shock)	~25% (half with myocardial dysfunction)	Balanced crystalloid; norepinephrine → vasopressin →

System	Frequency	Key management
		epinephrine; hydrocortisone; dobutamine for low LVEF
Respiratory (ARDS)	~7%	SpO ₂ 90–96%; lung-protective ventilation; rescue therapies for refractory hypoxia
Renal (AKI)	up to ~67%	Maintain perfusion, avoid nephrotoxins; RRT/CRRT for standard indications
Hepatic (liver dysfunction)	~50% of septic shock	Avoid hypotension/hepatotoxins; USG if ↑bilirubin
Haematologic (DIC)	up to ~35% of septic shock	Cryoprecipitate (fibrinogen <150 mg/dL), platelets ($\leq 50 \times 10^9/L$ + bleeding), FFP for bleeding with prolonged PT/INR

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Oxygen-delivery / shock cascade flowchart:** Label — $DO_2 = CO \times CaO_2$; $CO = HR \times SV$; $SV \propto (Preload \times Contractility)/SVR$; $CaO_2 = (Hb \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$; branch to the four shock types (Distributive / Cardiogenic / Obstructive / Hypovolemic); endpoint *anaerobic metabolism* → ↑lactate → cellular injury.
- ▶ **Septic-shock pathogenesis schematic:** Label — *Pathogen* → PAMPs/DAMPs → PRRs (TLR); Cytokines (IL-1 β , IL-6, TNF- α); Neutrophil + NETs; Endothelial activation → glycocalyx breakdown → capillary leak/oedema; Tissue factor → microthrombi → DIC; Complement C3a/C5a, C5b-9 (MAC); NO-mediated vasodilation → ↓SVR → hypotension; Mitochondrial dysfunction → tissue hypoxia.

Clinical / Diagnostic significance

- ▶ **Lactate** is central to diagnosis, risk stratification and monitoring; serial lactate (or capillary-refill-guided) resuscitation tracks response, though a major trial found capillary-refill-targeted resuscitation non-inferior to lactate-targeted for 28-day mortality.
- ▶ **Shock index** (HR/SBP; normal 0.5–0.7, abnormal >0.9) flags occult hypoperfusion and transfusion need.
- ▶ “**Windows**” of organ perfusion — CNS (confusion), kidney (oliguria <0.5 mL/kg/h), skin (mottling, prolonged capillary refill, cold clammy skin) — allow bedside recognition before labs return.
- ▶ POCUS/echocardiography differentiates shock type and detects sepsis-induced cardiomyopathy and mixed shock.

- ▶ Restrictive vs liberal fluid strategy and routine low-dose vasopressin-plus-norepinephrine showed no 90-day/28-day mortality difference — argues against rigid protocols.

High-yield exam pointers

- ▶ **Shock = supply–demand O₂ imbalance** → tissue hypoxia, reversible early, irreversible late.
- ▶ Four types by haemodynamics: **Distributive** (↓SVR, ↑CO) vs the three low-CO types (↑SVR); memorise the CVP/PCWP/CO/SVR table.
- ▶ **Septic shock = sepsis + vasopressor need for MAP ≥65 + lactate >2 despite fluids**; mortality up to 40%.
- ▶ Pathogenesis triad: **PAMPs/DAMPs–PRR inflammation** → **endothelial/glycocalyx injury & capillary leak** → **coagulopathy/microthrombi (DIC)**, plus NO-driven vasodilation and mitochondrial dysfunction.
- ▶ **Antibiotics within 1 h** of shock recognition — 7–8% added mortality per hour's delay.
- ▶ **Crystalloid (balanced) ~30 mL/kg**; guide further fluids by dynamic, not static (CVP), measures; avoid starches.
- ▶ Vasopressor ladder: **norepinephrine** → **vasopressin** → **epinephrine**; **hydrocortisone 200 mg/day** for refractory shock; **dobutamine/epinephrine** for sepsis-induced cardiomyopathy.
- ▶ Don't forget **source control and culture before antibiotics**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 314 "Approach to the Patient with Shock" (definition, oxygen-delivery determinants, classification, stages, vasopressor pharmacology, undifferentiated-shock management) and Ch 315 "Sepsis and Septic Shock" (Sepsis-3 definitions, pathogenesis, Surviving Sepsis Campaign management, organ-specific complications). Coverage note: All major specifics (hemodynamic profiles, Sepsis-3/qSOFA/SOFA criteria, drug doses, fluid volumes, complication frequencies) are sourced from these two chapters; the Sepsis-1 SIRS/Sepsis-2 historical criteria and shock-index cut-offs are also taken verbatim from Ch 314/315.



Definition of multidrug-resistant tuberculosis (MDR-TB) and molecular drug-susceptibility testing in its diagnosis

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — **Multidrug-resistant tuberculosis (MDR-TB)** is disease caused by *Mycobacterium tuberculosis* bacilli that are resistant at least to **isoniazid and rifampin**, the two most potent bactericidal first-line agents. Because rifampin resistance rarely occurs alone and is an excellent surrogate marker for MDR-TB, the WHO programmatically groups MDR-TB with rifampin-resistant

TB (MDR/RR-TB). **Molecular drug-susceptibility testing (mDST)** refers to nucleic-acid–based assays that detect *M. tuberculosis* and resistance-conferring mutations directly and rapidly (hours to days), and is now the WHO-recommended first-line approach to confirm both TB and drug resistance. An estimated 400,000 MDR/RR-TB cases occurred in 2023 (India accounting for ~27%), making rapid detection a priority.

Definitions: spectrum of drug-resistant TB (WHO 2021)

- **Drug-resistant TB** arises from spontaneous point mutations in the mycobacterial genome (rates 10^{-7} – 10^{-10} per drug) selected out by inadequate/monotherapy; it may be **primary** (infection with an already-resistant strain) or **acquired** (resistance developing during treatment).

Category	Definition
Mono-resistant TB	Resistance to one first-line drug only
Poly-resistant TB	Resistance to >1 first-line drug, but <i>not</i> both isoniazid + rifampin
Rifampin-resistant TB (RR-TB)	Resistance to rifampin (with or without resistance to other drugs); managed as MDR-TB
Multidrug-resistant TB (MDR-TB)	Resistance to at least isoniazid AND rifampin
Pre-XDR-TB	MDR/RR-TB that is also resistant to any fluoroquinolone
Extensively drug-resistant TB (XDR-TB)	MDR/RR-TB with resistance to any fluoroquinolone PLUS at least one other Group A drug (i.e., bedaquiline and/or linezolid)

- *Group A drugs* = levofloxacin/moxifloxacin, bedaquiline, linezolid — the backbone of modern oral MDR-TB regimens; resistance to these defines the most severe phenotypes.

Rationale for molecular DST — why it replaces phenotypic testing

- **Universal DST** to at least rifampin on every initial isolate is the WHO standard of care; **rifampin resistance is an excellent proxy for MDR-TB**, triggering expanded testing for isoniazid, fluoroquinolones and other second-line drugs.
- **Phenotypic (culture-based) DST is slow**: liquid (MGIT) DST needs ~1–2 weeks *after* growth (growth itself takes 1–3 weeks); solid-medium DST may take ≥8 weeks — too slow to guide initial therapy and to interrupt transmission of resistant strains.
- **Molecular DST is rapid and decentralisable**: detects resistance mutations directly from sputum in hours–days, needs minimal biosafety/training, and detects resistance even in smear-negative/paucibacillary specimens.
- **Placement by health-care level**: at the *peripheral/community* level — screening and referral; at the *district (secondary)* level — automated real-time NAAT (Xpert MTB/RIF, which also reports

rifampin resistance) replacing smear microscopy; at the *tertiary* level — molecular tests, rapid liquid culture and full DST. Truenat's portability extends molecular testing to peripheral microscopy centres.

Genotypic basis — resistance genes targeted by molecular DST

- ▶ Molecular assays interrogate the gene regions where resistance mutations cluster:

Drug	Principal resistance gene(s)	Approx. share of resistance
Rifampin	<i>rpoB</i> (β -subunit of RNA polymerase)	~95%
Isoniazid	<i>katG</i> (catalase-peroxidase)	50–95%
	<i>inhA</i> promoter (low-level)	up to 45%
Pyrazinamide	<i>pncA</i>	up to 98%
Ethambutol	<i>embB</i>	50–65%
Fluoroquinolones	<i>gyrA</i> / <i>gyrB</i> (DNA gyrase)	75–95%
Aminoglycosides	<i>rrs</i> (16S rRNA); <i>eis</i> promoter (C-12T)	up to 80%

- ▶ The ~95% concordance of *rpoB* mutations with rifampin resistance is the molecular basis for using rifampin resistance as the diagnostic gateway to MDR-TB.

Molecular tests used to diagnose MDR-TB

- ▶ **Xpert MTB/RIF assay** — fully automated, cartridge-based real-time **nucleic-acid amplification test (NAAT)** on the GeneXpert platform; simultaneously detects *M. tuberculosis* and rifampin resistance (*rpoB*) in <2 hours. WHO-recommended **first-line diagnostic test for all adults and children** with suspected TB, including PLWH and for CSF in suspected TB meningitis.
 - Pulmonary TB: overall sensitivity ~85% (98% in smear-positive, ~70% in smear-negative); specificity 98%.
 - For rifampin resistance vs phenotypic DST: sensitivity 96%, specificity 98%.
- ▶ **Xpert MTB/RIF Ultra** — same GeneXpert platform, greater sensitivity (~90% including “trace calls”); largest gains in smear-negative/culture-positive cases (+17%) and PLWH (+12%). Rifampin-resistance sensitivity 94%, specificity 99%.
- ▶ **Truenat MTB / MTB Plus** (chip-based, portable, battery-operated; usable at peripheral level) — sensitivities 73% and 80%; **Truenat MTB-Rif Dx** detects rifampin resistance (sensitivity 84%, specificity 97%).

- ▶ **Line probe assays (LPAs)** — DNA strip tests; after DNA extraction, PCR amplification of resistance-gene regions, then **labelled, probe-hybridised products detected by colorimetric development**.
 - *First-line LPA* — detects **isoniazid (katG, inhA) and rifampin (rpoB)** resistance in smear-positive specimens/culture isolates.
 - *Second-line LPA* — WHO-recommended initial test for **fluoroquinolone and second-line injectable** resistance in confirmed RR-/MDR-TB.
- ▶ **Whole-genome sequencing (WGS) / targeted next-generation sequencing (tNGS)** — comprehensive detection of resistance mutations; **tNGS is WHO-recommended** for comprehensive DST directly after diagnosis (still needs phenotypic confirmation for some new/repurposed drugs).
- ▶ **Other platforms** — high-throughput centralised assays (Abbott RealTime MTB & RIF/INH, FluoroType MTBDR, BD Max MDR-TB, cobas MTB-RIF/INH; sensitivity >91%, specificity 97–100%) and TB-LAMP (loop-mediated isothermal amplification — a replacement for smear microscopy but does **not** detect rifampin resistance).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm (flow chart):** *Presumptive TB* → Xpert MTB/RIF or Ultra (initial NAAT) → branch ① *RIF-sensitive* → standard first-line regimen; branch ② *RIF-resistant* → treat as MDR/RR-TB + send **first-line LPA (INH) and second-line LPA (fluoroquinolone/injectable)** + liquid culture + phenotypic DST → classify as **MDR / pre-XDR / XDR** → design appropriate regimen (e.g., BPaLM). Label boxes: *Sputum, NAAT, rpoB, katG/inhA, gyrA, MGIT culture, phenotypic DST*.
- ▶ **Resistance-gene map of *M. tuberculosis*:** bacillus with labelled gene–drug pairs — *rpoB*→rifampin, *katG/inhA*→isoniazid, *pncA*→pyrazinamide, *embB*→ethambutol, *gyrA/gyrB*→fluoroquinolones, *rrs/eis*→aminoglycosides.

Clinical / Diagnostic significance

- ▶ **Speed changes outcomes:** a same-day rifampin-resistance result lets clinicians start an effective MDR regimen immediately, averting amplification of resistance, treatment failure and ongoing transmission.
- ▶ **MDR-TB is suspected** in treatment failure (smear/culture still positive at ≥3 months), relapse after treatment interruption, contacts of known MDR cases, and patients from high-MDR settings — all warrant urgent molecular DST.
- ▶ A **positive Xpert/Ultra** in an appropriate setting justifies starting therapy; a **negative result does not exclude TB** — culture remains the gold standard and “trace calls” must be interpreted by context (treated as true-positive in PLWH, children and extrapulmonary specimens).

- ▶ mDST guides regimen choice: confirmed MDR/RR-TB (and pre-XDR) in patients ≥ 14 years is now treated with the 6-month all-oral **BPaLM** (bedaquiline–pretomanid–linezolid–moxifloxacin) regimen, with fluoroquinolone DST deciding whether moxifloxacin is retained.
- ▶ mDST does **not** replace phenotypic culture-based DST for monitoring emergence of additional resistance and for drugs not yet reliably covered by molecular tests; NAAT is **not** suitable for monitoring treatment response (detects non-viable bacilli).
- ▶ **Extrapulmonary MDR-TB**: Xpert/Ultra is the preferred initial test on CSF (suspected TB meningitis) and on selected non-respiratory specimens (lymph-node, pleural, synovial, gastric-lavage, fine-needle aspirates), simultaneously yielding the rifampin-resistance result that would otherwise be unobtainable from paucibacillary samples.
- ▶ **Pyrazinamide and second-line resistance** in MDR/RR-TB can be assessed by reverse-hybridisation LPA and by tNGS, refining whether a shorter all-oral regimen is feasible or a longer individualised regimen is required.

High-yield exam pointers

- ▶ MDR-TB = resistance to at least isoniazid + rifampin. RR-TB is managed as MDR-TB.
- ▶ Pre-XDR = MDR/RR + fluoroquinolone resistance; XDR = MDR/RR + fluoroquinolone + a Group A drug (bedaquiline/linezolid) — WHO 2021 definitions.
- ▶ Xpert MTB/RIF detects TB + rifampin resistance (*rpoB*) in <2 hours — WHO first-line initial test; RIF-resistance sensitivity 96%, specificity 98%.
- ▶ Xpert Ultra is more sensitive (especially smear-negative & PLWH); Truenat is portable/battery-operated for peripheral settings.
- ▶ *rpoB* = rifampin; *katG/inhA* = isoniazid; *gyrA/gyrB* = fluoroquinolones; *rrs* = aminoglycosides; *pncA* = pyrazinamide; *embB* = ethambutol.
- ▶ First-line LPA → INH + RIF; second-line LPA → fluoroquinolones + injectables; tNGS → comprehensive DST.
- ▶ Rifampin resistance is the proxy/gateway for MDR-TB; ~95% of RIF resistance is due to *rpoB* mutation.
- ▶ Molecular DST (hours–days) is far faster than phenotypic DST (weeks), enabling early effective therapy.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Tuberculosis" (definitions of MDR/RR/pre-XDR/XDR-TB, nucleic-acid amplification technology — Xpert MTB/RIF, Xpert Ultra, Truenat, line probe assays, WGS/tNGS, drug-susceptibility testing, resistance-gene targets) and "Antimycobacterial Agents" (*rpoB* / *gyrA*–*gyrB* resistance mechanisms).

- ▶ CDMT 2026 — “Pulmonary Disorders” (essential laboratory tests for *M. tuberculosis*: NAAT-TB and NAAT-R [resistance markers] performance, culture/phenotypic DST timing and characteristics).



Dengue fever with complications

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Dengue is an acute arboviral infection caused by any of four dengue viruses, DENV-1-4, transmitted predominantly by *Aedes aegypti* and, less efficiently, *Aedes albopictus*. Clinical disease ranges from asymptomatic infection or classical “break-bone fever” to **severe dengue**, formerly called dengue hemorrhagic fever/dengue shock syndrome. Complicated dengue is defined clinically by **plasma leakage causing shock or respiratory distress, severe bleeding, or severe organ dysfunction**.

Etiology, transmission and pathogenesis

- ▶ Dengue viruses are **flaviviruses** with four antigenically distinct serotypes; infection with one serotype gives durable homologous protection but not reliable long-term protection against the other serotypes.
- ▶ Transmission is mainly **human-mosquito-human**. The vector breeds close to human habitation in relatively fresh water in jars, vases, discarded containers, coconut husks, old tires and similar collections; biting is typically daytime.
- ▶ Rare non-vector routes include needlestick or mucocutaneous healthcare exposure, vertical transmission, blood products, bone marrow transplantation and solid-organ transplantation.
- ▶ Most primary infections are subclinical. Symptomatic patients develop a **febrile phase**, a possible **critical/plasma-leak phase** around defervescence, and a **recovery phase**.
- ▶ Severe disease is promoted by host and viral factors, especially **immune-mediated enhancement** during heterotypic reinfection. Severe dengue is associated with vascular permeability; Harrison notes a key role for **DENV NS1 protein** in the vascular-leak phenomenon.
- ▶ Risk is higher with secondary infection, some viral variants such as Southeast Asian DENV-2, serotype 2 disease in CDMT, diabetes/obesity, older age and comorbid cardiovascular, pulmonary, renal or cerebrovascular disease.

Clinical phases and warning signs

Phase	Usual timing and features	Exam emphasis
Febrile phase	Incubation is about 4-7 days in Harrison and usually 7-10 days in	May show facial flushing, conjunctival redness, pharyngeal

Phase	Usual timing and features	Exam emphasis
	CMDT. Abrupt high fever, chills, frontal headache, retro-orbital pain, severe myalgia/back pain, arthralgia, anorexia, nausea/vomiting and cutaneous hyperesthesia.	erythema, lymphadenopathy, hepatomegaly, transient macular rash, epistaxis or petechiae.
Critical phase	Often as fever declines, typically around days 3-5; only a subset enters this phase.	Look actively for plasma leak, hemoconcentration, falling platelets, narrow pulse pressure, restlessness, lethargy and shock.
Recovery phase	Reabsorption of extravascular fluid as leak resolves; BP improves and diuresis occurs.	Reduce fluids to avoid overload; patchy pruritic erythematous rash and desquamation may occur; fatigue/depression may persist.

- **Warning signs requiring admission/close observation:** severe abdominal pain, persistent vomiting, clinical fluid accumulation/serosal effusion, mucosal or GI bleeding, lethargy or restlessness, increasing liver size/hepatomegaly, rising hematocrit with thrombocytopenia, postural symptoms or narrowing pulse pressure.
- **Classical uncomplicated dengue** may show a saddle-back fever, trunk-to-extremity maculopapular rash near defervescence, scattered petechiae and a positive tourniquet test.
- **Tourniquet test:** 10 or more new petechiae in 1 square inch after 5 minutes of BP cuff inflation midway between systolic and diastolic pressure suggests microvascular fragility; it is more associated with severe dengue but is not by itself a marker of major bleeding.

Classification and complications

WHO-style category	Key clinical meaning	Typical action
Dengue without warning signs	Fever with dengue symptoms, no leak/bleeding/organ-risk features.	Outpatient care only if reliable hydration, follow-up and warning-sign education are assured.
Dengue with warning signs	Dengue plus warning signs suggesting impending critical phase.	Admit/observe; serial vitals, urine output, hematocrit, platelets and clinical fluid status.
Severe dengue	Presumptive or confirmed dengue plus severe plasma leakage causing shock/respiratory distress, severe bleeding, or severe organ dysfunction.	Emergency triage, monitored setting/ICU, judicious IV fluids, blood products if bleeding, organ support.

- ▶ **Vascular leak/shock:** intravascular volume depletion, hypoalbuminemia, pleural effusion, ascites, narrow pulse pressure, cyanosis, hypothermia, altered consciousness, metabolic acidosis and circulatory collapse. Shock usually lasts **2-3 days** if treated through the critical period.
- ▶ **Bleeding:** petechiae, ecchymoses, epistaxis, palatal/gingival bleeding, GI bleeding and severe hemorrhage; DIC may complicate shock and progressive organ impairment.
- ▶ **Organ dysfunction:** hepatitis and fulminant hepatitis, encephalitis or altered mental status/seizures, myocarditis/arrhythmias, acute kidney injury, ocular disease including iritis, retinal hemorrhage and maculopathy.
- ▶ **Other complications:** pneumonia, bone marrow failure, bacterial superinfection, orchitis, oophoritis, oral bleeding/gingivitis, phrenic neuropathy, Guillain-Barre syndrome, transverse myelitis, cerebral vasculitis, subdural hematoma and acute disseminated encephalomyelitis.
- ▶ **Pregnancy:** infection near term risks hemorrhage in mother and infant; severe dengue increases obstetric complications, cesarean delivery, fetal distress and maternal morbidity.

Investigations and diagnosis

- ▶ Diagnosis is clinical in an epidemic/endemic setting but should be **laboratory confirmed** because dengue mimics malaria, influenza, chikungunya, leptospirosis, scrub typhus, typhoid, rickettsial infections, meningococcemia, Zika, yellow fever and other viral hemorrhagic fevers.
- ▶ **Early illness, first 5 days:** dengue RT-PCR/nucleic acid amplification or **NS1 antigen** detection by ELISA/rapid test. Harrison emphasizes antigen detection and nucleic acid amplification early.
- ▶ **After febrile phase/recovery:** IgM ELISA, paired serology or seroconversion. Early, rapidly rising **IgG from about day 4** suggests secondary infection rather than primary infection.
- ▶ Interpret serology cautiously because flavivirus cross-reactivity occurs after infection with or vaccination for antigenically related viruses such as yellow fever, Zika and Japanese encephalitis.
- ▶ Baseline and serial tests: CBC with hematocrit and platelet count, AST/ALT, bilirubin if jaundice, albumin, electrolytes, urea/creatinine, glucose, PT/INR/aPTT and fibrinogen if bleeding/DIC is suspected, ABG/lactate in shock, urinalysis and pregnancy test where relevant.
- ▶ Bedside severity assessment: pulse pressure, postural BP, capillary refill, temperature, mental status, urine output, hepatomegaly and bleeding. Ultrasound or lateral decubitus CXR can detect pleural effusion/ascites before they are clinically obvious.

Management of dengue with complications

- ▶ There is **no proven specific antiviral therapy** for dengue. Chloroquine, statins and balapiravir have not shown clear benefit; management is supportive and time-critical.
- ▶ **Triage** every suspected case for warning signs and severe dengue. Admit patients with warning signs, comorbid illness, pregnancy, poor oral intake, bleeding, rising hematocrit, rapidly falling platelets or unreliable follow-up. Severe dengue needs monitored care/ICU.

- ▶ **Fever and pain:** use acetaminophen/paracetamol. Avoid aspirin and preferably avoid NSAIDs such as ibuprofen because of gastritis, platelet dysfunction and bleeding risk.
- ▶ **Fluids:** encourage oral fluids when stable; give early IV isotonic crystalloid when warning signs, hemoconcentration, poor intake or shock are present. Titrate to pulse pressure, BP, capillary refill, mental status, urine output, hematocrit trend, bleeding and signs of fluid overload.
- ▶ **Shock:** treat as plasma-leak hypovolemia. Restore intravascular volume promptly but avoid blind over-resuscitation. If shock persists after appropriate volume replacement, use blood products for hemorrhage and vasopressors for ongoing circulatory failure in monitored care.
- ▶ **Bleeding and thrombocytopenia:** platelet count alone does not predict clinically important bleeding. Consider platelet transfusion for active bleeding or severe thrombocytopenia $<10,000/\text{mcL}$; routine prophylactic platelet transfusion in non-bleeding dengue is not useful and may delay platelet recovery.
- ▶ **Recovery phase:** as vascular leak resolves, effusions are reabsorbed and diuresis begins. Reduce or stop IV fluids promptly to prevent pulmonary edema and respiratory distress.
- ▶ Provide organ-specific support: oxygen/ventilation for respiratory distress or ARDS, renal monitoring and dialysis if AKI is severe, correction of hypoglycemia/electrolytes/acidosis, management of encephalitis/seizures, and treatment of bacterial superinfection when clinically suspected.

Prevention and prognosis

- ▶ Prevention depends on **Aedes control**: remove stagnant water and discarded containers, cover water storage, use larvicidal/public-health measures, window screening, long sleeves, repellents and long-lasting insecticides. Emphasize early morning and late afternoon exposure risk.
- ▶ Screen blood transfusions for dengue in endemic settings where feasible; defer donation by acutely febrile or recently infected persons.
- ▶ **Vaccines:** Dengvaxia/CYD-TDV is a live attenuated tetravalent vaccine whose use is limited to persons with prior dengue infection because seronegative vaccinees have increased risk of severe dengue at first natural infection. TAK-003 has shown efficacy against symptomatic and hospitalized dengue in trials, with ongoing serotype-specific and policy considerations.
- ▶ Prognosis is excellent in uncomplicated dengue. Mortality in severe dengue falls sharply with early recognition, monitored fluids and bleeding control; Harrison notes case fatality can be as low as about 1% in experienced tropical centers, while CMDT cites about 2.5% of severe cases overall.
- ▶ Poor prognostic markers: shock, AKI in dengue shock syndrome, acute hepatitis/fulminant hepatitis, DIC, severe bleeding, persistent altered consciousness, metabolic acidosis, pregnancy near term, older age and major comorbid illness.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Natural history of dengue:** x-axis days 0-10; label febrile phase, defervescence, critical/plasma-leak phase, recovery phase, fever curve, platelet fall, hematocrit rise, shock window, fluid reabsorption/diuresis.
- ▶ **Severe dengue triad:** central “Severe dengue” box with three arms labelled plasma leakage -> shock/respiratory distress, severe bleeding -> GI/mucosal/DIC, severe organ dysfunction -> liver/CNS/heart/kidney/eye.

Clinical / Diagnostic significance

- ▶ Dengue is a must-consider diagnosis in acute fever with severe myalgia, retro-orbital pain, rash, leukopenia and thrombocytopenia after residence in or travel to an endemic area.
- ▶ The life-saving clinical point is **not the platelet count alone** but recognition of the critical phase: defervescence plus rising hematocrit, falling platelets, abdominal pain, vomiting, restlessness/lethargy, effusions or narrow pulse pressure.
- ▶ A falling hematocrit in an unstable patient suggests bleeding; a rising hematocrit with worsening perfusion suggests plasma leakage needing fluids.
- ▶ Differentiate from malaria, scrub typhus, leptospirosis and enteric fever in India; coinfection can occur, so a positive dengue test should not end evaluation if the clinical course is atypical.
- ▶ Avoid iatrogenic harm: NSAIDs/aspirin, unnecessary platelet transfusion and continued IV fluids during recovery can worsen outcomes.

High-yield exam pointers

- ▶ Write the **three severe dengue criteria:** severe plasma leakage, severe bleeding, severe organ dysfunction.
- ▶ Mention **warning signs at defervescence;** this is the usual time of deterioration.
- ▶ Pathogenesis keyword: **heterotypic secondary infection/antibody-dependent enhancement** plus **NS1-mediated vascular leak.**
- ▶ Investigations: **NS1/RT-PCR early, IgM/IgG later,** serial CBC hematocrit and platelets, LFT, albumin, renal function, coagulation profile, ultrasound/CXR for effusions.
- ▶ Management is **supportive, fluid-titrated and monitored;** no routine antiviral.
- ▶ Use **acetaminophen,** avoid aspirin/NSAIDs.
- ▶ Do **not** transfuse platelets just because the count is low; consider if bleeding or **<10,000/mcL.**
- ▶ In recovery, stop/reduce fluids because reabsorption of leaked fluid can cause pulmonary edema.
- ▶ Prevention answer must include **Aedes source reduction,** personal protection, blood safety and vaccine caveats.

SOURCE & COVERAGE

Harrison 22e — “Arthropod-Borne and Rodent-Borne Virus Infections”; CMDT 2026 — “Viral & Rickettsial Infections”; Critical Care — “Resuscitation From Circulatory Shock”.



Dengue fever

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Dengue is an acute, self-limiting yet potentially fatal *arthropod-borne flaviviral* illness caused by four antigenically distinct serotypes (DENV-1, -2, -3, -4; genus *Orthoflavivirus*, family *Flaviviridae*) transmitted chiefly by the day-biting *Aedes aegypti* (and *Ae. albopictus*) mosquito. It is the most prevalent arboviral disease of humans (~400 million infections/year, ~100 million clinically apparent), endemic in >100 countries, with Asia bearing ~70% of the global burden. The clinical spectrum ranges from asymptomatic infection and undifferentiated “**break-bone fever**” through a plasma-leakage **critical phase** to **severe dengue** (dengue haemorrhagic fever / dengue shock syndrome), the latter driven largely by **immune-mediated (antibody-dependent) enhancement** on secondary heterotypic infection.

Etiology, Vector and Epidemiology

- ▶ **Agent:** single-stranded positive-sense RNA orthoflavivirus, ~40–60 nm enveloped virion; four serotypes that cross-react serologically but confer only *transient* cross-protection. Lifelong immunity is serotype-specific — **infection with one serotype does NOT protect against the other three**.
- ▶ **Vector:** *Aedes aegypti* (principal) and *Ae. albopictus* (Asian tiger mosquito); anthropophilic, breed in fresh water in domestic containers (jars, tyres, coconut husks), **bite during daylight** (early morning, late afternoon).
- ▶ **Reservoir/cycle:** humans are the main amplifying host in the urban cycle; nonhuman primates maintain a sylvatic cycle.
- ▶ **Transmission:** principally human→mosquito→human; rarely needlestick/mucocutaneous, vertical (peripartum), and via blood transfusion or organ/marrow transplant.
- ▶ **Distribution:** year-round transmission between latitudes ~25°N and 25°S; spread driven by urbanisation, travel and climate. Along with malaria, dengue is one of the two commonest vector-borne diseases and the second commonest cause of febrile illness in returning travellers.

Pathogenesis — Antibody-Dependent Enhancement and Plasma Leakage

- ▶ **Primary infection** is usually subclinical or causes uncomplicated febrile dengue; it generates serotype-specific neutralising antibody (protective) plus *cross-reactive, non-neutralising* antibody whose protection wanes over weeks to months.
- ▶ **Antibody-dependent enhancement (ADE):** on **secondary infection with a different (heterotypic) serotype**, pre-existing non-neutralising antibody binds virus and, via Fc receptors, *enhances* uptake into mononuclear phagocytes → higher viral load and an amplified, dysregulated cytokine response → the central lesion of **increased vascular permeability and plasma leakage**.
- ▶ **NS1 (non-structural protein 1)** has a key, recently recognised role in driving the endothelial vascular-leak phenomenon of severe dengue.
- ▶ **Net effect:** capillary leak → intravascular volume depletion, haemoconcentration, hypoalbuminaemia, serosal effusions; with thrombocytopenia, coagulopathy and (in severe disease) DIC contributing to haemorrhage and shock.
- ▶ **Risk factors for progression to severe dengue:** enhancing non-neutralising antibody (secondary heterotypic infection — *the* major determinant), age (susceptibility falls markedly after 12 years), female sex, particular serotype sequences (DENV-1 then DENV-2 is especially severe), virulent Southeast-Asian DENV-2 variants; and per CMDT, suboptimally controlled type-2 diabetes, obesity, and comorbidity (cardiovascular/renal/pulmonary disease, older age).

Clinical Course and WHO Classification

After an **incubation of ~4–14 days** (typically 4–7 days), symptomatic illness evolves through **three phases**:

- ▶ **Febrile phase (days 1–~5):** abrupt high-grade fever, frontal headache, **retro-orbital pain**, severe myalgia/arthralgia (“break-bone fever”), facial flushing, transient macular rash, conjunctival injection, pharyngeal erythema, lymphadenopathy, hepatomegaly; a **positive tourniquet test** and petechiae may appear.
- ▶ **Critical / plasma-leakage phase (around defervescence, days 3–5, lasting 24–48 h):** the window for **plasma leakage** — pleural effusion, ascites, rising haematocrit with falling platelet count, hypoalbuminaemia, and, if a critical volume is lost, **shock**. Warning signs herald this phase.
- ▶ **Recovery phase:** reabsorption of extravascular fluid, haemodynamic stabilisation, diuresis; a confluent pruritic rash with islands of sparing may desquamate; prolonged fatigue/depression in convalescence.

Feature	WHO 1997 classification	WHO 2009 (revised) classification
Categories	Dengue fever (DF); Dengue haemorrhagic fever (DHF) graded I–IV; Dengue shock syndrome (DSS)	Dengue without warning signs; Dengue with warning signs; Severe dengue

Feature	WHO 1997 classification	WHO 2009 (revised) classification
DHF/severe defined by	Fever + thrombocytopenia + haemorrhage + plasma leakage (DHF); circulatory failure = DSS	Plasma leakage (shock / respiratory distress), severe bleeding, or severe organ involvement
DHF grades	I: fever + constitutional + positive tourniquet test only; II: grade I + spontaneous bleeding; III: circulatory failure (weak rapid pulse, narrow pulse pressure ≤ 20 mmHg, hypotension) = DSS; IV: profound shock, unrecordable BP/pulse = DSS	Stratifies management by warning signs (see below)

- ▶ **Warning signs (2009 WHO):** abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation (ascites/pleural effusion), mucosal bleeding, lethargy/restlessness, tender hepatomegaly (>2 cm), and a rising haematocrit with rapid fall in platelet count.
- ▶ **Severe dengue (Harrison/2009 criteria):** definite/presumptive dengue **plus** (1) plasma leakage causing **shock or respiratory distress**, **or** (2) severe bleeding, **or** (3) severe organ dysfunction (e.g. transaminases markedly raised, impaired consciousness, myocarditis).
- ▶ **Organ involvement:** hepatitis, encephalitis/encephalopathy, myocarditis, acute kidney injury (AKI in shock syndrome carries high mortality), retinal haemorrhage/maculopathy.

Diagnosis and Investigations

- ▶ **Non-specific haematology:** leukopenia (with neutropenia), **thrombocytopenia**, and rising **haematocrit** (haemoconcentration = marker of plasma-leak severity); modestly elevated AST/ALT; normal ESR in most.
- ▶ **Phase-dependent virological/serological testing:**

Test	Useful window	Comment
NS1 antigen (ELISA / rapid test)	Days 1–~5 (febrile)	Early diagnosis; often combined with IgM at point of care
RT-PCR / viral isolation	First ~5 days	Confirms infection, allows serotyping
IgM ELISA	From ~day 4–5 onward	Indicates acute/recent infection
IgG ELISA / paired serology	Convalescence	Early, rapidly rising IgG (~day 4) suggests a secondary infection (primary = late, low-titre IgG)

- ▶ **Tourniquet (Hess) test:** ≥ 10 new petechiae per square inch on the forearm after BP-cuff inflation midway between systolic and diastolic for 5 min — a bedside index of capillary fragility; more often positive in severe dengue.
- ▶ **Imaging:** lateral-decubitus CXR / ultrasound detects pleural effusion and ascites before they are clinically obvious.
- ▶ **Caveat:** serologic **cross-reactivity** with other flaviviruses (Zika, yellow fever, Japanese encephalitis, prior vaccination) confounds IgG/IgM interpretation.
- ▶ **Differential diagnosis:** malaria, chikungunya (more chronic arthritis), Zika, leptospirosis, rickettsial/scrub typhus, typhoid, influenza, other viral haemorrhagic fevers.

Management

- ▶ **No specific antiviral exists** — care is **supportive**, hinging on meticulous fluid management and serial monitoring (vitals, urine output, **haematocrit**, platelets, albumin, AST/ALT).
- ▶ **Antipyretic/analgesic: acetaminophen (paracetamol); avoid aspirin and NSAIDs** (gastritis/bleeding risk, platelet effects).
- ▶ **Fluids:** judicious **isotonic crystalloid** titrated to clinical parameters; escalate to **colloid** and **blood products** in shock per WHO algorithmic protocols. In the recovery phase, anticipate **fluid reabsorption** and avoid overload/pulmonary oedema.
- ▶ **Severe dengue / DSS:** hospitalise, rapid triage, early IV fluids **before** overt shock; vasopressors and blood/component replacement for refractory shock or bleeding; manage AKI, hepatic and CNS complications.
- ▶ **Platelets:** counts do **not** reliably predict bleeding; **platelet transfusion only for severe thrombocytopenia** ($<10,000/\mu\text{L}$) or **active bleeding** — prophylactic transfusion gives no proven benefit and may delay count recovery.
- ▶ **Prognosis:** overall mortality of severe disease $\sim 2.5\%$ and falling with early recognition; at experienced tropical centres CFR may be as low as $\sim 1\%$. Thrombocytopenia, acute hepatitis and AKI in DSS predict poor outcome.

Prevention and Vaccines

- ▶ **Vector control** is the cornerstone: source reduction (eliminate breeding sites), screening, insecticides/repellents (especially early morning and late afternoon), and novel strategies (*Wolbachia*-infected or genetically modified *Aedes*). Screen blood donations in endemic areas.
- ▶ **CYD-TDV (Dengvaxia):** recombinant **live-attenuated tetravalent** vaccine on the **yellow-fever 17D backbone**; 0/6/12-month schedule; $\sim 56\%$ overall efficacy. **Increases risk of severe dengue in seronegative recipients** (“first serologic hit”) → WHO recommends use **only in the previously dengue-seropositive**, with pre-vaccination screening; indicated $\sim 9\text{--}45$ years; not for pregnant/immunosuppressed persons.

- ▶ **TAK-003 (Qdenga)**: live tetravalent, **two doses 3 months apart**; ~62% efficacy against symptomatic and ~83.6% against hospitalised dengue; protective against all four serotypes in seropositive children and DENV-1/-2 in seronegatives (weaker for DENV-3); approved in several European countries.
- ▶ **Newer candidates**: **Butantan-DV** (single-dose tetravalent — prevents DENV-1/-2) and **TV003/TV005** (single-dose) in late-phase evaluation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Triphasic course of dengue (timeline graph)**. X-axis = days of illness (1–10); plot three overlapping curves and label: “**Febrile phase**”, “**Critical / plasma-leakage phase**”, “**Recovery phase**”; **Temperature** curve (high then defervescence at day ~3–5, optional “saddle-back” rise); **Platelet count** (falling, nadir in critical phase); **Haematocrit** (rising in critical phase, falling in recovery); mark the “**Warning-signs / leakage window**” at defervescence, and label complications — **shock, effusions, bleeding**.
- ▶ **Antibody-dependent enhancement (ADE) schematic**. Labels: **Primary DENV infection** → **serotype-specific neutralising antibody (protective)** vs **cross-reactive non-neutralising antibody (waning)**; **Secondary heterotypic DENV** → **antibody–virus complex** → **Fc-receptor uptake into macrophages** → **increased viral load + cytokine surge** → **NS1-mediated capillary leak** → **plasma leakage / DHF–DSS**.

Clinical / Diagnostic significance

- ▶ **Defervescence is the danger period**, not the end of illness — the critical plasma-leak phase begins as fever falls; serial haematocrit + platelet trends are the key bedside guide.
- ▶ A **rising haematocrit with falling platelets** is the earliest objective signal of significant plasma leakage and impending shock.
- ▶ **NS1 antigen** enables diagnosis in the first few febrile days (before antibodies appear); combine with IgM for higher yield.
- ▶ **Secondary heterotypic infection** is the principal driver of severe disease — a vital concept for hyperendemic regions and for the seronegative-vaccination hazard.
- ▶ Recognising **narrow pulse pressure (≤ 20 mmHg)** as early DSS allows fluid resuscitation before profound shock.
- ▶ Avoiding NSAIDs/aspirin and prophylactic platelet transfusion reflects evidence-based, harm-avoiding dengue care.

High-yield exam pointers

- ▶ Four serotypes DENV-1–4; immunity is **serotype-specific**; flavivirus; vector ***Aedes aegypti*, a day-biter**.
- ▶ Triphasic illness: **febrile** → **critical (plasma leak at defervescence)** → **recovery**.

- ▶ **WHO 2009:** dengue *without* warning signs / *with* warning signs / **severe dengue**; WHO 1997: DF, DHF grades I–IV, DSS.
- ▶ **Severe dengue** = dengue + plasma leakage (shock/respiratory distress) OR severe bleeding OR severe organ dysfunction.
- ▶ **Antibody-dependent enhancement on secondary heterotypic infection**; NS1 drives vascular leak.
- ▶ Labs: **leukopenia, thrombocytopenia, rising haematocrit**, raised transaminases; NS1 → RT-PCR → IgM → IgG; **early high IgG = secondary infection**.
- ▶ **Tourniquet test** = ≥ 10 petechiae/inch² after 5-min cuff.
- ▶ Treatment: **supportive + fluids + paracetamol**; **avoid NSAIDs/aspirin**; platelets only if $< 10,000/\mu\text{L}$ or bleeding.
- ▶ Vaccines: **Dengvaxia (CYD-TDV)** — seropositive only, risk in seronegatives; **Qdenga (TAK-003)** — two-dose tetravalent.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Arthropod-Borne and Rodent-Borne Virus Infections” (Flavivirids: Dengue and Severe Dengue; Viral Haemorrhagic Fever section) — pathogenesis, antibody-dependent enhancement, NS1, three-phase course, tourniquet-test definition, severe-dengue criteria, vaccines (CYD-TDV/Dengvaxia, TAK-003/Qdenga, Butantan-DV, TV003/TV005).
- ▶ **CMDT 2026** — “Viral & Rickettsial Infections: Dengue” — epidemiology, clinical findings, laboratory diagnosis (NS1/IgM/IgG/PCR), WHO 1997 vs 2009 classification, supportive management, platelet-transfusion threshold, prevention and vaccines.
- ▶ **Coverage note:** The explicit **DHF grading I–IV** table is the standard **WHO 1997** classification — universally accepted internal medicine but cited by name rather than tabulated verbatim in Harrison 22e (which adopts the 2009 scheme) / CMDT 2026; the consolidated **2009 warning-signs list** is standard WHO and partially enumerated in CMDT. Incubation period is given as ~4–7 days (Harrison) and 7–10 days (CMDT); both are within the accepted 4–14-day range.



Diagnosis and Laboratory Monitoring of HIV Infection

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Diagnosis of HIV infection rests on demonstrating either **antibodies to HIV and/or the p24 antigen** (serologic/screening tests) or **direct detection of the virus or its components** (nucleic acid/antigen tests). Laboratory monitoring then quantifies the **degree of immune**

damage (CD4+ T-cell count) and the **magnitude of viral replication** (plasma HIV RNA). Together these tools establish the diagnosis, stage the disease, time opportunistic-infection (OI) prophylaxis, and gauge the response to antiretroviral therapy (ART). The CDC recommends that HIV screening be offered as a routine part of health care.

The diagnostic window & basis of testing

- ▶ Antibodies to HIV generally appear in the circulation **3–12 weeks** after infection; with modern fourth-generation tests, antibody/antigen is detectable in ~99% within **6 weeks**, median ~2 weeks.
- ▶ The **window period** (interval from infection to detectability) has shortened progressively with assay generation: **22 days** with antibody testing → **16 days** with p24 antigen testing → **12 days** with nucleic acid testing (NAT).
- ▶ Standard screening detects **antibody and/or p24 antigen**; direct tests detect HIV RNA, proviral DNA, or p24 antigen.
- ▶ The screening enzyme immunoassay (ELISA/EIA) has sensitivity >99.5% but imperfect specificity; in low-risk populations (e.g., volunteer blood donors) as few as ~10% of EIA-positives are truly infected, so every reactive screen needs confirmation.

Screening & confirmatory tests — the CDC algorithm

- ▶ **Step 1 (initial/screening):** a fourth-generation HIV-1/2 antigen-antibody combination immunoassay — detects antibodies to HIV-1 and HIV-2 *plus* HIV-1 **p24 antigen** (closes much of the early window). Scored highly-reactive, non-reactive, or indeterminate.
- ▶ **Step 2 (confirmation/differentiation):** a reactive screen → **HIV-1/HIV-2 antibody differentiation immunoassay** (e.g., *Bio-Rad Geenius*), which both confirms and distinguishes HIV-1 from HIV-2.
- ▶ **Step 3 (NAT for discordant results):** if the differentiation assay is **negative or indeterminate** → **HIV-1 RNA (NAT)**. A **positive NAT with negative antibody** = **acute HIV-1 infection**; a negative NAT in this setting indicates a **false-positive** screen.
- ▶ The **Western blot** is **no longer used** for confirmation. A positive fourth-generation assay confirmed by a second HIV-1– or HIV-2–specific immunoassay *or* a plasma HIV RNA level is adequate for diagnosis.
- ▶ **Point-of-care/rapid tests** (blood or oral fluid) give results in 10–20 min, need minimal training, and have sensitivity/specificity >99% for chronic infection (lower in acute infection); a reactive rapid test must be confirmed by the standard algorithm. A home oral-swab test (*OraQuick*) is FDA-approved.

Test	What it detects	Role in algorithm
4th-gen Ag/Ab combination immunoassay	HIV-1 & HIV-2 antibody + HIV-1 p24 antigen	Initial screen (sensitivity >99.5%)
HIV-1/HIV-2 antibody differentiation immunoassay (Geenius)	Distinguishes HIV-1 vs HIV-2 antibody	Confirmation after reactive screen
HIV-1 RNA (NAT)	Plasma viral RNA	Resolves screen+ / differentiation- → acute HIV
Rapid antibody test (blood/oral fluid)	HIV-1/HIV-2 antibody	Field/POC screen; confirm if reactive

Direct detection of virus & its components

- ▶ **p24 antigen capture assay** — EIA detecting HIV core protein p24; ~30% of untreated patients have detectable free p24, rising to ~50% after weak-acid dissociation of antigen-antibody complexes (down to ~15 pg/mL). High early (pre-seroconversion) levels make it useful in suspected **acute HIV syndrome**; now incorporated into the 4th-generation screen.
- ▶ **Nucleic acid amplification tests (quantitative HIV RNA)** — provide both diagnosis (in misleading-serology settings) and prognosis/treatment monitoring:

Assay	Method	Lower reliable limit
RT-PCR	Reverse transcription + PCR amplification of HIV-1 RNA	20 copies/mL
bDNA (branched DNA)	Signal amplification of particle-associated RNA	50 copies/mL
NASBA	Isothermal amplification	80 copies/mL
TMA	Transcription-mediated amplification (T7 polymerase)	100 copies/mL

- ▶ **DNA PCR amplifies proviral DNA** from peripheral blood mononuclear cells (sensitive to 1 copy/10,000–100,000 cells) — valuable for **neonatal diagnosis** (maternal antibody crosses placenta, making serology unreliable) and in **hypogammaglobulinemia/advanced disease**.
- ▶ **“Gold standard” for diagnosis = a positive EIA together with a positive HIV RNA assay.** Because high sensitivity costs specificity, NAT should be used for diagnosis only when standard serology fails to give a definitive answer.

Special / difficult diagnostic situations

- ▶ **False-positive EIA** — anti-class II (HLA) antibodies (post-pregnancy, transfusion, transplant), autoantibodies (collagen-vascular/autoimmune disease), hepatic disease, recent **influenza vaccination**, acute viral infections, and prior HIV-vaccine receipt; confirm with a specific immunoassay or HIV RNA.

- ▶ **Acute (primary) HIV** — antibody may be absent; rely on **p24 antigen** and/or **HIV RNA** (RNA is typically very high). Caution: low-level viremia **<1000 copies/mL** with negative serology may be a false-positive RNA.
- ▶ **Recent vs established infection** — a “**detuned**” (less-sensitive) EIA scores positive only in established infection, helping date seroconversion for surveillance.
- ▶ **Reversion to negative EIA** can occur in patients treated very early; it does not mean cure.

Laboratory monitoring — CD4+ T-cell count

- ▶ The **CD4+ T-cell count** is the **best single indicator of immediate immunologic competence** and the basis for staging and OI prophylaxis.
- ▶ **Thresholds:** CD4 **<200/μL** → high risk of *Pneumocystis jirovecii* pneumonia → **start PCP prophylaxis**; CD4 **<50/μL** → risk of CMV, *Mycobacterium avium* complex (MAC), and *Toxoplasma* → **MAC primary prophylaxis** (unless ART is started immediately).
- ▶ **CDC staging (age ≥6 yr to adult):** Stage 1 = CD4 **≥500/μL** (≥26%); Stage 2 = **200–499/μL** (14–25%); Stage 3 (AIDS) = **<200/μL** (<14%) *or* an AIDS-defining OI. **CD4% of 15 ≈ CD4 count of 200/μL.**
- ▶ **Frequency:** at diagnosis, then **every 3–6 months** for the first 2 years; more often if declining. After ≥2 years on ART with HIV RNA persistently **<50 copies/mL** and CD4 **300–500/μL** → annually; if CD4 **>500/μL** monitoring is **optional**.
- ▶ **CD4 can mislead:** falsely high in **HTLV-1 co-infection**; use the **CD4 percentage** in hypersplenism, post-splenectomy, or marrow-suppressing therapy (e.g., IFN-α). Counts also fall transiently with intercurrent illness/vaccination and show diurnal/inter-laboratory variation — *trend matters more than a single value.*

Laboratory monitoring — HIV RNA, resistance & tropism

- ▶ **Plasma HIV RNA (viral load)** is the most accurate indicator of viral replication and the **response to ART**. Measure at diagnosis; after starting ART, monitor about **every 4 weeks** until a new steady state, then **every 3–6 months**.
- ▶ **Goal of effective ART:** HIV RNA falls to **<50 copies/mL within ~6 months**. Commercial assays reliably detect to ~20–50 copies/mL; avoid the term “undetectable” (virus is not zero). Never base decisions on a single value, as RNA fluctuates with immune activation, intercurrent infection, or immunization.
- ▶ **HIV drug-resistance testing** — **genotypic** (sequence vs known resistance profiles) or **phenotypic** (growth of patient virus across drug concentrations). Recommended **at initial diagnosis** and at **ART initiation**, and in **virologic failure**; requires HIV-1 RNA **>500–1000 copies/mL** for an accurate result.

- ▶ **Co-receptor tropism assay** (e.g., *Trofile*) before using the CCR5 antagonist **maraviroc**, which works only against **CCR5-tropic** virus (early disease tends CCR5-tropic, shifting to CXCR4 later).
- ▶ **Other markers** — hs-CRP, IL-6, D-dimer, and sCD14 correlate with all-cause mortality but are not used routinely.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **CDC diagnostic algorithm (flowchart)**: Box 1 “HIV-1/2 antigen/antibody combination immunoassay” → if **non-reactive** = “Negative (consider acute HIV → NAT if recent exposure)”; if **reactive** → Box 2 “HIV-1/HIV-2 antibody differentiation immunoassay” with three outputs — “HIV-1 antibodies +”, “HIV-2 antibodies +”, “**indeterminate/negative**”; the indeterminate/negative arm → Box 3 “HIV-1 NAT” → “NAT + = **acute HIV-1 infection**” / “NAT – = **HIV negative (false-positive screen)**”. Label arrows +/–.
- ▶ **CD4 vs opportunistic-disease graph**: Y-axis “**CD4 count (cells/μL)**” with marked lines at 500, 200, 50; plot disease onset bands — *herpes zoster* / *oral candidiasis* (~300–500), **PCP** / **Kaposi sarcoma** (≤200), **CMV retinitis** / **MAC** / **CNS lymphoma** / **cryptococcosis** (≤50). Title: *Relationship between CD4 count and opportunistic infections*.

Clinical / Diagnostic significance

- ▶ A **single reactive screen never diagnoses HIV** — the differentiation assay ($\pm$ NAT) is mandatory; this avoids labelling false-positives.
- ▶ The **fourth-generation Ag/Ab test + NAT** strategy diagnoses **acute HIV** that older antibody-only tests miss — critical for interrupting onward transmission.
- ▶ **CD4 count drives prophylaxis** (<200 → PCP; <50 → MAC/Toxo/CMV) and defines **AIDS** (Stage 3).
- ▶ **Viral load** confirms ART efficacy (target <50 copies/mL) and, with persistent suppression, supports **U=U** (untransmittable) and reduced monitoring frequency.
- ▶ **Resistance + tropism testing** individualises the regimen and is prerequisite for CCR5 antagonists.

High-yield exam pointers

- ▶ **Initial test** = 4th-generation HIV-1/2 antigen/antibody combination immunoassay (antibody + p24 antigen); EIA sensitivity >99.5%.
- ▶ **Confirmation** = HIV-1/HIV-2 antibody differentiation immunoassay (Genieus); Western blot is obsolete.
- ▶ **Discordant** (screen+, differentiation–) → HIV-1 NAT; NAT+ antibody– = acute HIV.

- ▶ **Window period:** antibody 22 d → p24 antigen 16 d → NAT 12 d.
- ▶ **Gold standard for diagnosis** = positive EIA + positive HIV RNA.
- ▶ CD4 <200/ μ L → PCP prophylaxis; <50/ μ L → MAC prophylaxis; CD4% 15 $\approx$ 200/ μ L.
- ▶ **CDC Stage 3 (AIDS):** CD4 <200/ μ L (or <14%) or an AIDS-defining illness.
- ▶ **Viral load** <50 copies/mL by 6 months = effective ART; monitor every 3–6 months; never act on a single value.
- ▶ **Resistance testing** needs HIV RNA >500–1000 copies/mL; tropism (Trofile) before maraviroc.
- ▶ **DNA PCR** for neonatal diagnosis (passive maternal antibody confounds serology).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Human Immunodeficiency Virus Disease: AIDS and Related Disorders” (diagnosis algorithm, window periods, p24 antigen and HIV RNA/DNA assays, CD4 and viral-load monitoring, resistance and tropism testing, CDC staging Tables 208-1/208-2/208-8).
- ▶ **CMDT 2026** — “HIV Infection & AIDS” (current fourth-generation Ag/Ab → differentiation → NAT algorithm, rapid/home tests, Table 36-2 commonly ordered tests, CD4-count interpretation and OI thresholds).

Coverage note: Both sources describe the U.S. CDC laboratory algorithm. The Indian NACO / WHO “three sequential rapid-test” (Strategy III) diagnostic algorithm used in resource-limited programmatic settings is standard practice but is not detailed in this corpus and has not been elaborated here.



Diagnosis and Management of Falciparum Malaria

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Malaria is a protozoan infection transmitted by the bite of an infected female *Anopheles* mosquito; *Plasmodium falciparum* is the species responsible for nearly all malaria deaths. It is distinguished from the other human plasmodia by its ability to invade red cells of **all ages** (producing very high parasitaemias) and by **cytoadherence and sequestration** of parasitised erythrocytes in vital organs, which underlies the life-threatening complications. Falciparum malaria must never be a clinical diagnosis alone — it requires parasitological confirmation — and severe disease is a medical emergency demanding immediate parenteral artesunate.

Pathophysiology relevant to diagnosis and severity

- ▶ After hepatic schizogony, merozoites invade RBCs and multiply 6- to 20-fold every 48 h; symptoms begin once densities reach $\sim$ 50/ μ L.

- ▶ *P. falciparum*–infected RBCs develop surface “knobs” expressing the variant adhesin **PfEMP1**, which mediates **cytoadherence** to endothelial receptors — **ICAM-1** and **endothelial protein C receptor (EPCR)** in the brain, **VAR2CSA/chondroitin sulfate A** in the placenta, and **CD36** in most other organs.
- ▶ **Rosetting** (binding to uninfected RBCs) and **agglutination** add to microvascular obstruction → tissue hypoxia and lactic acidosis.
- ▶ Because mature forms sequester, **only young ring forms circulate** in peripheral blood; peripheral parasitaemia therefore *underestimates* the true parasite burden — a key diagnostic caveat.

Clinical features and recognition of severe disease

- ▶ **Uncomplicated malaria:** non-specific prodrome (malaise, headache, fatigue, myalgia, abdominal discomfort) followed by fever; classic periodic paroxysms are *unusual* in falciparum. Few signs other than fever, mild anaemia, jaundice and splenomegaly. **Thrombocytopenia is usual** — a normal platelet count should question the diagnosis. There is no rash.
- ▶ Generalised **seizures** are specifically associated with falciparum malaria and may herald cerebral malaria.
- ▶ **Severe falciparum malaria** is defined by vital-organ dysfunction or parasitaemia >2% in a non-immune patient. Uncomplicated disease, promptly treated, has mortality <0.1%; once severe features appear, mortality rises steeply.

WHO criterion (severe falciparum malaria)	Threshold
Cerebral malaria (unarousable coma)	GCS <11, or Blantyre Coma Score <3; coma >30 min post-convulsion
Severe anaemia	Hb <5 g/dL (Hct <15%) with parasitaemia >10,000/μL
Acidosis	pH <7.25, HCO ₃ ⁻ <15 mmol/L, base deficit >8, or lactate ≥5 mmol/L
Hypoglycaemia	Plasma glucose <2.2 mmol/L (<40 mg/dL)
Acute kidney injury	Creatinine >265 μmol/L (>3 mg/dL)
Pulmonary oedema / ARDS	SpO ₂ <92% on air, RR >30, non-cardiogenic oedema
Shock	SBP <80 mmHg (adults) with impaired perfusion
Hyperparasitaemia	>5% non-immune (>10% any patient)
Bleeding/DIC, ≥2 convulsions/24 h, haemoglobinuria, jaundice (bilirubin >3 mg/dL with parasitaemia >100,000/μL), prostration	—

- ▶ **Poor-prognosis markers:** hyperlactataemia, acidotic (“respiratory distress”) breathing, deep coma, repeated convulsions, anuria, hypoglycaemia, >20% of parasites being pigment-containing

trophozoites/schizonts, or pigment in >5% of neutrophils. Concomitant bacteraemia (notably non-typhoidal *Salmonella*) complicates ~6% of children and adults with >20% parasitaemia.

Diagnosis

- ▶ **Demonstration of the parasite (gold standard):** thick and thin Giemsa-stained smears (Giemsa at pH 7.2; Field's, Wright's or Leishman's acceptable), examined immediately.
 - *Thick film* — unfixed, lyses RBCs and **concentrates parasites 40–100×**; high sensitivity (~0.001% parasitaemia); count asexual parasites per 200 WBC (assume WBC 8000/ μ L $\rightarrow$ parasites/ μ L = count $\times$ 40).
 - *Thin film* — methanol-fixed; allows **species identification** and quantification (parasitised RBC per 1000 RBC); in severe disease, assess proportion of mature forms and pigment-laden neutrophils.
 - Falciparum hallmarks: predominance of small **ring forms**, multiply-infected cells, appliqué/accolé forms, **banana-shaped gametocytes**, **Maurer's clefts**, and high parasite density.
 - A single negative smear does not exclude malaria — **repeat 12-hourly over 2–3 days** before excluding the diagnosis.
- ▶ **Rapid diagnostic tests (RDTs):** immunochromatographic detection of PfHRP2 (falciparum-specific), parasite LDH (pLDH) or aldolase.
 - Useful where reliable microscopy is unavailable; some carry a pan-malaria/vivax band to distinguish species.
 - Limitations: do **not quantify** parasitaemia; PfHRP2 **stays positive for weeks** after cure (a problem in high transmission, but an advantage when diagnosing severe malaria in a partly treated patient with negative film); false negatives from **pfhrp2/3 gene deletions** (notably the Horn of Africa).
- ▶ **PCR/molecular:** most sensitive for low-density and mixed infections and for speciation; used in reference labs — too sensitive for routine primary diagnosis in endemic areas. **Serology has no role** in acute illness.
- ▶ **Supportive laboratory findings:** normochromic normocytic anaemia, thrombocytopenia, normal/low WBC; in severe disease — metabolic acidosis, hypoglycaemia, hyponatraemia, elevated lactate, urea, creatinine, bilirubin and transaminases.

Treatment of uncomplicated falciparum malaria

- ▶ **WHO first-line = Artemisinin-based Combination Therapy (ACT)** — a fast-acting artemisinin derivative (artesunate/artemether/dihydroartemisinin) plus a slowly eliminated partner drug, given for **3 days**. Six WHO-recommended ACTs:

ACT regimen	Note
Artemether-lumefantrine (Coartem)	Most widely used; preferred in 1st-trimester pregnancy; take with fat/food (1.5/9 mg/kg bd × 3 days)
Artesunate-amodiaquine	First-line in much of Africa
Artesunate-mefloquine	SE Asia, South America
Dihydroartemisinin-piperaquine	Longest post-treatment prophylaxis (piperaquine t _{1/2} ~3 wk)
Artesunate-sulfadoxine-pyrimethamine	First-line in some countries
Artesunate-pyronaridine	Most recently approved

- ▶ Add a **single low dose of primaquine 0.25 mg base/kg** as a *gametocytocide* (to block transmission) in low-transmission/elimination settings — safe even in G6PD deficiency; **not** in pregnancy/infants.
- ▶ **Atovaquone-proguanil** (20/8 mg/kg/day × 3 days, with food) is an effective alternative for imported/traveller malaria.
- ▶ **Second-line / no ACT available:** oral **quinine 10 mg salt/kg tds × 7 days plus doxycycline** (3 mg/kg/day; avoid <8 yr and pregnancy) **or clindamycin** (10 mg/kg bd).
- ▶ Watch for vomiting within 1 h of an oral dose → repeat the dose; treat fever with paracetamol to reduce vomiting. Confirm parasite clearance with daily counts; failure to clear by day 7 → switch to a different ACT.

Treatment of severe falciparum malaria

- ▶ **IV artesunate is the drug of choice everywhere** — large RCTs showed mortality reduction of 35% in Asian adults/children (SEAQUAMAT) and 22.5% in African children (AQUAMAT) versus quinine. It is FDA-approved, simple, safe, needs no dose adjustment for hepatic/renal failure, and is given in pregnancy in all trimesters.
 - **Dose: 2.4 mg/kg IV at 0, 12 and 24 h, then once daily;** children <20 kg get **3 mg/kg per dose**. Continue parenteral therapy ≥24 h, then complete a **full 3-day oral ACT** once the patient can swallow (avoid mefloquine follow-on — post-malaria neurological syndrome).
 - **Pre-referral rectal artesunate** reduces mortality in rural children who cannot reach parenteral care.
- ▶ **Alternatives if artesunate unavailable:** IM **artemether** 3.2 mg/kg stat then 1.6 mg/kg/day; or **quinine dihydrochloride** 20 mg salt/kg loading over 4 h, then 10 mg salt/kg over 2–8 h every 8 h (rate-controlled infusion; risk of hypotension and hypoglycaemia; cardiac monitoring; reduce maintenance dose by 30–50% if renal failure persists >48 h — never the loading dose). In confirmed artemisinin-resistance areas, give **artesunate + quinine together**.

- ▶ **Supportive / intensive care** (severe malaria = ICU-level care):
 - **Fluids:** cautious — the line between under- and over-hydration is thin; **fluid boluses are dangerous** in severe malaria (unlike sepsis) and precipitate pulmonary oedema.
 - **Hypoglycaemia:** monitor glucose 4–6 hourly; treat with 20% dextrose 2 mL/kg over 10 min then 10% dextrose infusion; keep glucose >4 mmol/L.
 - **Seizures:** IV/rectal benzodiazepines; **levetiracetam** is the preferred anticonvulsant; avoid prophylactic high-dose phenobarbital (20 mg/kg) without ventilatory support (respiratory arrest).
 - **Anaemia:** transfuse if **Hct <20%** (threshold ~15% in high-transmission settings); fresh whole blood/packed cells slowly.
 - **AKI / severe acidosis:** early **haemofiltration or haemodialysis** (superior to peritoneal dialysis).
 - **Sepsis cover:** add broad-spectrum antibiotics (covering non-typhoidal *Salmonella*) in children and in adults with >20% parasitaemia or unexplained deterioration; take blood cultures.
 - **Exchange transfusion** is sometimes used for very high parasitaemia (>5–10%) but benefit is unproven.
 - **Ineffective/harmful adjuncts (do NOT use):** corticosteroids, mannitol, heparin, dextran, urea, desferrioxamine, anti-TNF- α , large fluid/albumin boluses.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Peripheral smear of P. falciparum (thin film): label — delicate ring/trophozoite, appliqué (accolé) form, double-chromatin ring, multiply-infected RBC, Maurer's clefts, banana-shaped (crescentic) gametocyte, pigment in neutrophil*.*
- ▶ **Pathogenesis of sequestration:** label — *infected RBC with knobs, PfEMP1 adhesin, endothelial receptors (ICAM-1/EPCR in brain, CD36, VAR2CSA in placenta), cytoadherence to venular endothelium, rosetting with uninfected RBCs, microvascular obstruction → coma/lactic acidosis.*

Clinical / Diagnostic significance

- ▶ **Speed saves lives:** start parenteral artesunate immediately in any patient with severe features; do not wait for full work-up.
- ▶ Cerebral malaria is a diffuse symmetrical encephalopathy (no focal signs, no meningism); retinal whitening and pale-centred haemorrhages on fundoscopy support the diagnosis. Death rates ~20% (adults) and ~15% (children) even with treatment.

- ▶ **Blackwater fever** — massive intravascular haemolysis with haemoglobinuria — and **delayed post-artesunate haemolysis** (1–3 weeks after clearing hyperparasitaemia, from synchronous loss of “pitted” once-parasitised cells) require monitoring of Hb after discharge.
- ▶ **Pregnancy**: falciparum causes placental sequestration, low birth weight and severe maternal disease (hypoglycaemia, pulmonary oedema) — treat with IV artesunate in all trimesters.
- ▶ **Resistance surveillance** uses molecular markers: **pfkelch13** (artemisinin), **pfcr1** (chloroquine), **pfmdr1** (mefloquine), **pfpm2** amplification (piperaquine).

High-yield exam pointers

- ▶ Falciparum invades RBCs of **all ages** → high parasitaemia; sequestration means **only rings** seen peripherally — count underestimates true burden.
- ▶ **Thick film** = most sensitive (concentrates 40–100×, detect & quantify); **thin film** = species ID; **Giemsa at pH 7.2** is the preferred stain.
- ▶ **RDTs** detect **PfHRP2 / pLDH / aldolase**; PfHRP2 stays positive weeks after cure; beware **pfhrp2/3 deletions** causing false negatives.
- ▶ Severe disease defined by WHO criteria — memorise coma (GCS <11/Blantyre <3), lactate ≥5, glucose <2.2 mmol/L, creatinine >3 mg/dL, Hb <5 g/dL, parasitaemia >5–10%.
- ▶ **IV artesunate 2.4 mg/kg at 0, 12, 24 h then daily** is first-line for severe malaria everywhere (SEAQUAMAT 35%, AQUAMAT 22.5% mortality reduction vs quinine).
- ▶ **Avoid fluid boluses** in severe malaria; manage hypoglycaemia, seizures (levetiracetam), AKI (early dialysis) and add antibiotics for possible bacteraemia.
- ▶ **ACT × 3 days** is first-line for uncomplicated falciparum; add **single-dose primaquine 0.25 mg/kg** as gametocytocide (safe in G6PD deficiency).
- ▶ A **normal platelet count** argues against falciparum malaria; malaria causes **no rash**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Malaria” (Ashley & White): pathophysiology, severe-malaria criteria (Tables 231-2/231-3), diagnostic methods (Table 231-5), treatment regimens (Tables 231-6/231-7), artesunate dosing and supportive care.
- ▶ **CMDT 2026** — “Protozoal & Helminthic Infections” (malaria section, Tables 40-2/40-3): current WHO ACT list, IV artesunate as FDA-approved standard of care, exchange-transfusion caveat, drug-specific notes.

Coverage note: The corpus covers this topic comprehensively; no significant gaps. Trial eponyms (SEAQUAMAT/AQUAMAT) are universally accepted designations for the artesunate-versus-quinine mortality data quoted verbatim from Harrison.



Diagnosis and treatment of Brucellosis

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Brucellosis is a bacterial **zoonosis** transmitted directly or indirectly to humans from infected animals, chiefly domesticated ruminants and swine. It is colloquially called **undulant fever** because of its remittent character. Although it usually presents as an acute febrile illness, its manifestations vary widely and definitive diagnostic signs are often absent; the clinical impression must therefore be confirmed by **bacteriologic and/or serologic tests**. The causative organisms are small, gram-negative, unencapsulated, nonsporulating **coccobacilli** of the genus *Brucella* that behave *in vivo* as **facultative intracellular** parasites of macrophages, explaining the chronicity, relapses and the need for prolonged combination therapy.

Aetiology & relevant microbiology

- *Brucella melitensis* — from **sheep, goats and camels**; the commonest cause of symptomatic human disease; tends to be **acute and aggressive**.
- *B. abortus* — from **cattle/buffalo**; often **insidious onset** and more likely to become chronic.
- *B. suis* — from **swine**; characteristically causes **focal abscesses**. *B. canis* — from **dogs**; generally milder but can cause serious disease such as endocarditis.
- Organisms grow aerobically on peptone-based medium at 37°C; growth of some types is improved by supplementary CO₂. They are killed by **boiling and pasteurisation** but resist freezing and drying — their resistance to drying renders them stable as an **aerosol**, facilitating airborne and laboratory transmission. They survive up to **2 months in soft cheeses** made from goat/sheep milk.
- **Routes:** ingestion (unpasteurised dairy, especially **soft cheeses**, milk, ice-cream), inhalation, and mucosal/percutaneous exposure. **Occupational risk:** farmers, shepherds, goatherds, veterinarians, abattoir and meat-plant workers, and **microbiology laboratory** staff. Accidental inoculation of **live vaccine strains** (*B. abortus* S19, RB51; *B. melitensis* Rev 1) can cause disease. *B. melitensis* and *B. suis* are recognised **bioterrorism** agents.

Clinical clues that prompt the diagnosis

- **Fever** is almost invariable, with profuse **night sweats**; untreated, it shows an **undulating** pattern persisting for weeks before an afebrile remission that may be followed by **relapse**. Constitutional features: apathy, fatigue, anorexia, weight loss, myalgia, headache, chills.
- **Musculoskeletal** symptoms/signs accompany the fever in about **half** of patients — a feature (along with the undulant pattern) that historically distinguished brucellosis from typhoid and malaria.
- Three recognisable patterns: (1) a **typhoid-like** febrile illness but less severe; (2) **fever with acute monoarthritis** of the hip or knee in a **young child**; (3) **long-lasting fever with low-back or hip pain in an older person** (especially men).

- ▶ A history of **travel to/residence in an endemic area**, unpasteurised milk-product consumption, animal contact, lab work, or **similar illness in the family** (documented in almost 50% of cases) is a strong pointer. Incubation period ranges from **1 week to several months**.
- ▶ **Focal involvement** (present in the majority): osteoarticular ~40% (sacroiliitis, spondylitis of **lumbar/low-thoracic** vertebrae, septic arthritis of knee/hip/shoulder/sternoclavicular joints); hepatosplenomegaly (~one-quarter); lymphadenopathy (10–20%); dry cough (~one-quarter); **epididymo-orchitis** (up to 10% of men); neurobrucellosis (depression, lethargy, **lymphocytic meningoencephalitis**); and **endocarditis** in ~1% (most often the **aortic valve**, the leading cause of brucellosis-related death).

Diagnostic approach

- ▶ **Non-specific labs**: routine biochemistry usually normal (hepatic enzymes/bilirubin may rise); peripheral leukocyte count **normal or low with relative lymphocytosis**; mild anaemia; thrombocytopenia and even DIC may occur; **ESR and CRP are often normal**. CSF/joint fluid shows **lymphocytosis with low glucose**; CSF **adenosine deaminase may be raised** and cannot distinguish from tubercular meningitis. Tissue biopsy may show **non-caseating granulomas without acid-fast bacilli**.
- ▶ **Culture (definitive)**: isolation from **blood, bone marrow, CSF, joint fluid or tissue** confirms the diagnosis; success in **50–70%** of cases. Automated systems (e.g., Bactec) usually flag positive **within 7 days**. The **laboratory must be alerted** — cultures need handling under containment for dangerous pathogens, and *Brucella* may be **misidentified** as *Agrobacterium*, *Ochrobactrum* or *Psychrobacter* (*Moraxella*) *phenylpyruvicus*. **MALDI-TOF MS** aids identification in well-resourced labs (note: *Ochrobactrum* is now reported as a *Brucella* subspecies, which can cause clinically important confusion).
- ▶ **Serology (often the only positive finding)**: IgM appears early, followed by IgG and IgA; all are active in **agglutination tests** (tube/plate/microagglutination — the mainstay). As agglutinins decline, antibody is still detected by **complement-fixation, Coombs antiglobulin and ELISA**. **Titre interpretation**: in endemic areas / occupational exposure, **1:320–1:640 or higher** is diagnostic; in **non-endemic** areas $\geq 1:160$ is significant; repeat at **2–4 weeks** to demonstrate a **rising titre**. **Rose Bengal test** is used for screening. **Cross-reactions** occur with *Yersinia enterocolitica* O:9, *E. coli* O157, *Francisella tularensis*, *Salmonella* group N, *Stenotrophomonas maltophilia* and *Vibrio cholerae*. **Rough strains* (*B. canis*, *B. ovis*) *give false-negative smooth-antigen serology*; *vaccine strain RB51 elicits no antibody** to smooth antigens.
- ▶ **PCR / NAAT**: more sensitive and quicker than culture and without the biohazard; targets include the **rrs-rrl (16S–23S) spacer, outer-membrane protein genes, IS711 and BCSP31**. False-negatives occur, and the significance of **prolonged post-treatment PCR positivity** is uncertain.

Brucellar spondylitis vs tuberculous spine (Table 174-1)

Feature	Brucellosis	Tuberculosis
Site	Lumbar and others	Dorsolumbar
Vertebrae	Multiple or contiguous	Contiguous
Diskitis	Late	Early
Vertebral body	Intact until late	Morphology lost early
Canal compression	Rare	Common
Osteophyte	Anterolateral (*parrot-beak*)	Unusual
Deformity	Wedging uncommon	Anterior wedge, gibbus
Psoas abscess	Rare	More likely

Tuberculosis is the single most important differential, since several antibrucella drugs (rifampin, aminoglycosides, fluoroquinolones) also treat TB — so TB must be excluded or a full antituberculous regimen used, to avoid masking TB or breeding resistance with rifampin monotherapy.

Treatment

- **Principles:** the aims are to **relieve current symptoms and prevent relapse**. Monotherapy (early streptomycin or tetracycline) caused frequent relapse, so **≥2 agents** are mandatory. Many drugs that look sensitive *in vitro* (e.g., β -lactams) are **therapeutically ineffective**, partly because of the **low intravacuolar pH**. **Acute non-focal disease (<1–2 months): 6 weeks** of **≥2 agents**; **complex/focal disease: ≥3 months**. **Adherence is critical** — poor adherence, not resistance, underlies almost all apparent failures (though rising TMP-SMX resistance is reported).

Setting	Regimen	Duration	Relapse
Gold standard, adult acute	Streptomycin 0.75–1 g IM daily + doxycycline 100 mg BD	Streptomycin 14–21 d; doxycycline 6 wk	5–10%
WHO / national alternative	Rifampin 600–900 mg/day + doxycycline 100 mg BD	6 weeks	~10% (trial); >20% non-trial*
Aminoglycoside substitute	Gentamicin 5–6 mg/kg/day in place of streptomycin (US/UK guidelines)	1–2 weeks	— (short courses fail)
Children / pregnant women (avoid tetracyclines)	High-dose TMP-SMX (2–3 standard tablets BD in adults, weight-based)	6 weeks	—

Setting	Regimen	Duration	Relapse
Complicated / poor adherence	Triple therapy: doxycycline + rifampin + initial aminoglycoside	≥3 months	lower
Neurobrucellosis	Ceftriaxone added to a standard regimen	3–6 months	—
Endocarditis	≥3 drugs — aminoglycoside + tetracycline + rifampin (many add ceftriaxone)	prolonged	—

\Rifampin lowers doxycycline levels and increases its clearance, partly explaining the higher non-trial relapse rate.*

- **Fluoroquinolones** show good *in vitro* activity and leukocyte penetration but **disappointing monotherapy** results; **ofloxacin or ciprofloxacin + rifampin for 6 weeks** is a possible alternative. A major meta-analysis and the *Ioannina Recommendations* did **not** endorse fluoroquinolones first-line (outside trials), though newer data are more supportive. **Triple-drug regimens** are superior in meta-analyses but are **not indicated for uncomplicated disease**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Undulant (remittent) fever chart:** plot temperature (°C) on the y-axis against time (days/weeks) on the x-axis. Labels: “*Undulating/remittent fever spikes*,” “*Profuse night sweats*,” “*Afebrile remission*,” “*Relapse*,” and “*≈50% with musculoskeletal pain*.”
- **Brucellar spondylitis (lateral lumbar spine schematic):** Labels — “*Anterosuperior end-plate erosion (epiphysitis)*,” “*Anterolateral parrot-beak osteophyte*,” “*Vertebral body intact until late*,” “*Late diskitis*,” “*Whole-vertebra sclerosis on recovery*” (contrast with TB: gibbus, early disk/body destruction, psoas abscess).

Clinical / Diagnostic significance

- Suspect brucellosis in any PUO with **night sweats and back/joint pain** plus an **exposure history** (unpasteurised dairy, animal contact, abattoir/lab work) — in endemic areas it is the default diagnosis until excluded.
- **Always exclude tuberculosis** before/alongside therapy because of shared drugs and overlapping spinal disease; misclassification risks rifampin monotherapy-driven TB resistance.
- **Blood/bone-marrow culture + paired serology (rising titre) ± PCR** form the practical diagnostic triad; warn the lab to enable safe handling and correct identification.

- ▶ Combination therapy for ≥ 6 weeks with reinforced adherence prevents relapse; escalate to triple therapy / ≥ 3 months for spondylitis, neurobrucellosis and endocarditis, with ceftriaxone for CNS disease and valve-directed multidrug therapy for endocarditis.
- ▶ Pregnant women have increased fetal loss; teratogenicity is not described. There is no increased severity in HIV/immunosuppression.

High-yield exam pointers

- ▶ Undulant fever + night sweats + arthralgia/back pain; ~50% have musculoskeletal involvement.
- ▶ **B. melitensis* (goat/sheep) = commonest and most aggressive; *B. abortus* = insidious/chronic; *B. suis* = focal abscess; *B. canis** = milder but can cause endocarditis.
- ▶ Bone-marrow/blood culture is definitive (50–70%); Bactec positive ≤ 7 days; alert the lab (containment + misidentification risk).
- ▶ SAT titre: $\geq 1:160$ (non-endemic), 1:320–1:640 (endemic) is significant; confirm with rising titre. Beware *Yersinia* O:9 cross-reaction; rough strains/RB51 give false-negative smooth-antigen serology.
- ▶ Sacroiliitis/spondylitis is the classic focal lesion; differentiate from TB spine (parrot-beak osteophyte, body intact till late, rare canal compression/psoas abscess).
- ▶ Doxycycline + streptomycin (gentamicin) is the most effective (gold-standard) regimen; doxycycline + rifampin is the convenient WHO alternative with higher relapse.
- ▶ Children/pregnant $\rightarrow$ TMP-SMX-based (avoid tetracyclines/streptomycin).
- ▶ Neurobrucellosis $\rightarrow$ add ceftriaxone, 3–6 months; endocarditis $\rightarrow$ ≥ 3 drugs (aminoglycoside + tetracycline + rifampin).
- ▶ Relapse usually reflects poor adherence, not resistance.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 174 "Brucellosis" (N.J. Beeching), including Table 174-1 (brucellar vs tuberculous spine). Coverage note: The provided chapter text ends mid-sentence within the endocarditis paragraph, so the full list of adjunctive endocarditis agents and valve surgery (universally accepted standard practice for *Brucella* endocarditis) is stated from standard internal-medicine teaching, not verbatim from the supplied excerpt. The excerpt contains no dedicated human-prevention/prognosis sections (only animal vaccination/control under epidemiology), so those angles are intentionally not expanded.



Pathophysiology and Management of Severe Sepsis

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Sepsis is an infectious syndrome causing considerable morbidity, mortality, and long-term sequelae among survivors. Under the historic Sepsis-1/Sepsis-2 framework, **severe sepsis** meant sepsis plus hypoperfusion or end-organ dysfunction (oliguria, acute mental-status change, or lactic acidosis), while **septic shock** was sepsis-induced hypotension persisting despite adequate volume resuscitation. The current **Sepsis-3 (2016)** consensus *eliminated the term “severe sepsis”* and redefined **sepsis** as *life-threatening organ dysfunction caused by a dysregulated host response to infection*, with **septic shock** as the subset showing profound circulatory, cellular, and metabolic abnormalities and markedly higher mortality. Thus, what was formerly called “severe sepsis” is, in present nomenclature, simply **sepsis**.

Evolving definitions — where “severe sepsis” fits

Consensus (year)	Sepsis criterion	“Severe sepsis”	Septic shock
Sepsis-1 (1992)	Suspected infection + ≥ 2 SIRS (temp <36 or $>38^{\circ}\text{C}$; HR >90 ; RR >20 or $\text{PaCO}_2 <32$; WBC <4000 or $>12,000/\mu\text{L}$ or $>10\%$ bands)	Sepsis + hypoperfusion / organ dysfunction (oliguria, altered mentation, lactic acidosis)	Sepsis-induced hypotension (SBP <90 or $\downarrow \geq 40$ from baseline) despite adequate volume resuscitation
Sepsis-2 (2003)	Expanded list of clinical & laboratory criteria beyond SIRS	Retained	As above
Sepsis-3 (2016)	Suspected/confirmed infection + $\uparrow\text{SOFA} \geq 2$ from baseline	Term abolished (folded into “sepsis”)	Vasopressor needed for MAP >65 mmHg and lactate >2 mmol/L despite fluid resuscitation

- Epidemiology: ~48.9 million sepsis cases occur globally each year with ~11 million deaths (1 in 5 of all global deaths; 85% in low/middle-income countries). Sepsis affects ~6% of hospitalised US adults, with ~15% overall mortality rising to **up to 40% in septic shock**.
- ~88% are community-onset; ~53% are culture-positive with a roughly even gram-positive/gram-negative split. Commonest primary sites: urinary tract (~49%), respiratory (~33%), intra-abdominal (~14%), skin/soft tissue (~10%). Key organisms: *S. aureus*, *Streptococcus*, *Enterococcus* (gram +) and *E. coli*, *Klebsiella*, *Pseudomonas* (gram –).

Pathophysiology — the dysregulated host response

The unifying mechanism is an **exuberant, dysregulated immune response** to infection causing systemic vasodilation, capillary leak, microvascular thrombosis, and impaired oxygen delivery/utilisation, culminating in multi-organ injury.

- **Triggers & recognition:** Pathogen components (**PAMPs** — e.g., LPS, cell-wall components, microbial nucleic acids) and host-derived **DAMPs** (histones, **HMGB1**, S100 proteins, oxidised

phospholipids, dsDNA, ATP) are sensed by **pattern-recognition receptors (PRRs)** — TLRs (10 in humans), C-type lectin receptors, RAGE, RIG-I, and NOD-like receptors.

- ▶ **Myeloid responses:** Activated **neutrophils** upregulate adhesion molecules (CD11b) and release **neutrophil extracellular traps (NETs)** — DNA webs studded with cathepsin-G, myeloperoxidase, and neutrophil elastase — which, with platelets and fibrin, form microthrombi. **Emergency granulopoiesis** (driven by IL-6, GM-CSF, G-CSF) releases immature neutrophils and predicts poor outcome. **Monocytes** (classical CD14⁺CD16⁻, intermediate, non-classical) differentiate into dendritic cells and **M1 (pro-inflammatory) macrophages** releasing IL-1 β , IL-6, and TNF- α .
- ▶ **Lymphoid responses & immunosuppression:** NK cells amplify inflammation (IFN- γ , granzyme) but also release IL-10. Progressive **lymphocyte apoptosis, exhaustion, and reduced proliferation**, plus myeloid-derived suppressor cells, produce a state of **sepsis-induced immunosuppression** predisposing survivors to secondary infection.
- ▶ **Endothelial activation:** PAMPs/DAMPs degrade the endothelial **glycocalyx** and upregulate **ICAMs and VCAM-1**, tissue factor, and PAI-1, while loss of **VE-cadherin** and tight junctions causes capillary leak $\rightarrow$ interstitial oedema, increased oxygen-diffusion distance, and hypoperfusion. Excess endothelial **nitric oxide (NO)** drives vasodilation.
- ▶ **Coagulopathy:** Endothelial/leukocyte **tissue factor** triggers the extrinsic cascade $\rightarrow$ thrombin $\rightarrow$ fibrin; vWF (Weibel-Palade bodies) aggregates platelets; all three complement pathways activate, releasing C3a/C5a anaphylatoxins and assembling the **membrane-attack complex (C5b-9)**. Natural anticoagulants (antithrombin, tissue-factor-pathway inhibitor, activated protein C) fall while antifibrinolytics (PAI, TAFI) rise, producing microvascular thrombosis; consumption of platelets/factors then causes bleeding (**DIC**).
- ▶ **Cellular injury:** Hypotension (vasodilation, myocardial depression, hypovolaemia), interstitial oedema, and microcirculatory thrombosis impair oxygen delivery; **ROS and reactive nitrogen species** (peroxynitrite) oxidise proteins/lipids and damage DNA. Even with adequate oxygen, **mitochondrial and metabolic dysfunction** disrupts ATP generation and ion homeostasis.

Clinical recognition, scoring & diagnosis

- ▶ Presentation is **non-specific** — fever, tachycardia, lethargy, myalgia — with or without localising features (cough, pyuria, abdominal pain) or signs of organ failure (oliguria, altered mentation). **There is no gold-standard diagnostic test.**
- ▶ **SOFA score** grades dysfunction in six systems: neurologic (GCS), cardiovascular (MAP / vasoactive agents), respiratory (PaO₂/FiO₂ or ventilation), hepatic (bilirubin), renal (creatinine), and coagulation (platelets). An increase of ≥ 2 operationalises Sepsis-3.
- ▶ **qSOFA** (RR ≥ 22 , GCS < 15 , SBP ≤ 100) ≥ 2 flags poor outcome — more specific but less sensitive than SIRS.

- ▶ Baseline workup: CBC with differential, basic metabolic panel, LFTs, **serum lactate**, coagulation panel, urinalysis, and **cultures of blood and suspected sites before antibiotics**, plus targeted imaging (x-ray/CT/ultrasound) to localise and enable **source control**.
- ▶ **Sepsis mimics** (~25% of suspected ICU cases): heart failure/cardiac arrest, non-infective COPD/pneumonitis, mesenteric ischaemia, inflammatory bowel disease, hypovolaemia, autonomic dysfunction, and adrenal insufficiency — mandating continuous re-evaluation.

Management — resuscitation per the 2021 Surviving Sepsis Campaign

Initial priorities: timely blood-pressure and organ support, antimicrobials, and source control; target ICU admission within 6 h for the critically ill.

- ▶ **Antibiotics:** In bacterial septic shock, every 1-h delay adds an estimated 7–8% **mortality** → give **empiric antibiotics within 1 h of shock recognition**. Without shock and with diagnostic uncertainty, a time-limited evaluation is acceptable, giving antibiotics by **3 h** if no alternative diagnosis emerges. Choice is guided by site, community vs health-care exposure, prior resistance, and host factors: third-generation cephalosporin (ceftriaxone/cefotaxime) if *Pseudomonas* unlikely; **cefepime, piperacillin-tazobactam, or a carbapenem** if *Pseudomonas* likely; **two** gram-negative agents if highly resistant organisms are a risk; add **vancomycin or linezolid** for MRSA risk. Add an **echinocandin** only for high fungal risk; **remdesivir/oseltamivir** for SARS-CoV-2/influenza. De-escalate and shorten courses with culture data.
- ▶ **Source control:** Drain/debride/decompress (intra-abdominal abscess, bowel perforation, pyelonephritis, cholangitis, necrotising soft-tissue infection) **as rapidly as possible**; remove infected indwelling catheters.
- ▶ **Fluids:** **Balanced crystalloid** (e.g., lactated Ringer's) is preferred over 0.9% saline (which risks hyperchloraemic acidosis); **avoid pentastarch/hydroxyethyl starch** (kidney injury, death). Give a bolus over 5–10 min at ~30 mL/kg (individualise in ESRD/systolic HF). Guide further fluids by **dynamic assessment** (capillary refill, passive-leg-raise, point-of-care ultrasound), *not* static CVP-based protocolised targets.
- ▶ **Vasopressors:** **Norepinephrine first-line** (MAP target ≥ 65 mmHg), add **vasopressin** second, **epinephrine** third. Place an arterial line for continuous monitoring.
- ▶ **Inotrope:** For myocardial dysfunction (sepsis-induced cardiomyopathy) with persistent hypoperfusion, add **dobutamine** to norepinephrine or use epinephrine alone.
- ▶ **Corticosteroids:** IV **hydrocortisone 200 mg/day** (50 mg q6h) if ongoing vasopressor requirement.

Organ-specific complications & targeted management

System (frequency)	Key findings	Management essentials
Neurologic (54% — encephalopathy)	Altered consciousness/cognition; seizure, stroke	Treat infection; correct metabolic/electrolyte derangement; limit neurotoxic drugs (e.g., cefepime), opiates, benzodiazepines; EEG/MRI/LP as indicated
Cardiovascular (25% shock; ½ with myocardial dysfunction)	Hypotension, skin mottling, prolonged capillary refill, oliguria	Balanced crystalloid ~30 mL/kg; norepinephrine → vasopressin → epinephrine; hydrocortisone 200 mg/d; dobutamine/PAC if mixed cardiogenic picture
Respiratory (7% — ARDS)	Tachypnoea, hypoxia; bilateral infiltrates, PaO ₂ /FiO ₂ <300	Target SpO ₂ 90–96% ; HFNC preferred over NIV; plateau pressure <30 cmH₂O , tidal volume 6–8 mL/kg IBW ; rescue: prone positioning, neuromuscular blockade, VV-ECMO
Renal (up to 67% — AKI)	Oliguria/anuria, ↑creatinine/BUN, acidaemia, hyperkalaemia	Maintain perfusion, avoid nephrotoxins; RRT for standard indications (refractory acidaemia, hyperkalaemia, uraemia, volume overload); CRRT preferred in shock; bicarbonate if pH ≤7.2
Hepatic/GI (50% liver dysfunction)	RUQ pain, jaundice, asterixis; ↑bilirubin/ALP	Treat infection, avoid hypotension/hepatotoxins; stress-ulcer prophylaxis for high-risk; enteral feeding within 48 h once shock controlled; insulin if glucose >180 mg/dL
Haematologic (35% septic shock — DIC)	Thrombocytopenia, ↑fibrin split products, ↓fibrinogen, prolonged PT/INR	Cryoprecipitate for fibrinogen <150 mg/dL; platelets if ≤50×10 ⁹ /L + bleeding; FFP for prolonged PT/INR + bleeding; PRBC for Hb <7.0 g/dL

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Sepsis pathogenesis schematic** (label clearly): *Pathogen* → PAMPs/DAMPs → PRR (TLR) on **monocyte/neutrophil**; *Tissue factor* on endothelium/leukocytes → *clotting cascade* → *thrombin* → *fibrin*; *NETs*; *platelet aggregates* + vWF; ↓*antithrombin*, ↑*PAI-1*; *complement C3a/C5a*, *MAC (C5b-9)*; *endothelial ICAMs/VCAM-1*, *glycocalyx degradation*, *loss of VE-*

System (frequency)	Key findings	Management essentials
	<i>cadherin</i> → <i>interstitial oedema</i>; <i>NO-mediated vasodilation</i>; <i>mitochondrial/metabolic dysfunction</i>; <i>M1 macrophage</i>; <i>lymphocyte exhaustion/apoptosis</i>. ► Sepsis-3 management algorithm: <i>Suspected infection</i> → <i>screen</i> ($\Delta\text{SOFA} \geq 2$ / $q\text{SOFA}$) → <i>cultures</i> + <i>lactate</i> → <i>empiric antibiotics</i> ≤ 1 h (shock) → <i>30 mL/kg balanced crystalloid</i> → <i>dynamic reassessment</i> (PLR/POCUS/capillary refill) → <i>norepinephrine</i> ($\text{MAP} \geq 65$) → <i>vasopressin</i> → <i>epinephrine</i> → <i>hydrocortisone 200 mg/d</i> → <i>source control</i> → <i>ICU</i> ≤ 6 h.	

Clinical / Diagnostic significance

- **Lactate** is both a diagnostic threshold for septic shock (>2 mmol/L) and a resuscitation marker; a randomised trial found capillary-refill-guided resuscitation was non-inferior to lactate-targeted resuscitation for 28-day mortality — relevant in resource-limited settings.
- **Sepsis-induced coagulopathy (SIC)** scoring (platelets, PT, SOFA) detects coagulopathy earlier and more sensitively than overt-DIC criteria.
- Machine-learning **phenotypes** (α , β , γ , δ) carry distinct mortality (2%, 5%, 15%, 32%) and may refine future trial design and prognostication.
- A restrictive-vs-liberal early-fluid trial and protocolised CVP/ScvO₂ targets showed **no mortality benefit**, underpinning the modern shift to individualised, dynamic resuscitation.

High-yield exam pointers

- Sepsis-3 abolished “severe sepsis”: today it is **sepsis** (organ dysfunction, $\Delta\text{SOFA} \geq 2$) and **septic shock** (vasopressor for $\text{MAP} > 65$ + lactate > 2 despite fluids).
- **Antibiotics within 1 h** of septic-shock recognition; ~7–8% **added mortality per hour** of delay.
- **Norepinephrine** → **vasopressin** → **epinephrine**; MAP target ≥ 65 mmHg.
- **Balanced crystalloid** ~30 mL/kg; avoid starch (HES); guide by dynamic measures, not CVP.
- **Hydrocortisone 200 mg/day** for vasopressor-dependent shock.
- **ARDS:** 6–8 mL/kg tidal volume, plateau < 30 cmH₂O, SpO₂ 90–96%; rescue with prone/NMB/VV-ECMO.
- **AKI:** RRT for **standard indications only**; bicarbonate if $\text{pH} \leq 7.2$; PRBC transfuse at **Hb** < 7 g/dL.
- Most frequent primary site = **urinary tract**; septic-shock mortality **up to 40%**.

SOURCE & COVERAGE

Harrison’s Principles of Internal Medicine, 22e — Ch 315 “Sepsis and Septic Shock” (Strich & Chertow). **Coverage note:** The exam phrasing “severe sepsis” reflects the older Sepsis-1/Sepsis-2 nomenclature; Harrison 22e follows **Sepsis-3 (2016)**, which eliminated the term — the answer therefore maps “severe sepsis” onto current “sepsis”/“septic shock” definitions. SIRS thresholds

and the original severe-sepsis/septic-shock criteria are quoted from the chapter's historical-definitions paragraph. All drug doses, vasopressor sequence, ventilation targets, transfusion triggers, and organ-specific frequencies are taken verbatim from the chapter text and Tables 315-1/315-2.



Discuss the neurologic disorders in Human Immunodeficiency Virus (HIV) disease

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Neurologic disease in HIV includes direct effects of HIV on the nervous system, opportunistic infections and neoplasms due to immunosuppression, immune reconstitution inflammatory syndromes, and treatment-related toxicities. Neurologic involvement may occur at any stage, from acute seroconversion meningitis to advanced AIDS with focal brain lesions, dementia, myelopathy, or peripheral neuropathy. The approach in an exam answer is to classify by **anatomic syndrome**, **CD4 count**, and **treatable emergency**.

Classification of neurologic disorders in HIV

- ▶ **Primary HIV-related disorders:**
 - **Acute HIV aseptic meningitis / meningoencephalitis** during seroconversion, with fever, headache, photophobia, lymphocytic CSF, and sometimes cranial neuropathies.
 - **HIV-associated neurocognitive disorder (HAND):** asymptomatic neurocognitive impairment, mild neurocognitive disorder, and **HIV-associated dementia**.
 - **Vacuolar myelopathy**, usually in advanced HIV, resembling subacute combined degeneration with spastic paraparesis and posterior-column signs.
 - **Peripheral neuropathies:** distal symmetric polyneuropathy, inflammatory demyelinating polyneuropathy, mononeuritis multiplex, radiculopathy, and autonomic neuropathy.
- ▶ **Opportunistic infections of CNS:**
 - **Toxoplasma encephalitis, cryptococcal meningitis, tuberculous meningitis, progressive multifocal leukoencephalopathy (PML), CMV encephalitis / polyradiculopathy, VZV vasculopathy, neurosyphilis, and bacterial or fungal abscesses.**
- ▶ **Neoplasms:**
 - **Primary CNS lymphoma**, systemic lymphoma with CNS spread, and rarely Kaposi-related or other metastatic disease.
- ▶ **Immune-mediated / ART-related:**

- **IRIS** unmasking or worsening cryptococcosis, tuberculosis, PML, or toxoplasmosis after ART initiation.
- Drug toxicities: zidovudine myopathy, older nucleoside analogue mitochondrial toxicity, efavirenz neuropsychiatric symptoms, and chemotherapy-related neuropathy.

Primary HIV-related neurologic syndromes

Syndrome	Typical setting	Key clinical features	Diagnosis	Management
Acute aseptic meningitis	Primary HIV infection	Fever, headache, meningism, photophobia, cranial nerve palsy; may accompany rash, pharyngitis, lymphadenopathy	CSF lymphocytic pleocytosis, raised protein, normal or mildly low glucose; exclude HSV, VZV, TB, cryptococcus	Supportive care; initiate ART as per HIV guidelines after evaluation
HAND / HIV-associated dementia	Chronic HIV; more severe with low CD4 and high viral load	Subcortical pattern: psychomotor slowing, impaired attention and executive function, apathy, gait difficulty, poor fine motor speed	Neuropsychological testing; MRI may show cerebral atrophy or white-matter signal change; exclude depression, drugs, OI, B12, thyroid disease	Effective ART with CNS-active regimen when possible; treat comorbidities and rehabilitation
Vacuolar myelopathy	Advanced AIDS	Slowly progressive spastic paraparesis, hyperreflexia, extensor plantars, sensory ataxia, urinary urgency; often with dementia or neuropathy	MRI spinal cord may be normal or show atrophy; B12, copper, HTLV-1, syphilis, compressive myelopathy must be excluded	ART; physiotherapy, antispasticity measures, bladder care

Syndrome	Typical setting	Key clinical features	Diagnosis	Management
Distal symmetric polyneuropathy	Common in advanced or treated HIV	Burning feet, numbness, allodynia, reduced ankle reflexes; length-dependent sensory loss	Clinical plus nerve conduction if uncertain; screen diabetes, B12 deficiency, alcohol, renal disease, drugs	ART optimization, remove neurotoxic drugs, pregabalin/gabapentin/duloxetine/TCA, foot care

- ▶ **HIV-associated dementia** is classically a **subcortical dementia**: slowed thinking, impaired concentration, apathy, personality change, gait imbalance, tremor, and later incontinence.
- ▶ It must not be diagnosed until **opportunistic infection, CNS lymphoma, metabolic encephalopathy, depression, substance use, and drug toxicity** have been excluded.
- ▶ **Vacuolar myelopathy** is the important spinal cord answer: corticospinal tract and posterior column dysfunction, often without a compressive lesion on imaging.
- ▶ **Peripheral neuropathy** is among the commonest neurologic complications of HIV; severe pain and loss of ankle reflexes are high-yield clinical clues.

Opportunistic infections: CD4-linked approach

Disorder	Usual immune setting	Clinical clues	Imaging / CSF clues	Treatment principle
Toxoplasma encephalitis	CD4 usually <100 cells/microL; Toxoplasma IgG positive	Headache, fever, confusion, seizures, focal deficits	Multiple ring-enhancing basal ganglia or corticomedullary lesions with edema; CSF PCR may help	Pyrimethamine + sulfadiazine + leucovorin or TMP-SMX; continue at least 6 weeks, then maintenance until immune recovery
Cryptococcal meningitis	CD4 often <100 cells/microL	Subacute headache, fever, vomiting, altered sensorium; meningism may be mild	High opening pressure; cryptococcal antigen positive; lymphocytic or paucicellular CSF	Amphotericin B plus flucytosine induction, then fluconazole consolidation and maintenance; repeated therapeutic LP for raised pressure

Disorder	Usual immune setting	Clinical clues	Imaging / CSF clues	Treatment principle
Tuberculous meningitis / tuberculoma	Any stage, common in advanced disease	Chronic fever, headache, basal meningitis, cranial neuropathy, stroke, hydrocephalus	Basal exudates, infarcts, hydrocephalus; CSF lymphocytes, high protein, low glucose; NAAT/culture	Standard anti-TB therapy with corticosteroids; manage hydrocephalus and ART timing carefully
PML (JC virus)	CD4 usually <200 cells/microL	Subacute focal deficits, visual field loss, aphasia, ataxia; usually no fever or mass effect	Non-enhancing or faintly enhancing white-matter lesions without marked edema; CSF JC virus PCR	No specific antiviral of proven value; restore immunity with ART; distinguish from PML-IRIS
CMV encephalitis / polyradiculopathy	CD4 usually <50 cells/microL	Delirium, ventriculoencephalitis, retinitis; cauda equina syndrome with flaccid weakness and urinary retention	CSF neutrophils may occur in polyradiculopathy; CMV PCR supportive	IV ganciclovir, often with foscarnet in severe disease; start or optimize ART

- ▶ **CNS toxoplasmosis** is the commonest cause of multiple ring-enhancing brain lesions in advanced AIDS; empirical treatment is reasonable when the clinical-radiologic picture is typical, but failure to improve should prompt biopsy to exclude lymphoma.
- ▶ **Cryptococcal meningitis** is a raised intracranial pressure disease: repeated lumbar puncture is therapeutic and lifesaving; corticosteroids are not routine unless another indication exists.
- ▶ **PML** gives progressive demyelinating focal neurologic deficits without a bulky enhancing mass; deterioration after ART may represent PML-IRIS.
- ▶ **CMV polyradiculopathy** is suggested by rapidly progressive flaccid paraparesis, saddle sensory loss, areflexia, and bladder dysfunction in very advanced HIV.

Focal brain lesion in HIV: differential diagnosis

- ▶ **Multiple ring-enhancing lesions:**
 - Most likely **toxoplasma encephalitis**, especially basal ganglia lesions with edema and positive Toxoplasma IgG.
 - Differentials: tuberculoma, fungal abscess, bacterial abscess, metastasis, and lymphoma.
- ▶ **Solitary enhancing mass:**
 - Consider **primary CNS lymphoma**, toxoplasmosis, tuberculoma, glioma, or abscess.

- CNS lymphoma often involves deep periventricular structures or corpus callosum and may show EBV DNA in CSF.
- ▶ **Non-enhancing white-matter lesions:**
 - Think of PML, HIV encephalopathy, demyelination, or small-vessel disease.
- ▶ **Meningitis picture:**
 - Cryptococcus, tuberculosis, syphilis, bacterial meningitis, viral meningitis, and primary HIV meningitis.
- ▶ **Myelopathy / radiculopathy:**
 - Vacuolar myelopathy, CMV polyradiculopathy, VZV radiculitis, lymphoma, epidural abscess, TB spine, B12 deficiency, and compressive cord disease.

Diagnostic approach

- ▶ Assess **stage of HIV**: duration, ART adherence, opportunistic infection prophylaxis, CD4 count, plasma HIV RNA, prior OI, and current ART drugs.
- ▶ Define the neurologic syndrome:
 - **Meningitis / encephalitis, focal brain lesion, dementia, myelopathy, neuropathy, myopathy, or stroke.**
- ▶ Urgent investigations:
 - **MRI brain with contrast** is preferred for focal deficits, seizures, altered sensorium, suspected PML, lymphoma, or toxoplasmosis.
 - **CT brain before LP** when raised intracranial pressure, focal deficit, papilledema, or mass lesion is suspected.
 - **CSF**: opening pressure, cells, protein, glucose; Gram stain/culture; cryptococcal antigen; AFB smear/culture/NAAT; VDRL; viral PCRs including HSV/VZV/CMV/JC virus as indicated; cytology/flow cytometry for lymphoma.
 - Blood tests: CD4 count, HIV RNA, complete blood count, electrolytes, renal/liver function, B12, thyroid tests, syphilis serology, hepatitis coinfection, and toxoplasma IgG.
- ▶ Neurophysiology:
 - Nerve conduction studies for neuropathy, demyelinating neuropathy, mononeuritis multiplex, or radiculopathy.
 - EMG and creatine kinase for suspected HIV or zidovudine-associated myopathy.
- ▶ Brain biopsy is reserved for:
 - Atypical lesions, negative serology, solitary mass, diagnostic uncertainty, or no clinical/radiologic response to appropriate empirical therapy.

Management principles

- ▶ **Stabilize first:** airway, breathing, circulation; treat seizures, raised intracranial pressure, sepsis, severe hyponatremia, and hypoglycemia promptly.
- ▶ **Start pathogen-specific therapy early** when a treatable OI is likely; do not wait for every test if toxoplasmosis, bacterial meningitis, HSV encephalitis, or TB meningitis is strongly suspected.
- ▶ **ART is central**, but timing must be individualized:
 - In most OIs, initiate ART after acute stabilization and early anti-infective therapy.
 - In **cryptococcal meningitis** and **TB meningitis**, very early ART can worsen intracranial inflammation; delayed initiation after induction therapy is often preferred.
- ▶ Prevent and treat **IRIS**:
 - Suspect IRIS when a patient worsens after ART despite microbiologic control or when occult infection becomes clinically apparent.
 - Continue ART in most cases, continue OI therapy, and use corticosteroids for severe inflammatory complications after excluding uncontrolled infection.
- ▶ Provide **secondary prophylaxis** until immune reconstitution:
 - Toxoplasmosis and cryptococcosis need maintenance therapy until sustained CD4 recovery on ART.
- ▶ Supportive care:
 - Rehabilitation for cognitive, gait, and focal deficits; neuropathic pain control; bladder and bowel care; nutrition; fall prevention; psychiatric assessment; adherence counselling.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Flowchart: neurologic syndrome in HIV** — labels: acute meningitis, focal brain lesion, diffuse encephalopathy/dementia, myelopathy, peripheral neuropathy; next labels: MRI brain, CSF with opening pressure, CD4 count, targeted PCR/antigen tests, empirical therapy.
- ▶ **CD4-linked CNS complications chart** — labels: CD4 <200: PML, TB, lymphoma; CD4 <100: toxoplasmosis, cryptococcus; CD4 <50: CMV encephalitis/polyradiculopathy; any CD4: acute HIV meningitis, neurosyphilis, stroke.

Clinical / Diagnostic significance

- ▶ Neurologic symptoms in HIV are often the first clue to **advanced immunosuppression** or ART failure.
- ▶ **Ring-enhancing lesion plus seizures or hemiparesis** in advanced HIV is toxoplasmosis until proved otherwise, but lymphoma must be considered if solitary, EBV-positive CSF, or nonresponsive.
- ▶ **Headache with high CSF opening pressure** in AIDS is a cryptococcal emergency; pressure control is as important as antifungal therapy.

- ▶ **Subacute focal deficits without fever or mass effect** point toward PML; treatment is immune restoration, not conventional antiviral therapy.
- ▶ **Rapid flaccid paraparesis with urinary retention** suggests CMV polyradiculopathy, whereas slowly progressive spastic paraparesis suggests vacuolar myelopathy.
- ▶ **Cognitive decline** may be HAND, but reversible mimics such as depression, drugs, metabolic disease, OI, and CNS lymphoma must be actively excluded.
- ▶ ART has reduced classic HIV dementia and many OIs, but has increased the importance of recognizing IRIS and chronic neurocognitive impairment.

High-yield exam pointers

- ▶ Classify HIV neurology as **direct HIV, opportunistic infection, neoplasm, immune-mediated/IRIS, and drug-related**.
- ▶ HAND is a **subcortical** cognitive-motor-behavioral syndrome; severe form is HIV-associated dementia.
- ▶ Vacuolar myelopathy causes **spastic paraparesis with posterior-column signs** in advanced AIDS.
- ▶ Toxoplasmosis: **multiple ring-enhancing basal ganglia lesions**; treat with pyrimethamine-sulfadiazine-leucovorin or TMP-SMX.
- ▶ Cryptococcal meningitis: **measure opening pressure** and repeat LPs for raised pressure.
- ▶ PML: JC virus, **non-enhancing white-matter demyelination**, no proven specific antiviral; optimize ART.
- ▶ CMV neurologic disease occurs at very low CD4 counts and may cause **ventriculoencephalitis or polyradiculopathy**.
- ▶ Primary CNS lymphoma is an AIDS-defining malignancy; think of it in a **solitary enhancing mass** or toxoplasma nonresponse.
- ▶ Always mention **CD4 count, HIV RNA, MRI with contrast, CSF studies, ART timing, and IRIS**.

SOURCE & COVERAGE

Harrison 22e — “Human Immunodeficiency Virus Disease: AIDS and Related Disorders”;
CMDT 2026 — HIV infection/AIDS and opportunistic infection management.



Serological Tests in the Diagnosis of Infectious Diseases

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Serology is the laboratory detection and quantitation of pathogen-specific **antibodies** (or, by extension, microbial **antigens**) in serum and other body fluids, used to infer infection from the **host's immune response** rather than by isolating the organism. Harrison emphasises that serologic diagnosis is the *measurement of the host's response to pathogen exposure* and can typically be made **only in retrospect**, requiring paired **acute- and convalescent-phase serum samples**. It is the mainstay for organisms that are difficult or impossible to culture, but its sensitivity and specificity are variable and it is increasingly complemented (and replaced) by **antigen detection** and **nucleic-acid amplification tests (NAATs)**.

Basic principles & interpretive concepts

- ▶ **Antigen–antibody reaction** is the basis: a known antigen detects unknown antibody (or a known antibody detects unknown antigen) in the patient's specimen.
- ▶ **Indirect (antibody) detection vs direct (antigen) detection** — antibody tests reflect the *host response*; antigen tests detect *structural components of the pathogen* itself.
- ▶ **Antibody class**: IgM appears early and indicates **recent/acute** infection; IgG appears later, persists, and indicates **past exposure, convalescence or immunity**.
- ▶ **Seroconversion** — change from antibody-negative to antibody-positive; the **window period** is the interval after infection before antibody becomes detectable (a key cause of false-negatives, classically in HIV).
- ▶ **Diagnostic criterion**: a **fourfold (two-dilution) rise in titre** between acute and convalescent sera, or **seroconversion**, confirms recent infection; a single titre is harder to interpret.
- ▶ **Limitation flagged by Harrison**: for chronic infections, serology alone often **cannot distinguish active from latent infection** or identify repeat exposure, and sensitivity depends on the **organism** and the patient's immune status.

Classification of serological / immunodiagnostic techniques

Principle	Representative test(s)	Typical infectious-disease use
Agglutination	Widal, Weil–Felix, latex agglutination , cold agglutinins, heterophile (Paul–Bunnell/Monospot)	Enteric fever, rickettsioses, cryptococcal/CSF antigen , <i>Mycoplasma</i> , EBV mononucleosis
Precipitation / flocculation	VDRL, RPR (nontreponemal)	Syphilis screening
Complement fixation	CFT (historical Wassermann)	Older viral/fungal serology
Neutralization	ASO (anti-streptolysin O) titre	Recent streptococcal infection / rheumatic fever
Immunofluorescence	FTA-ABS, direct/indirect IFA	Treponemal confirmation, many viruses

Principle	Representative test(s)	Typical infectious-disease use
Enzyme immunoassay (ELISA/EIA)	Ag/Ab combo assays, capture (MAC) ELISA	HIV screen, hepatitis, dengue, many others
Immunoblot / Western blot	Confirmatory immunoblot	Historical HIV & Lyme confirmation
Chemiluminescence / lateral-flow rapid tests	Immunochromatographic strips	Point-of-care HIV, dengue NS1, malaria, cryptococcal LFA

(The taxonomy above is standard textbook microbiology — see Coverage note; the specific applications below are anchored in the provided chapters.)

Antibody-based serology in specific infections

- ▶ HIV — combined antigen/antibody (4th-generation) immunoassays detect both p24 antigen and anti-HIV antibody. Harrison's natural-history model (Fiebig staging) shows p24 antigenaemia appearing first in acute infection, transiently disappearing, then antibody rising at seroconversion, with viral load persisting — illustrating why early antibody-only testing missed acute disease and why molecular (PCR) viral-load testing transformed diagnosis and staging.
- ▶ Syphilis (*Treponema pallidum*) — notoriously difficult to stage by serology alone; requires two tiers: a nontreponemal test (Harrison cites RPR — rapid plasma reagin; also VDRL) for screening and activity, plus a treponemal test (fluorescent treponemal antibody, FTA-ABS; also TPHA/TP-PA) for confirmation. *CSF serology for *T. pallidum*** (CSF-VDRL) is highly useful in selected neurosyphilis patients.
- ▶ Lyme disease (*Borrelia burgdorferi*) — IgM and IgG antibody testing; Harrison gives IgM early-disease sensitivity ≈50% and specificity ≈80%, and notes IgG may reflect prior exposure rather than active disease in endemic regions — a classic example of serology's interpretive pitfalls (two-tier EIA → immunoblot).
- ▶ Tuberculosis (immunodiagnosis of host T-cell response) — tuberculin skin test (PPD) and interferon-γ release assays (IGRAs), which measure *cytokine release from T lymphocytes in response to M. tuberculosis-specific antigens. Both have limited sensitivity in immunodeficient hosts, and neither distinguishes latent from active infection — emphasising that serology is notoriously insensitive for TB*.
- ▶ Fungal CSF serology — antibody/antigen testing for *Coccidioides* is sensitive and useful in selected patients.

Antigen-detection assays (direct serodiagnosis)

- ▶ Viral structural antigens — hepatitis B surface antigen (HBsAg), HIV p24 antigen, SARS-CoV-2 spike protein.

- ▶ **Bacterial surface antigens / urinary antigen tests** — **Streptococcus pneumoniae* and **Legionella pneumophila* serogroup 1**.
- ▶ **Fungal antigens** — **Cryptococcus antigen* (CrAg; highly sensitive) and **Histoplasma**; less-specific cell-wall components: galactomannan (*Aspergillus*) and β -D-glucan (*Aspergillus** and other fungi).
- ▶ **CSF latex agglutination** — for ***Haemophilus influenzae* type b, group B *Streptococcus*, *S. pneumoniae*, and *Neisseria meningitidis*. **Harrison notes these are not recommended for screening (no more sensitive than Gram's stain) but help** presumptively identify organisms already seen on Gram's stain; **in contrast**, cryptococcal antigen** testing is highly sensitive and clinically useful.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **HIV serological markers in natural history (Fiebig-type curve)** — x-axis: Time (weeks → years); y-axis: Relative level; plot three curves labelled **p24 antigen**, **HIV antibody (Ab)**, **Viral load (VL)**; add a dashed **limit of detection** line; mark phases **Acute HIV → Chronic HIV → AIDS** and the **window period / seroconversion**.
- ▶ **Acute vs convalescent antibody response** — x-axis **time from onset**, y-axis **antibody titre**; two curves **IgM** (early, transient) and **IgG** (later, persistent); annotate the **fourfold rise in titre** between acute and convalescent samples as the diagnostic criterion.

Clinical / Diagnostic significance

- ▶ Serology is the **diagnostic approach of choice** when the organism is **unculturable or fastidious**, and for **epidemiological/seroprevalence surveys** and **immunity/vaccination status** (e.g., anti-HBs, rubella IgG).
- ▶ **Two-tier strategies** (sensitive screen → specific confirmatory) maximise accuracy — exemplified by **syphilis** (nontreponemal → treponemal) and **Lyme** (EIA → immunoblot).
- ▶ **IgM positivity supports acute infection**; **paired sera with a fourfold rise** give definitive evidence; **CSF antibody/antigen** localises CNS infection (neurosyphilis, cryptococcal, coccidioidal).
- ▶ **Pitfalls**: window-period false-negatives, **cross-reactivity** and false-positives (biological false-positive VDRL), inability to separate **active from latent/past** infection, and **reduced sensitivity in immunocompromised patients** — all argue for correlation with **clinical suspicion** and, increasingly, **NAAT/PCR**, which provide real-time diagnosis and can predict drug resistance.

High-yield exam pointers

- ▶ Serology = **host antibody response**; usually a **retrospective** diagnosis needing **acute + convalescent sera**; **fourfold titre rise** or **seroconversion** is confirmatory.
- ▶ **IgM = recent/acute**; **IgG = past/immunity**; beware the **window period**.

- ▶ Syphilis — nontreponemal RPR/VDRL + treponemal FTA-ABS/TPHA; biological false-positive VDRL is a classic trap.
- ▶ HIV — 4th-gen Ag/Ab combo (p24 + antibody); p24 antigen precedes antibody (narrows window).
- ▶ Lyme IgM early sensitivity ~50%, specificity ~80%; IgG may mean only past exposure.
- ▶ TB — PPD/IGRA test cell-mediated immunity, are insensitive in immunodeficiency, and cannot separate latent from active disease.
- ▶ Antigen tests: HBsAg, HIV p24, SARS-CoV-2 spike, pneumococcal/Legionella urinary antigen, cryptococcal antigen, galactomannan/ β -D-glucan.
- ▶ CSF latex agglutination (Hib, GBS, pneumococcus, meningococcus) is *not for screening* but aids Gram-stain-guided identification; CrAg is highly sensitive.
- ▶ Classic eponymous agglutination tests: Widal (enteric fever), Weil–Felix (rickettsia), Paul–Bunnell/Monospot (EBV), cold agglutinins (*Mycoplasma*), ASO (streptococcal).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 126 “Microbial Genomics and Infectious Disease” (serologic vs antigen vs nucleic-acid diagnosis; HBsAg/HIV p24/SARS-CoV-2 spike; pneumococcal/Legionella urinary antigen; cryptococcal/histoplasma antigen; galactomannan/ β -glucan; HIV antibody–p24–viral-load seroconversion/Fiebig figure; syphilis RPR/FTA; Lyme IgM/IgG sensitivity-specificity; PPD/IGRA) and Ch 124 “Approach to the Patient with an Infectious Disease” (pathogen-specific serology/antigen/PCR testing; CSF latex agglutination for Hib, GBS, *S. pneumoniae*, *N. meningitidis*; cryptococcal antigen; CSF serology for *T. pallidum* and *Coccidioides*; high-titre antibody/IVIG).

Coverage note (spec gap = true): The provided chapters carry no dedicated “serology” section, so the technique-classification table (agglutination, precipitation/flocculation, complement fixation, neutralization, immunofluorescence, ELISA/EIA, Western blot, immunochromatography) and the eponymous tests Widal, Weil–Felix, Paul–Bunnell/Monospot, ASO, cold agglutinins, and dengue NS1/MAC-ELISA are supplied from universally accepted standard internal-medicine/microbiology knowledge, not directly from these two Harrison chapters. The disease-specific applications (HIV, syphilis, Lyme, TB, fungal/CSF antigen) and antigen-detection examples are faithfully grounded in the text above.



Ebola Virus Disease (Filovirid — Orthoebolavirus Infection)

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Ebola virus (EBOV)* is an enveloped, non-segmented, negative-sense RNA virus of the family **Filoviridae**, genus *Orthoebolavirus*, and is the cause of **Ebola virus disease (EVD)** — the prototype of the filovirid viral haemorrhagic fevers (along with Marburg disease). EVD is a *World Health Organization Risk Group 4* zoonosis that begins as a non-specific influenza-like illness and rapidly evolves to gastrointestinal loss, coagulopathy, multi-organ dysfunction and shock, with a historically very high case-fatality rate. It is highly **infectious but not highly contagious**, spreading by direct contact with body fluids rather than by aerosol.

Etiology & Virology

- ▶ Family **Filoviridae** has nine official genera; only two contain human pathogens — *Orthoebolavirus* and *Orthomarburgvirus*. Collectively these cause **filovirid (filovirus) disease (FVD)**.
- ▶ **Ebola disease (EBOD)** is caused by four of the orthoebolaviruses; **Marburg disease (MARD)** by the two orthomarburgviruses (Marburg virus, Ravn virus).
- ▶ The virion is **pleomorphic and filamentous** (also torus-/”6”-shaped); width ≈91–98 nm, length <1 µm; enveloped, with a helical ribonucleoprotein capsid studded with **GP1,2 glycoprotein spikes**.
- ▶ Genome ≈19 kb, linear negative-sense RNA with **seven genes encoding seven structural proteins**: nucleoprotein (NP), polymerase cofactor (VP35), matrix protein (VP40), glycoprotein (GP1,2), transcriptional activator (VP30), ribonucleoprotein-associated protein (VP24) and the L protein (RNA-dependent RNA polymerase). Orthoebolaviruses *additionally* encode three non-structural proteins — *sGP*, *ssGP* and Δ -peptide.

Orthoebolavirus	Virus (abbrev.)	Pathogenicity in humans
<i>O. zairense</i>	Ebola virus (EBOV) — “Zaire”	Highly pathogenic; cause of the 2013–16 West Africa epidemic
<i>O. sudanense</i>	Sudan virus (SUDV)	Pathogenic; re-emerged Uganda/South Sudan 2022–23
<i>O. bundibugyoense</i>	Bundibugyo virus (BDBV)	Pathogenic
<i>O. taiense</i>	Taï Forest virus (TAFV)	Pathogenic (rare; only one human case)
<i>O. restonense</i>	Reston virus (RESTV)	Apparently non-pathogenic to humans
<i>O. bombaliense</i>	Bombali virus (BOMV)	Non-pathogenic (detected in bats)

Epidemiology & Transmission

- ▶ First recognised in **1976** in simultaneous outbreaks in *Zaire (now DR Congo)* and *South Sudan*; >20 outbreaks since, confined to equatorial **Western, Middle and Eastern Africa**.
- ▶ The **2013–2016 West Africa outbreak** (Guinea, Sierra Leone, Liberia, with exported cases) was the largest ever — **28,652 cases and 11,325 deaths** — and was the first to constitute a regional and global threat; CMDT cites an average case-fatality rate of **~60%**.
- ▶ **Reservoir:** the cave-dwelling **Egyptian rousette fruit bat* (*Rousettus aegyptiacus*) *is the proven reservoir for Marburg/Ravn viruses; fruit/insectivorous bats are the suspected (but unproven) reservoir for orthoebolaviruses**. Only ≈ 50 natural host-to-human spillover events have been recorded since 1967.
- ▶ **Spillover to humans:** contact with reservoir hosts or with infected/dead mammals — hunting or eating “bushmeat” (apes, monkeys, duikers, bush pigs).
- ▶ **Human-to-human spread:** direct person-to-person contact or exposure to **infected body fluids/tissues** (blood, vomitus, stool, sweat, semen, breast milk), parenteral inoculation (needlestick, needle reuse), and contact with corpses during **traditional burial/ritual washing**. *There is no natural aerosol or respiratory-droplet transmission.*
- ▶ Virus is **not transmissible before symptom onset**; infectivity rises with illness severity and viral load. Health-care workers and family caregivers bear the highest risk; nosocomial amplification drives outbreaks.

Pathogenesis

- ▶ Entry is via skin breaks or mucosa; **GP1,2 spikes** determine tropism by engaging the intracellular receptor NPC1 (Niemann-Pick C1 cholesterol transporter).
- ▶ **First targets are macrophages, monocytes and dendritic cells**. Structural proteins VP35, VP40 and VP24 **suppress innate immunity** (notably the type-I interferon pathway), permitting uncontrolled replication — serum titres exceed 10^6 PFU/mL with dissemination to almost all tissues (hepatocytes, adrenal cortex, fibroblasts, endothelium).
- ▶ **Immune dysregulation:** infected macrophages release a “cytokine storm”; dendritic cells fail to present antigen; massive **lymphoid (T-cell) apoptosis** in nodes, spleen and thymus causes the profound lymphopenia and predisposes to secondary bacterial/fungal infection.
- ▶ **Coagulopathy & endothelial dysfunction:** thrombocytopenia, raised tissue factor, consumption of clotting factors, raised D-dimer, falling protein C → features of **DIC**, fibrin deposition and microvascular thrombosis. Hepatocyte necrosis impairs clotting-factor synthesis.
- ▶ **Vascular leak:** cytokines, nitric oxide and direct endothelial infection raise vascular permeability → fluid redistribution, interstitial oedema, and **hypovolaemic/septic (distributive) shock**. *Massive external blood loss is actually uncommon* (though severe around childbirth).

Clinical Features & Disease Course

- ▶ **Incubation 2–25 days** (Harrison; CMDT 2–21 days), most often 7–10 days.

- ▶ Orthoebolavirus and orthomarburgvirus disease are clinically indistinguishable at the bedside.

Phase	Timing	Features
Prodrome (early)	Days 0–5	Abrupt fever, chills, severe headache, intense myalgia/arthralgia, asthenia, pharyngitis, cough; maculopapular rash
Peak / GI phase	≈Day 5–7 onward	Profuse nausea, vomiting, watery diarrhoea , abdominal pain → large volume/electrolyte loss; hypotension
Multi-organ / shock	Day 7–14	Hypovolaemic & septic shock , AKI, respiratory failure, encephalitis (confusion, agitation, seizures, coma), myocarditis/pericarditis, uveitis
Haemorrhagic	Late	Subconjunctival/conjunctival injection, petechiae, gingival bleeding, oozing from puncture sites; epistaxis, haematemesis, melena (overt bleeding in only ~1–5%)
Recovery / convalescence	Week 2–3+	Slow clearance of viraemia in survivors; prolonged sequelae

- ▶ **Typical laboratory findings:** early **leukopenia** (with left shift) then leukocytosis; **thrombocytopenia** (as low as 50,000/μL); **transaminitis** with **AST > ALT**, raised γ-GT; rising urea/creatinine with proteinuria; **electrolyte derangement** (hypo-/hyperkalaemia, hyponatraemia, hypocalcaemia); **hypoglycaemia**, hypoalbuminaemia; prolonged PT/PTT, raised D-dimer; raised CPK (rhabdomyolysis); markedly raised CRP.
- ▶ **Complications & sequelae:** secondary infection, persistent AKI, neuro-cognitive deficit, myocarditis, venous thrombosis; survivors report arthralgia/myalgia, fatigue, alopecia, **uveitis** and hearing loss, memory loss, and **post-EVD depression/anxiety/PTSD**.
- ▶ **Viral persistence in immune-privileged sites** — **semen** (up to ~9–12 months), CNS (recrudescent meningoencephalitis), eye (uveitis) and placenta — can cause **sexual transmission** and the rare re-ignition of outbreaks from survivors.

Diagnosis & Investigations

- ▶ EVD cannot be diagnosed clinically; an *exposure history* (bushmeat, bats, caves/mines, sick contacts, rural hospital clusters) plus compatible illness raises suspicion. Notify infectious-disease specialists and public-health authorities **immediately**.

- ▶ **Acute-phase blood/serum** is the preferred specimen (high virion titres).
- ▶ **Test of choice: reverse-transcription PCR (RT-PCR)** targeting filovirid genes; field-deployable platforms such as the **Cepheid GeneXpert** give rapid, standardised in-field results. RNA peaks $\approx$ day 7. A negative early sample (<3 days) should be repeated if symptoms persist.
- ▶ **Antigen-capture ELISA** and rapid antigen tests aid diagnosis (RDT sensitivity currently restricts use largely to post-mortem samples); **IgM/IgG capture ELISA** detect antibody in later disease and survivors.
- ▶ Virus isolation/electron microscopy require **maximum-containment (BSL-4)** facilities. Samples are inactivated (guanidinium for PCR, irradiation/heat for ELISA) and handled as extreme biohazards.
- ▶ **Key differentials:** *falciparum malaria* and *typhoid fever* (most important), plus enterohaemorrhagic *E. coli*, gram-negative/meningococcal sepsis, leptospirosis, rickettsioses, fulminant viral hepatitis, measles, **Lassa fever and yellow fever**; also snakebite, warfarin poisoning and other causes of coagulopathy.

Treatment & Prevention

- ▶ **Supportive care is the backbone:** aggressive IV fluid and **electrolyte repletion**, vasopressors, oxygen/ventilation, renal replacement, correction of hypoglycaemia, antipyretics/antiemetics/antidiarrhoeals, plus **empirical antimalarials and broad-spectrum antibiotics** in endemic settings. Intensive supportive care alone has cut mortality from 25–90% toward $<20\%$ in well-resourced units.
- ▶ **Specific therapeutics — anti-EBOV monoclonal antibodies** (validated by the PALM randomised controlled trial, DR Congo 2018–20):
 - **mAb114 — ansuvimab (Ebanga)** — single mAb.
 - **REGN-EB3 — atoltivimab/maftivimab/odesivimab (Inmazeb)** — triple-mAb cocktail.
 - Both are single IV infusions given as early as possible; the **2022 WHO guideline strongly recommends** either for PCR-confirmed Zaire EVD (including pregnant women, children and neonates ≤ 7 days of mothers with confirmed EVD), and conditionally **recommends against remdesivir and ZMapp**.
- ▶ **Vaccines:**
 - **rVSV-ZEBOV (Ervebo, Merck)** — live, single-dose recombinant vesicular stomatitis virus expressing EBOV GP; protective from **~ 10 days**; deployed as **reactive “ring” vaccination** of contacts-of-contacts and for pre-exposure protection of health workers (FDA/EMA approved 2019). *Preferred in outbreaks*.
 - **Ad26.ZEBOV (Zabdeno) + MVA-BN-Filo (Mvabea)** — heterologous **two-dose prime-boost** (~ 8 weeks apart); suited to peri-outbreak/pre-exposure use, not for rapid outbreak control.

- ▶ **Infection prevention & control:** isolation of cases, contact tracing, barrier nursing, PPE (gloves, gown, face shield/goggles; N95/N100 and powered respirators for aerosol-generating procedures), single-use equipment, and **safe burials**. Filovirions are enveloped and readily inactivated — **bleach 1:100 for surfaces, 1:10 for excreta/corpses**.
- ▶ **Survivor measures:** sexual abstinence or condom use for **≥12 months** (or until semen tests RNA-negative); vaccine/PEP for high-risk exposed health workers (e.g. needlestick).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **EVD disease-course timeline** (Harrison Fig 216-6): x-axis *Days since onset* (−10 → +28); phases labelled **Incubation, Early phase, Peak phase, Recovery**. Stack the curves/bars — *non-specific prodrome* (fever, fatigue, myalgia, headache), *GI symptoms, rash, haemorrhage, shock, renal/respiratory/neurologic/cardiac dysfunction, uveitis*; overlay **viraemia (survivor vs non-survivor)**, **IgM, IgG**, and lab trends (↓WBC/↓PLT early, ↑AST/ALT, ↓glucose, ↑BUN/creatinine, coagulopathy ↑PT/PTT/D-dimer).
- ▶ **Filovirion structure:** label the **filamentous enveloped particle** with **GP1,2 surface spikes**, lipid envelope, **VP40 matrix**, helical **nucleocapsid (NP, VP35, VP30, VP24, L) wrapping the −ssRNA genome** (~19 kb).

Clinical / Diagnostic significance

- ▶ A **febrile traveller/contact returning from an Ebola-affected country** must be isolated, risk-assessed and tested by RT-PCR while excluding **malaria and typhoid** first — these are commoner and treatable.
- ▶ **AST > ALT**, marked thrombocytopenia, rising creatinine/BUN and high viral load are **adverse prognostic markers**; children <5 years, adults >40 years, pregnancy and immunosuppression carry the worst outcomes (maternal mortality ~86% in 2014–16).
- ▶ Early **fluid/electrolyte resuscitation plus a monoclonal antibody** is now standard of care and has transformed prognosis; the “70–90% mortality” figure is outdated.
- ▶ **Survivor surveillance** (semen testing, ophthalmology for uveitis, audiology, mental-health support) is essential to prevent relapse, sexual transmission and outbreak re-ignition.

High-yield exam pointers

- ▶ Family *Filoviridae*; genus *Orthoebolavirus*; **negative-sense ssRNA**, ~19 kb, **7 genes/7 structural proteins**; receptor NPC1.
- ▶ Four human-pathogenic ebolaviruses — **EBOV (Zaire, most lethal)**, **SUDV**, **BDBV**, **TAFV**; **Reston = non-pathogenic** to humans.
- ▶ **WHO Risk Group 4 / BSL-4**; highly infectious, not aerosol-contagious.
- ▶ Reservoir = **fruit bats (proven for Marburg = Rousettus aegyptiacus); spillover via bushmeat/primates**.

- ▶ Incubation 2–21 days; prodrome → GI loss → shock/MODS; overt haemorrhage in only ~1–5%.
- ▶ Diagnosis = RT-PCR (GeneXpert) on acute serum; AST > ALT, thrombocytopenia, leukopenia.
- ▶ Treatment = supportive care + mAb (Inmazeb / Ebanga) validated by the PALM trial; remdesivir/ZMapp not recommended.
- ▶ Vaccine = rVSV-ZEBOV (Ervebo), single-dose, ring vaccination; Zabdeno+Mvabea = 2-dose pre-exposure.
- ▶ Persistence in semen (~12 months), CNS, eye, placenta → late sexual transmission and outbreak re-ignition.
- ▶ IPC: isolation, contact tracing, PPE, safe burials, bleach 1:10 for corpses/excreta.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Filovirids: Orthoebolavirus and Orthomarburgvirus Infections" (etiology, virology, epidemiology, pathogenesis, clinical course, diagnosis, PALM-trial therapeutics, vaccines, control).
- ▶ CDMT 2026 — "Viral & Rickettsial Infections: Viral Haemorrhagic Fevers — Ebola Viral Disease" (current case definition, clinical findings, WHO 2022 treatment guideline, Inmazeb/Ebanga, Ervebo and Zabdeno-Mvabea vaccines, prognosis, when-to-admit).



Extensively Drug-Resistant Tuberculosis (XDR-TB)

Asked in: Paper III Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Extensively drug-resistant TB (XDR-TB) is disease caused by *Mycobacterium tuberculosis* in which MDR-TB is compounded by additional resistance to any fluoroquinolone AND to at least one additional Group A drug (i.e., bedaquiline and/or linezolid). It sits at the apex of a graded spectrum of drug-resistant TB built on multidrug-resistant TB (MDR-TB) — bacilli resistant *at least to isoniazid and rifampin*, the two most potent first-line bactericidal agents. XDR-TB represents the most difficult-to-treat, costly and lethal form of TB, demanding all-oral, individualized, drug-susceptibility-testing (DST)–guided regimens delivered in specialized centres.

Spectrum & Definitions of Drug-Resistant TB

- ▶ Resistance is graded by the *number and class* of drugs lost; the updated (post-2021) hierarchy reflected in Harrison is summarised below.

Category	Resistance pattern (per Harrison 22e)
Mono-resistant TB	Resistance to a single first-line drug (e.g., isoniazid-resistant, rifampin-susceptible)

Category	Resistance pattern (per Harrison 22e)
RR-TB (rifampin-resistant)	Resistance to rifampin (with/without other drugs); monoresistance to R is rare and treated as MDR
MDR-TB	Resistance at least to isoniazid + rifampin
Pre-XDR-TB	MDR/RR-TB strain also resistant to any fluoroquinolone
XDR-TB	MDR/RR-TB + fluoroquinolone resistance + resistance to ≥ 1 additional Group A drug (bedaquiline and/or linezolid)

- ▶ **Primary resistance** = patient infected from the outset by a resistant strain; **acquired resistance** = develops in the infecting strain during inadequate treatment.
- ▶ Drug-resistant TB “almost invariably follows **monotherapy**” — failure to prescribe ≥ 2 effective drugs, poor adherence, malabsorption, or poor-quality drugs.

Molecular Basis & Mechanism of Resistance

- ▶ Resistance arises by **spontaneous chromosomal point mutations** occurring at low, predictable rates (10^{-7} – 10^{-10} per drug). There is *no plasmid-mediated* resistance and *no cross-resistance* between unrelated classes, so multi-class resistance is the *product* of individual probabilities — and is therefore generated almost solely by drug pressure on poorly-treated patients.

Drug	Key resistance gene(s) (frequency)
Rifampin	* <i>rpoB</i> * (95%)
Isoniazid	* <i>katG</i> (50–95%); <i>inhA</i> * promoter (up to 45%)
Pyrazinamide	* <i>pncA</i> * (up to 98%)
Ethambutol	* <i>embB</i> * (50–65%)
Fluoroquinolones	* <i>gyrA</i> – <i>gyrB</i> * (75–95%) — target DNA gyrase/topoisomerase IV
Aminoglycosides	* <i>rrs</i> (up to 80%); <i>eis</i> promoter C-12T* mutation
Bedaquiline	* <i>atpE</i> (ATP synthase subunit c); Rv0678/ <i>mmpR</i> , <i>pepQ</i> * (efflux — cross-resistance to clofazimine)
Linezolid	23S rRNA; ribosomal proteins *L3 (rplC), L4 (rplD)*

Epidemiology & Global Burden

- ▶ Of ~10.8 million incident TB cases in 2023, an estimated **400,000 MDR/RR-TB** cases occurred; only **189,000** were enrolled on treatment owing to limited DST capacity.

- ▶ >50% of all MDR/RR-TB occurs in: India (27%), Russian Federation (7.4%), Indonesia (7.4%), China (7.3%) and the Philippines (7.2%); the former Soviet states have the highest *proportion* of MDR among new cases (up to one-third).
- ▶ *The vast majority of XDR-TB cases remain undiagnosed* because reliable DST methods and laboratory capacity are lacking in low-income settings.

Diagnosis & Drug-Susceptibility Testing

- ▶ Culture remains the gold standard (liquid MGIT faster than solid Löwenstein-Jensen).
- ▶ Rapid molecular DST is mandatory before regimen design: nucleic-acid amplification Xpert MTB/RIF / Ultra detects *M. tuberculosis* + rifampin resistance (proxy for MDR); line-probe assays (LPAs) extend to isoniazid, fluoroquinolone and second-line resistance.
- ▶ For any RR/MDR diagnosis, DST for fluoroquinolones and (where possible) bedaquiline/linezolid is essential — these define the pre-XDR/XDR transition and dictate whether moxifloxacin can be retained.
- ▶ Continued monthly bacteriologic (culture) monitoring detects failure (persistent positivity or reversion after conversion) and emerging amplification of resistance.

WHO Classification of Anti-TB Drugs (for longer regimens)

- ▶ For complex MDR/XDR regimens, second-line drugs are ranked into three groups; regimens use all three Group A drugs + ≥1 Group B, adding Group C only to complete an effective combination.

Group	Drugs	Rule
A (use all three)	Levofloxacin/moxifloxacin · Bedaquiline · Linezolid	Ensures ≥4 likely-effective agents; ≥3 continue if bedaquiline stopped
B (add ≥1)	Clofazimine · Cycloserine / terizidone	At least one always included
C (complete regimen)	Delamanid · Pyrazinamide · Ethambutol · Imipenem-cilastatin/meropenem · Amikacin (or streptomycin) · Ethionamide/prothionamide · p-Aminosalicylic acid	Used when A/B cannot be

- ▶ Kanamycin and capreomycin are NO LONGER used (higher failure/relapse, toxicity); the injectables amikacin/streptomycin are reserved (≥18 yr, proven susceptibility, with audiometry).

Treatment of XDR-TB & Highly-Resistant Disease

- ▶ **Principle:** select agents *likely to be effective and tolerated*, build from the Group A/B/C hierarchy, give all-oral, fully-supervised therapy. **Levofloxacin/moxifloxacin, bedaquiline and linezolid should always be included** in longer regimens where active.
- ▶ **Pre-XDR-TB / MDR-RR (FQ retained or excluded):** the preferred regimen is the **6-month all-oral BPaLM** — Bedaquiline + Pretomanid + Linezolid 600 mg + Moxifloxacin (success rates ~90%). In **documented fluoroquinolone resistance, drop moxifloxacin → BPaL**. (*Excluded: pregnancy/breastfeeding, disseminated, CNS and osteoarticular TB, and prior >1-month exposure to these drugs.*)
- ▶ **XDR-TB:** because there is FQ + Group A drug resistance, the patient often does **not qualify for the standardized short regimens**; XDR-TB “follows the same principles” as a **longer (≥18–20-month) individualized regimen** (continued 15–17 months after culture conversion, ~6–7-month intensive phase), assembled from remaining effective Group A/B/C agents per DST.
- ▶ **Adjuncts:** aggressive management with early DST, strict DOT, monthly bacteriology and intensive patient support; **surgical resection (lobectomy/wedge)** for localized disease with adequate pulmonary reserve.
- ▶ **Key drug profile (the agents that define XDR):**

Drug	Class / mechanism	Dose	Major toxicity
Bedaquiline	Diarylquinoline — inhibits mycobacterial ATP synthase proton pump	400 mg/d × 2 wk, then 200 mg thrice-weekly	QT prolongation (black-box), hepatotoxicity, ↑ mortality signal; CYP3A4-metabolised
Linezolid	Oxazolidinone — binds 50S ribosome (protein synthesis)	600 mg once daily	Myelosuppression/pancytopenia, optic & peripheral neuropathy, lactic acidosis, serotonin syndrome (weak MAOI)
Pretomanid	Nitroimidazole prodrug (PA-824) — inhibits mycolic acid synthesis	200 mg daily	Hepatotoxicity
Moxifloxacin/levofloxacin	Fluoroquinolone — inhibits DNA gyrase	Standard	QT prolongation, GI/CNS
Clofazimine (Gp B)	Riminophenazine — reactive oxidants/membrane	—	Orange-brown skin discoloration, QT
Delamanid (Gp C)	Nitroimidazole — mycolic acid synthesis	100 mg twice daily	QT prolongation

Drug	Class / mechanism	Dose	Major toxicity
DIAGRAMS TO DRAW — IMAGE SUGGESTIONS ▶ Pyramid/ladder of drug-resistant TB (base → apex): <i>Drug-susceptible TB</i> → <i>Isoniazid mono-resistant</i> → <i>RR-TB</i> → <i>MDR-TB (H+R)</i> → <i>Pre-XDR-TB (+ fluoroquinolone)</i> → <i>XDR-TB (+ Group A drug: bedaquiline/linezolid)</i>. Label each tier with the defining resistance. ▶ Box diagram of WHO Group A/B/C drugs with three labelled boxes: Group A — Levofloxacin/Moxifloxacin, Bedaquiline, Linezolid; Group B — Clofazimine, Cycloserine/Terizidone; Group C — Delamanid, Pyrazinamide, Ethambutol, Carbapenem+clavulanate, Amikacin, Ethionamide/Prothionamide, PAS.			

Clinical / Diagnostic significance

- ▶ **Suspect resistance** in: previously treated TB, contacts of resistant cases, patients from high-MDR regions ($\geq 5\%$ incident MDR), and **failure of sputum-culture conversion at 2 months** — retest immediately and switch regimen.
- ▶ **DST drives everything**: FQ and bedaquiline/linezolid susceptibility distinguish pre-XDR from XDR and decide whether BPaLM, a shorter, or a longer regimen is used.
- ▶ **Cardiac safety**: multiple regimen drugs (bedaquiline, delamanid, clofazimine, fluoroquinolones) prolong QT — perform **baseline + serial ECG**; *withhold if QTc > 500 ms or history of ventricular arrhythmia*. Audiometry if amikacin used; haematology/visual monitoring on linezolid.
- ▶ **Active TB drug-safety monitoring (aDSM)**, informed consent, and HIV co-management (avoid efavirenz with bedaquiline; prefer dolutegravir-based ART) are integral.
- ▶ **Public-health imperative**: prompt diagnosis + effective regimen interrupts transmission of these strains and prevents *further* amplification of resistance.

High-yield exam pointers

- ▶ **XDR-TB** = MDR + fluoroquinolone resistance + resistance to ≥ 1 Group A drug (bedaquiline/linezolid). **Pre-XDR** = MDR + FQ resistance.
- ▶ **MDR** = resistant at least to isoniazid + rifampin. Monoresistant rifampin (RR) is managed as MDR.
- ▶ Resistance is by spontaneous point mutation; remember **rpoB (R)**, **katG/inhA (H)**, **pncA (Z)**, **embB (E)**, **gyrA/gyrB (FQ)**, **rrs (aminoglycoside)**, **atpE/Rv0678 (bedaquiline)**, **23S rRNA/rplC/rplD (linezolid)**.
- ▶ **Group A** (always all three): fluoroquinolone, bedaquiline, linezolid. **Group B**: clofazimine, cycloserine/terizidone.

- ▶ **BPaLM** = Bedaquiline + Pretomanid + Linezolid 600 mg + Moxifloxacin, 6 months, ~90% success — drop moxifloxacin (→ **BPaL**) if FQ-resistant.
- ▶ **Kanamycin and capreomycin are abandoned**; regimens are now **all-oral**.
- ▶ **Bedaquiline** inhibits ATP synthase, carries a **black-box QT/mortality warning**; **linezolid** causes **myelosuppression + neuropathy**.
- ▶ XDR/complex disease → **individualized longer regimen ≥18–20 months**, 15–17 months after culture conversion, with DOT, monthly cultures, aDSM ± surgery.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 183 "Tuberculosis"** (XDR/pre-XDR definitions, epidemiology, resistance genetics, WHO Group A/B/C Table 183-3, MDR/RR & BPaLM regimens) and **Ch 186 "Antimycobacterial Agents"** (BPaLM/BPaL trials, drug mechanisms, doses and toxicities). *Coverage note:* Harrison reflects the post-2021 WHO **revised XDR-TB definition** and does not give a single named "XDR-TB regimen" — XDR-TB is managed under the **longer individualized ≥18–20-month** regimen built from Group A/B/C drugs (Table 183-3), with the short BPaLM/BPaL regimens primarily validated for MDR/RR and pre-XDR disease. Fluoroquinolone mechanism (DNA gyrase) is standard textbook pharmacology consistent with the *gyrA/gyrB* resistance data in the chapter.



Extrapulmonary Tuberculosis

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Extrapulmonary tuberculosis (EPTB) is *Mycobacterium tuberculosis* infection of any organ system other than the lung parenchyma, resulting from lymphohaematogenous dissemination from a primary or post-primary focus, contiguous spread, or (for gut TB) ingestion. It accounts for **10–40%** of all TB cases depending on host immune status and bacterial strain; among people living with HIV (PLWH) up to **two-thirds** have extrapulmonary or combined disease. In descending order of frequency the sites involved are **lymph nodes > pleura > genitourinary tract > bones and joints > meninges > peritoneum > pericardium**, though virtually any organ may be affected. Most forms are **paucibacillary and essentially non-infectious**, making them diagnostically challenging and demanding tissue/fluid sampling for confirmation.

Pathogenesis and general features

- ▶ Tubercle bacilli disseminate via **lymphatics and the bloodstream** during the early bacillaemic phase of primary infection; dormant foci later reactivate when cell-mediated immunity (CMI) wanes (HIV, diabetes, anti-TNF-α therapy, chronic kidney disease, malnutrition, immunosuppression).

- ▶ EPTB is **more common in settings of high HIV prevalence** because failure of CMI permits widespread haematogenous seeding.
- ▶ Because lesions are paucibacillary, **smear and culture yields are lower** than in cavitary pulmonary disease, and **histology (caseating granuloma)** plus **nucleic-acid amplification** are pivotal.
- ▶ Constitutional (“B”) symptoms — low-grade fever, night sweats, anorexia, weight loss — are common but may be absent except in HIV co-infection.

Organ-specific clinical syndromes

Site (approx. share of EPTB)	Key clinical features	Best diagnostic approach
Lymph node (≈35%; >40% in US series)	Painless posterior-cervical/supraclavicular swelling = <i>scrofula</i> ; discrete nodes → matted mass → cold abscess/sinus draining caseum; systemic symptoms uncommon unless HIV	FNAC (yield up to 80%) or excision biopsy; granuloma ± AFB; culture positive in 70–80%; Xpert MTB/RIF on node biopsy near-100% (Ultra)
Pleura (≈20%)	Effusion from hypersensitivity to mycobacterial antigens (recent primary) or contiguous spread; fever, pleuritic pain, dyspnoea	Exudate, protein >50% of serum (≈4–6 g/dL), glucose normal–low, pH ≈7.3, WBC 500–6000/μL lymphocytic , rare mesothelial cells; ADA elevated (CMDT: >70 U/L ≈90% sens/spec); pleural biopsy granuloma/culture ≈80%; <i>pleural fluid Xpert NOT recommended (low sensitivity)</i>
Genitourinary (≈10–15%)	Cryptic/protean; dysuria, frequency, nocturia, haematuria, flank pain; female — tubes/endometrium → infertility; male — epididymis → tender mass/fistula	Sterile (culture-negative) pyuria in acidic urine ; 3 early-morning urine cultures positive in ≈90%; IVP/CT/MRI: calcification, ureteric stricture, hydronephrosis
Skeletal (≈10%)	Spine 40%, hip 13%, knee 10%; Pott’s disease = spondylitis of ≥2 adjacent vertebral bodies → disc involvement, kyphosis (gibbus) , paravertebral “cold” abscess (psoas)	CT/MRI; aspiration/bone biopsy (culture usually positive); synovial fluid/biopsy for peripheral joints
CNS — meningitis & tuberculoma (≈5%)	Subacute basal meningitis; weeks of fever/malaise → headache, cranial-nerve (esp. ocular) palsies, vasculitic infarcts, hydrocephalus, coma;	CSF: lymphocytic pleocytosis (≤1000/μL), high protein 1–8 g/L , low glucose ; Xpert/Ultra preferred initial test (~80%) ; culture gold standard (≈80%);

Site (approx. share of EPTB)	Key clinical features	Best diagnostic approach
	tuberculoma → seizures/focal signs	MRI: basal enhancement, hydrocephalus; tuberculoma = ring-enhancing lesion
Gastrointestinal (≈3.5%)	Ileocaecum most affected; pain, obstruction, mass, hematochezia; mimics Crohn disease; anal fistula → suspect rectal TB	Histology + culture of intraoperative/endoscopic specimens
Peritoneal	Nonspecific pain, fever, ascites; coexisting cirrhosis confounds	Exudative, high-protein, lymphocytic fluid; smear/culture low-yield; laparoscopic peritoneal biopsy often required
Pericardial	Subacute or acute with friction rub; effusion → tamponade; case-fatality up to 40%	Exudative, lymphocytic, often haemorrhagic fluid; smear rarely positive; culture ≈⅓; high ADA/lysozyme/IFN-γ; risk of constrictive pericarditis

Miliary (disseminated) TB

- ▶ Due to **massive haematogenous spread**; primary infection in children, recent infection or reactivation in adults.
- ▶ Lesions are **yellowish 1–2 mm granulomas resembling millet seeds** (hence “miliary”).
- ▶ Protean presentation: fever, night sweats, weight loss, weakness; **hepatosplenomegaly and lymphadenopathy**.
- ▶ **Choroidal tubercles are pathognomonic** (fundoscopy positive in up to 30%); meningismus in <10%.
- ▶ CXR: **miliary reticulonodular pattern** (early film may be normal, especially in PLWH).
- ▶ Haematology: anaemia, leukopenia/lymphopenia, leukaemoid reactions, occasionally pancytopenia or DIC; deranged LFTs with hepatic involvement.
- ▶ TST **negative in up to half** of cases (anergy); bronchoalveolar lavage, transbronchial / liver / bone-marrow biopsy give bacteriologic/granulomatous confirmation.
- ▶ Variants: **cryptic miliary TB** (elderly, chronic intermittent fever) and **non-reactive (septicaemic) miliary TB** (overwhelming, pancytopenic, rapidly fatal, nongranulomatous lesions).
- ▶ **Glucocorticoids have not proved beneficial** in miliary TB; untreated it is lethal but curable with timely therapy.

Diagnostic principles in EPTB

- ▶ **High index of suspicion** is the single most important factor — invasive sampling of the involved site is the rule.

- ▶ **Tissue/fluid > cytology:** caseating granuloma on histology, AFB smear, mycobacterial culture (MGIT liquid culture positive in 10 days–3 weeks; Löwenstein-Jensen 4–8 weeks), and **drug-susceptibility testing**.
- ▶ **Nucleic-acid amplification** (Xpert MTB/RIF / Ultra) is the preferred initial test on CSF and a recommended replacement test for selected non-respiratory specimens (FNA, pleural/other biopsy, gastric lavage); it also detects **rifampicin resistance**. Sensitivity varies by specimen — **lowest in pleural fluid (50%; 71% with Ultra), highest in synovial fluid (97%) and lymph-node biopsy (100% with Ultra)**.
- ▶ **Biomarkers:** elevated **adenosine deaminase (ADA)**, lysozyme and IFN- γ support TB in pleural, pericardial and peritoneal fluid.
- ▶ **Urine LF-LAM (lipoarabinomannan)** assay aids diagnosis in advanced HIV (CD4 $\leq$ 200/ μ L inpatients, $<$ 100/ μ L outpatients).
- ▶ **Imaging:** CT for intra-abdominal disease and Pott's spine; MRI for bone and intracranial TB.

Treatment

- ▶ **Most forms of EPTB are treated with the standard 6-month regimen** used for pulmonary TB: 2 months HRZE (intensive) + 4 months HR (continuation) = 2HRZE/4HR, daily throughout.
- ▶ Standard adult doses: Isoniazid 5 mg/kg (max 300 mg), Rifampin 10 mg/kg (max 600 mg), Pyrazinamide 25 mg/kg (max 2 g), Ethambutol 15 mg/kg.
- ▶ **TB meningitis:** ATS/CDC/IDSA recommend **extending the continuation phase to 7–10 months** (i.e. $\approx$ 9–12 months total). **Children with bone/joint TB, TB meningitis or miliary TB should receive up to 12 months** (2-month induction + 10-month consolidation).
- ▶ **Adjunctive glucocorticoids** improve survival/reduce disability in **TB meningitis** (dexamethasone or prednisolone tapered over 6–8 weeks, per WHO) and **may be used** in tuberculous pericarditis (note: the IMPI trial showed no overall benefit; ATS/CDC/IDSA do not advise routine use). Steroids are **not beneficial** in miliary or pleural TB.
- ▶ **Surgery** is adjunctive — drainage of large cold/psoas abscesses (paraparesis from spinal cord compression is an emergency), decortication for tuberculous empyema, relief of ureteric stricture/hydronephrosis, pericardiectomy for constriction, and resection in bowel obstruction/perforation.
- ▶ **HIV co-infection:** start ART early (within 2 weeks) — **but delay ART for 8 weeks in CNS TB** because of IRIS risk; use rifampicin-compatible ART (e.g. double-dose dolutegravir, or efavirenz; rifabutin as alternative).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Descending-frequency chart of EPTB sites** — horizontal bars labelled: *Lymph node* $\approx 35\%$, *Pleura* $\approx 20\%$, *Genitourinary* $\approx 10\text{--}15\%$, *Bone/joint* $\approx 10\%$, *Meninges* $\approx 5\%$, *Gastrointestinal* $\approx 3.5\%$, *Peritoneum*, *Pericardium*.
- ▶ **Pott's disease (spinal TB) schematic** — label: *two adjacent vertebral bodies, destroyed intervertebral disc, anterior vertebral wedging/collapse, kyphotic angulation = gibbus, paravertebral "cold" abscess tracking to psoas/groin, spinal cord compression $\rightarrow$ paraplegia.*

Clinical / Diagnostic significance

- ▶ **Culture-negative sterile pyuria in acidic urine** is a classic clue to renal TB; 3 morning urine cultures clinch it.
- ▶ **Pleural fluid ADA / lymphocytic exudate with pleural biopsy** (not fluid Xpert) is the practical pathway to pleural TB; *choroidal tubercles* confirm miliary disease at the bedside.
- ▶ **Pott's disease** spares the disc early (unlike pyogenic osteomyelitis, which destroys the disc rapidly with sclerosis) — a key differentiating radiological point; paraparesis from a compressing abscess is a **medical emergency**.
- ▶ **Tuberculous meningitis** is uniformly fatal if untreated and leaves neurological sequelae in $\approx 25\%$ even when treated — early empirical therapy on a positive Xpert plus dexamethasone is mandatory.
- ▶ **Ileocaecal TB vs Crohn disease** is a recurring diagnostic dilemma; tissue for AFB/culture/granuloma and therapeutic response are decisive.
- ▶ EPTB diagnosis frequently mandates **invasive sampling** — FNAC/excision biopsy (node), needle pleural biopsy, D&C (endometrium), laparoscopy (peritoneum), pericardiocentesis/biopsy.

High-yield exam pointers

- ▶ EPTB = 10–40% of TB; **lymph node** is the commonest form (scrofula = cervical/supraclavicular nodes).
- ▶ **Pleural fluid**: lymphocytic exudate, ADA >70 U/L ($\approx 90\%$ sens/spec); **do NOT Xpert the fluid** — biopsy the pleura.
- ▶ **Renal TB**: sterile pyuria in acid urine; 3 morning urine cultures $\approx 90\%$ positive.
- ▶ **Pott's spine**: ≥ 2 adjacent vertebrae, disc spared early, **gibbus**, **psoas cold abscess**, paraplegia.
- ▶ **TB meningitis**: basal, cranial-nerve palsies, lymphocytic CSF (high protein, low glucose); **Xpert preferred**, culture gold standard; **add steroids**; extend therapy to 9–12 months.
- ▶ **Miliary TB**: millet-seed granulomas, **choroidal tubercles pathognomonic**, TST often negative; steroids not helpful.
- ▶ **Pericardial TB**: haemorrhagic lymphocytic effusion, high ADA, risk of constriction; tamponade is the acute danger.

- ▶ Standard treatment = 2HRZE/4HR for most EPTB; CNS/skeletal/miliary in children → up to 12 months.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Tuberculosis" (extrapulmonary forms, diagnosis, regimens, drug doses, special clinical situations).
- ▶ CMDT 2026 — "Pulmonary Disorders: Tuberculosis" (pleural fluid ADA, NAAT/Xpert diagnostics, imaging).



Gastrointestinal Tuberculosis

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Gastrointestinal (GI) tuberculosis (TB) is infection of the gut lumen, peritoneum, mesenteric lymph nodes and solid abdominal viscera by *Mycobacterium tuberculosis* (and, where bovine disease persists, *M. bovis*). It is the sixth commonest form of extrapulmonary TB and accounts for only ~3.5% of extrapulmonary cases in low-burden settings, but is common in India and other high-burden regions. The **terminal ileum and caecum** are the sites most often involved. Because it mimics Crohn disease, ileocaecal carcinoma, lymphoma and amoebiasis, it is a notorious "great imitator" requiring a high index of suspicion.

Epidemiology & Pathogenesis

- ▶ **Burden** — uncommon in the United States/Europe (mainly immigrants and patients with untreated AIDS); common in underdeveloped/high-prevalence countries including India.
- ▶ **Routes of seeding** (any may operate concurrently):
 - **Swallowing of infected sputum** with direct mucosal seeding (in active pulmonary TB).
 - **Haematogenous spread** from a pulmonary or miliary focus (explains peritoneal and solid-organ disease).
 - **Ingestion of milk** from cows with bovine TB (*M. bovis*) — relevant where pasteurisation is incomplete.
 - **Direct/contiguous spread and retrograde lymphatic spread** from ruptured mesenteric nodes and adjacent intra-abdominal organs (e.g., genital TB in women causing peritonitis).
- ▶ **Association with pulmonary TB** — coexistent **active pulmonary disease is present in <50%** of patients, so a normal chest radiograph does *not* exclude abdominal TB.
- ▶ **Ileocaecal predilection** is attributed to abundant lymphoid (Peyer patch) tissue, physiological stasis and increased contact time of bacilli with the mucosa at this site.

Pathology & morphological types

- ▶ The basic lesion is the **caseating epithelioid-cell granuloma**; in the gut these are characteristically **large, confluent, submucosal and few in number**, with surrounding lymphoid cuffs.
- ▶ Three classical macroscopic forms (standard surgical/pathological classification):
 - **Ulcerative** — multiple superficial, **transversely orientated (“girdle”) ulcers** of the antimesenteric border; the predominant pattern in florid disease and a cause of bleeding/perforation.
 - **Hypertrophic** — marked fibroblastic reaction with a thickened, mass-like bowel wall (especially ileocaecal), mimicking carcinoma and producing a palpable mass.
 - **Ultero-hypertrophic (stricturing)** — mixed pattern with ulceration plus fibrosis causing **strictures and obstruction**.
- ▶ Healing by fibrosis produces **short, concentric strictures**, a contracted caecum and a **patulous/incompetent ileocaecal valve**.

Clinical patterns & features

GI TB presents in four overlapping clinico-anatomical forms — luminal (intestinal), peritoneal, nodal and visceral.

- ▶ **Intestinal (luminal) TB** (commonest; ileocaecal):
 - Chronic **abdominal pain** (right iliac fossa pain at times mimicking appendicitis), **subacute/recurrent intestinal obstruction**, abdominal distension.
 - **Weight loss, low-grade fever, anorexia, night sweats**, diarrhoea or altered bowel habit.
 - A **palpable doughy mass** in the right iliac fossa (hypertrophic disease).
 - **Hematochezia/GI bleeding**, fistulae and, less often, free perforation.
 - With wall involvement, ulcers and fistulae **simulate Crohn disease** — the differential is “always difficult”; **anal fistulae should prompt evaluation for rectal TB**.
- ▶ **Tuberculous peritonitis** — follows rupture of caseous mesenteric nodes / spread from intra-abdominal organs (e.g., female genital TB) or haematogenous seeding. Three subtypes are recognised: **wet (ascitic)**, **dry/plastic (fibroadhesive)**, and **encysted (loculated)**. The classic triad is **nonspecific abdominal pain, fever and ascites**; “doughy abdomen” is described in the plastic form.
- ▶ **Nodal TB** — mesenteric/peripancreatic lymphadenopathy, often with central (caseous) necrosis on CT.
- ▶ **Visceral TB** — hepatic, splenic, pancreatic and peritoneal-fold involvement (uncommon).
- ▶ *Caveat*: coexisting **cirrhosis** greatly complicates recognition of tuberculous peritonitis, as both cause ascites.

Investigations / Diagnosis

- ▶ **Ascitic fluid (paracentesis) in peritonitis** — exudative fluid with **high protein**, **lymphocyte-predominant leucocytosis** (neutrophils occasionally early), and a **low serum–ascites albumin gradient (SAAG <1.1 g/dL)**. Direct smear and culture have **low yield**; culturing a large volume improves it. Elevated **adenosine deaminase (ADA)** supports the diagnosis (a value >~39 U/L is the commonly cited threshold).
- ▶ **Imaging** — **abdominal CT** shows thickening of the **caecum and ileocaecal valve**, mural thickening, **necrotic (“caseous”) mesenteric lymphadenopathy**, omental/peritoneal thickening and ascites; CT is also useful for other intra-abdominal/Pott disease.
- ▶ **Colonoscopy/ileoscopy with biopsy** — ulcerated mass, **ulcers with steep/undermined edges**, **transversely oriented ulcers**, **sessile inflammatory polyps**, **deformed patulous ileocaecal valve**, strictures, or pseudodiverticula, most often in the ileocaecal region; multiple deep biopsies from ulcer edges raise yield.
- ▶ **Histology/microbiology of biopsy or operative specimen** — diagnosis is confirmed by **caseating granuloma**, **acid-fast bacilli (AFB)** and/or **positive culture**. **PCR / nucleic-acid amplification on tissue** is now the most sensitive means of diagnosis.
- ▶ **Molecular tests** — **Xpert MTB/RIF** and **Xpert MTB/RIF Ultra** are the preferred initial tests on nonrespiratory specimens (FNA, biopsy, fluid); they confirm TB and detect **rifampin resistance** in <2 h.
- ▶ **Peritoneal biopsy (best obtained at laparoscopy)** is often required when fluid studies are nondiagnostic; laparoscopy permits direct visualisation and biopsy of peritoneum, liver and nodes.
- ▶ **Tuberculin skin test (PPD)** may be **negative**, especially with weight loss or AIDS, so a negative test does not exclude disease. Because surgery is needed in many obstructive/complicated cases, diagnosis is frequently established on **intra-operative histology and culture**.

Intestinal TB vs Crohn disease

Feature	Intestinal tuberculosis	Crohn disease
Ulcers	Transverse / circumferential (“girdle”)	Longitudinal, aphthous; cobblestoning
Distribution	Short segment, ileocaecal; patulous IC valve	Skip lesions; long segment; perianal disease
Granuloma	Caseating, large, confluent, submucosal, few	Non-caseating, small, discrete, numerous
AFB / culture / TB-PCR	May be positive	Negative
Strictures/fistulae	Short concentric strictures	Long strictures, multiple fistulae
Response to ATT	Mucosal healing on anti-TB therapy	No response to ATT

Note: misdiagnosing TB as Crohn (and giving steroids/anti-TNF) can cause fulminant dissemination — hence a **diagnostic anti-TB trial** is used when distinction is impossible.

Treatment / Management

- ▶ **First-line chemotherapy** is the same as for pulmonary TB: **2 months HRZE → 4 months HR** (2HRZE/4HR); this cures >90% of drug-susceptible cases. Many authorities extend the continuation phase to give a **total of 6–9 months** for extensive abdominal disease, but the corpus-supported standard is the **6-month regimen**.
- ▶ **Standard adult daily doses** (Harrison Table 183-2):
 - Isoniazid (H) 5 mg/kg, max 300 mg
 - Rifampin (R) 10 mg/kg, max 600 mg
 - Pyrazinamide (Z) 25 mg/kg, max 2 g
 - Ethambutol (E) 15 mg/kg
 - (paediatric doses are higher per kg, e.g., H 10 mg/kg).
- ▶ **Drug-resistant disease** — if rifampin resistance is detected (e.g., on Xpert), manage as MDR-TB with WHO Group A–C agents (bedaquiline, levofloxacin/moxifloxacin, linezolid, clofazimine, cycloserine, etc.).
- ▶ **Surgery** is reserved for complications — **obstruction unrelieved by medical therapy, perforation, massive haemorrhage, fistula or abscess**; stricturoplasty/limited resection is preferred over extensive resection. Anti-TB therapy must continue post-operatively.
- ▶ **Supportive care** — nutritional rehabilitation, correction of anaemia, and monitoring for hepatotoxicity (H/R/Z) and **ethambutol ocular toxicity**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled ileocaecal TB diagram:** terminal ileum, thickened/contracted caecum, incompetent (patulous) ileocaecal valve, transverse “girdle” ulcers, short fibrotic stricture, enlarged caseous mesenteric lymph nodes, and a hypertrophic ileocaecal mass.
- ▶ **Diagnostic algorithm box:** Suspected abdominal TB → CT abdomen + colonoscopy/ascitic tap → biopsy/fluid for histology (caseating granuloma), AFB, culture, Xpert MTB/RIF, TB-PCR → if nondiagnostic → laparoscopy + peritoneal biopsy → start 2HRZE/4HR.

Clinical / Diagnostic significance

- ▶ **Right-iliac-fossa mass + constitutional symptoms** in an endemic-area patient should trigger work-up for ileocaecal TB before labelling it appendicular mass or carcinoma.
- ▶ **Low-SAAG, high-protein, lymphocytic ascites with raised ADA** strongly suggests tuberculous peritonitis; laparoscopy is the most reliable confirmatory step.

- ▶ The **TB-vs-Crohn dilemma** has major therapeutic consequences — immunosuppression of misdiagnosed TB is dangerous; TB-PCR on biopsy and a therapeutic ATT trial resolve most cases.
- ▶ A **negative PPD and normal chest film do not exclude** the diagnosis (active pulmonary disease in <50%).

High-yield exam pointers

- ▶ Commonest GI site = **terminal ileum + caecum**; commonest extra-luminal form = **tuberculous peritonitis**.
- ▶ Three pathological types = **ulcerative, hypertrophic, ulcero-hypertrophic**; ulcers are **transverse**, valve becomes **patulous**.
- ▶ TB granuloma = **caseating, large, confluent, submucosal, few**; Crohn = **non-caseating, small, many**.
- ▶ **Xpert MTB/RIF/Ultra** = preferred rapid test (also gives rifampin resistance); **tissue TB-PCR** = most sensitive.
- ▶ Ascites: **exudate, high protein, lymphocytic, SAAG <1.1, raised ADA**; low smear/culture yield → **laparoscopic peritoneal biopsy**.
- ▶ Treatment = **2HRZE/4HR**, cures >90%; doses H 5 / R 10 / Z 25 mg/kg, E 15 mg/kg.
- ▶ Surgery only for **obstruction, perforation, bleeding, fistula** — continue ATT after.
- ▶ **Anal fistula** → think rectal TB; **bovine TB (M. bovis) via unpasteurised milk** is a recognised route.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Tuberculosis" (extrapulmonary section: *Gastrointestinal TB* and *Tuberculous peritonitis*; diagnosis — nucleic-acid amplification/Xpert MTB/RIF; Table 183-2 drug dosages; Table 183-4 regimens 2HRZE/4HR).
- ▶ **CMDT 2026** — "Gastrointestinal Disorders" (*Intestinal Tuberculosis*: ileocaecal predilection, CT/colonoscopy findings, PPD, biopsy/PCR diagnosis) and the ascites/SAAG and laparoscopy discussion for tuberculous peritonitis.
- ▶ **Coverage note**: The cited corpus (Harrison 22e + CMDT 2026) covers epidemiology, pathogenesis, ileocaecal disease, peritonitis, diagnostics and therapy directly. The three **morphological types** (ulcerative/hypertrophic/ulcero-hypertrophic), the wet/dry/encysted peritonitis subtypes, the detailed **TB-vs-Crohn histology/ulcer comparison**, and the **ADA cut-off (~39 U/L)** are presented as universally accepted standard textbook internal medicine/surgical pathology, used to organise (not contradict) the corpus, which states

only that intestinal TB “may simulate Crohn disease” and that ADA elevation supports a tuberculous aetiology.



Genital Ulcerations due to Infections

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Genital ulcer disease (GUD) is a syndrome of one or more breaks in the skin or mucosa of the genitalia, perineum or anus, most often sexually transmitted. It is clinically important because the same ulcers sharply **increase the risk of sexual acquisition and shedding of HIV**, and because the cause cannot be reliably named on inspection alone—syndromic, test-supported management is therefore standard. Five classic infectious causes dominate: **genital herpes (HSV)**, **primary syphilis**, **chancroid**, **lymphogranuloma venereum (LGV)** and **donovanosis (granuloma inguinale)**; today *genital herpes is by far the commonest cause worldwide*.

Aetiology and epidemiology

- ▶ **The five major infectious causes:** HSV-1/HSV-2 (genital herpes); *Treponema pallidum* (primary syphilis – the chancre); *Haemophilus ducreyi* (chancroid/soft sore); *Chlamydia trachomatis* serovars L1–L3 (LGV); *Klebsiella granulomatis* (donovanosis / granuloma inguinale).
- ▶ **Relative frequency:** In a 1996 study of genital ulcers in 10 U.S. cities with the highest rates of primary syphilis, PCR detected **HSV in 62%, T. pallidum in 13%, and H. ducreyi in 12–20%.* *With PCR testing, genital herpes is now the single commonest cause** of genital ulceration in both industrialised and most developing countries.
- ▶ In Asia and Africa, **chancroid** was once the commonest ulcer, followed by primary syphilis then herpes; control programmes, broad-spectrum antibiotic use and HIV-driven persistence of herpes have shifted the balance toward HSV.
- ▶ LGV had nearly disappeared from industrialised nations but is re-emerging as outbreaks of **proctitis in MSM**, frequently with concurrent **HIV and/or hepatitis C** infection.
- ▶ **Donovanosis** and LGV remain endemic causes of ulceration in some developing countries.

Clinical features — the five classic ulcers

- ▶ **Genital herpes (HSV)** — short incubation (2–7 days); a *vesicle* progresses to multiple small (1–2 mm), shallow, *painful/tender* ulcers on an erythematous base; tender, often bilateral inguinal nodes with the first episode; recurrences are common (more so with HSV-2). “Atypical” or trivial ulcers may be commoner than classic vesiculopustular lesions.
- ▶ **Primary syphilis (chancre)** — incubation 9–90 days (average ~2–6 weeks, rarely >6 weeks). A **single painless papule that erodes and becomes indurated** with a characteristic firm,

cartilaginous edge and base; usually solitary (multiple in a minority); base smooth, relatively non-vascular. Regional inguinal nodes are **firm, non-suppurative, painless and bilateral**, appearing within ~1 week. Heals spontaneously in 4–6 weeks (range 2–12 weeks). Sites: penis (heterosexual men); anal canal, rectum or mouth (MSM); cervix, vaginal wall, labia (women)—hence often unrecognised in women and MSM.

- ▶ **Chancroid (H. ducreyi) — incubation 1–14 days; begins as a pustule that breaks down into multiple, deep, excavated, very tender ulcers with undermined, ragged, irregular edges and a purulent base that bleeds easily**; tender, suppurative, loculated, usually unilateral inguinal nodes (bubo).
- ▶ **Lymphogranuloma venereum (C. trachomatis L1–L3) — a small, often painless, transient papulo-vesicular ulcer that is frequently not noticed; dominated instead by tender inguinal/femoral lymphadenopathy. The “sign-of-the-groove” (nodes above and below Poupart’s (inguinal) ligament) is suggestive but not specific. Anogenital LGV presents as severe proctitis/proctocolitis* that can mimic Crohn’s disease.*
- ▶ **Donovanosis / granuloma inguinale (K. granulomatis) — incubation 1–4 weeks (up to 6 months); elevated, beefy-red, velvety ulcer that bleeds readily; usually painless; true lymphadenopathy is absent but subcutaneous granulomas form pseudobuboes*.*

Comparison table (Harrison Table 141-7)

Feature	Syphilis (chancr e)	Genital herpes	Chancroid	LGV	Donovanosis
Organism	<i>T. pallidum</i>	HSV-1 / HSV-2	<i>H. ducreyi</i>	<i>C. trachomatis</i> L1–L3	<i>K. granulomatis</i>
Incubation	9–90 days	2–7 days	1–14 days	3 days–6 weeks	1–4 weeks (up to 6 mo)
Primary lesion	Papule	Vesicle	Pustule	Papule/pustule/vesicle	Papule
Number	Usually one	Multiple	Multiple, may coalesce	Usually one (often missed)	Variable
Edge / base	Sharply demarcated, indurated; smooth base	Erythematous, serous	Undermined, ragged; purulent, bleeds	Variable	Elevated, beefy-red, velvety; bleeds
Pain	Uncommon (painless)	Frequently tender	Very tender	Variable / mild	Uncommon

Feature	Syphilis (chancere)	Genital herpes	Chancroid	LGV	Donovanosis
Lymphadenopathy	Firm, non-tender, bilateral	Firm, tender, often bilateral (first episode)	Tender, suppurative, loculated, unilateral	Tender, may suppurate, unilateral	None; pseudobuboes

- ▶ **Memory aid:** *painful* ulcers = **herpes + chancroid**; *painless* ulcers = **syphilis + LGV + donovanosis**.

Non-classic and non-venereal causes (to exclude)

- ▶ Candidiasis and **traumatised genital warts**; genital involvement by widespread **dermatoses**.
- ▶ Cutaneous manifestations of **systemic disease** — e.g. genital mucosal ulceration in **Stevens-Johnson syndrome** or **Behçet's disease**.
- ▶ **Superinfection** of an originally STI lesion (e.g. MRSA complicating an HSV-2 ulcer).
- ▶ **Localised drug reactions** (e.g. topical paromomycin or boric acid preparations).
- ▶ A persistent ulcer must also raise suspicion of **carcinoma** and other non-venereal dermatoses.

Diagnostic approach

- ▶ ***Order a rapid serologic test for syphilis in every genital ulcer, and counsel and test all patients for HIV*** (and consider other STIs).
- ▶ **Syphilis:** dark-field microscopy, direct fluorescent antibody (DFA), or NAAT/PCR for *T. pallidum* from the lesion; serology = a **lipoidal (non-treponemal) test** (VDRL/RPR) plus a **treponemal test** (TPPA, EIA/CIA, FTA-ABS). Caveat: **~30% of chancres have an initially non-reactive serology** (both lipoidal and treponemal tests may be negative in very early primary syphilis)—so treat presumptively and repeat serology.
- ▶ **Herpes:** PCR/NAAT (most sensitive), culture, direct FA, or ELISA from the lesion; type-specific HSV-2 serology has limited value (may be falsely negative early/with HSV-1, and a positive result does not prove the current lesion is herpetic).
- ▶ **Chancroid:** culture (or PCR where available) for *H. ducreyi*—most useful when ulcers are painful and purulent with fluctuant nodes; **aspirate fluctuant nodes** for culture/PCR and Gram stain.
- ▶ **Persistent ulcer** (beyond the natural history—herpes 2–3 weeks, chancroid/syphilis up to ~6 weeks) that fails syndromic therapy → **biopsy** to exclude **donovanosis, carcinoma** and non-venereal causes.

Syndromic management (Harrison Table 141-8)

- ▶ **Principle:** after collecting all diagnostic specimens at the first visit, give **immediate syndrome-based treatment** without waiting for all results, because early therapy of HSV, syphilis and chancroid reduces morbidity and onward HIV transmission.
- ▶ **Herpes (confirmed/suspected):** oral **acyclovir, valacyclovir or famciclovir**.
- ▶ **Syphilis:** **benzathine penicillin G 2.4 million units IM single dose** (treat patient and recent—within ~3 months—seronegative partners). Penicillin G is the drug of choice for all stages; alternatives for non-pregnant penicillin-allergic patients are **doxycycline 100 mg PO BD** or **tetracycline 500 mg PO QID** for 2 weeks.
- ▶ **Chancroid (confirmed/suspected):** **ciprofloxacin 500 mg PO single dose, or ceftriaxone 250 mg IM single dose, or azithromycin 1 g PO single dose**.
- ▶ **LGV (e.g. proctitis):** **doxycycline 100 mg PO BD for 21 days** (alternative: azithromycin 1 g once weekly × 3 weeks).
- ▶ **Partner management, HIV testing/counselling and STI screening** are integral.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — “Five classic genital ulcers” comparison chart:** five labelled boxes/columns — *Syphilis (chancre)*, *Herpes*, *Chancroid*, *LGV*, *Donovanosis* — each labelled with **Organism, Incubation, Painful/Painless, Edge (indurated / undermined / beefy-red), Lymphadenopathy (non-tender bilateral / tender bilateral / suppurative unilateral bubo / sign-of-the-groove / pseudobuboes)**.
- ▶ **Diagram 2 — Syndromic algorithm for a genital ulcer:** boxes labelled *Genital ulcer* → *take history + examine* → *collect specimens (dark-field/PCR for *T. pallidum*, PCR/culture for HSV ± *H. ducreyi*) + RPR/VDRL + offer HIV test* → *vesicles/painful = treat herpes; painless indurated = treat syphilis (benzathine penicillin 2.4 MU IM); painful purulent + bubo = treat chancroid* → *review; persistent ulcer* → *biopsy (exclude donovanosis/carcinoma)*.

Clinical / Diagnostic significance

- ▶ GUD is a powerful **co-factor for HIV transmission and acquisition**—ulcer control is an HIV-prevention strategy.
- ▶ **Jarisch-Herxheimer reaction** can follow the first dose of penicillin in syphilis: self-limited fever, chills, myalgia, headache, tachycardia and increased respiratory rate from lipoproteins released by dying treponemes; occurs in ~50% of primary and ~90% of secondary cases—warn the patient (and pregnant women, in whom it may cause mild contractions).
- ▶ **Post-treatment serologic follow-up** of syphilis: monitor quantitative VDRL/RPR for a **fourfold (two-dilution) decline**; review primary/secondary syphilis at 6 and 12 months (more often if HIV-co-infected).

- ▶ LGV rectal biopsy shows crypt abscesses, granulomas and giant cells—**mimicking Crohn's disease**; recognition matters because LGV is curable with doxycycline.
- ▶ Recognise non-infectious ulcers (**Behçet's, Stevens-Johnson, fixed drug eruption, malignancy**) to avoid missing serious systemic disease.

High-yield exam pointers

- ▶ **Painful ulcers** → herpes + chancroid; **painless ulcers** → syphilis + LGV + donovanosis.
- ▶ **Genital herpes is now the commonest cause of GUD** worldwide (HSV 62%, *T. pallidum* 13%, *H. ducreyi* 12–20% in the classic 10-city study).
- ▶ **Chancre** = single, painless, indurated, *cartilaginous* ulcer with firm, non-tender, **bilateral** inguinal nodes; **~30% have non-reactive serology** initially.
- ▶ **Chancroid** = multiple, deep, painful ulcers with **undermined ragged edges** + tender **suppurative unilateral bubo**.
- ▶ **LGV** = inconspicuous ulcer + tender adenopathy with the “**sign-of-the-groove**”; re-emerging as proctitis in MSM; Rx **doxycycline 21 days**.
- ▶ **Donovanosis** = **beefy-red, velvety, bleeding ulcer, pseudobuboes**, diagnosed on **biopsy** (Donovan bodies).
- ▶ **Always do syphilis serology and offer HIV testing in every genital ulcer.**
- ▶ Syphilis Rx = **benzathine penicillin 2.4 MU IM single dose**; chancroid Rx = single-dose **azithromycin / ceftriaxone / ciprofloxacin**.
- ▶ **Biopsy any ulcer persisting beyond its natural history** (to exclude donovanosis and carcinoma).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 141 “Sexually Transmitted Infections: Overview and Clinical Approach” (Tables 141-7 clinical features and 141-8 initial management of genital/perianal ulcer) and Ch 187 “Syphilis” (primary chancre, serology, treatment, Jarisch-Herxheimer reaction). *Coverage note:* detailed clinical descriptions of chancroid, LGV and donovanosis are summarised within Ch 141; their dedicated chapters (Ch 162 chancroid, Ch 178 donovanosis, Ch 197 HSV) were not provided, so organism-level detail (e.g. LGV serovars L1–L3, Donovan bodies) is given from universally accepted standard internal-medicine teaching consistent with the provided text.



Immune Reconstitution Inflammatory Syndrome (IRIS)

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Immune reconstitution inflammatory syndrome (IRIS) is a *paradoxical clinical deterioration* that follows the recovery of pathogen-specific immunity, most classically after initiation of effective antiretroviral therapy (ART) in a person with advanced HIV disease. It represents a dysregulated, exaggerated inflammatory response — directed against the antigens of a treated, partially treated, or previously undiagnosed opportunistic infection (or, less often, a tumour or autoimmune antigen) — that emerges precisely *because* immune function is restored. It is therefore not a treatment failure but a sign of immune recovery, and is a diagnosis of exclusion.

Pathogenesis / Immunology

- ▶ Triggered by the rapid restoration of antigen-specific (predominantly CD4+ T-cell) immunity as plasma HIV-RNA falls and CD4 counts rise after ART.
- ▶ The underlying mechanism resembles a **type IV (delayed/cell-mediated) hypersensitivity reaction** — a vigorous immune response mounted against the antigens of organisms present in the tissues.
- ▶ Antigenic stimulus is provided both by *viable* organisms and by **antigens released as bacilli/fungi are killed** during effective antimicrobial chemotherapy; the recovering immune system suddenly “sees” this antigen load and reacts intensely.
- ▶ Characterised by a surge of pro-inflammatory cytokines — **IL-6, TNF- α , IFN- γ , IL-12p40, IL-10 and IFN- γ -inducible protein-10 (IP-10)** — whose suppression underlies the benefit of glucocorticoids.
- ▶ The term **immune reconstitution disease (IRD)** is sometimes used to separate IRIS due to *opportunistic infections/tumours* from IRIS related to *autoimmune* disease; IRD is especially common with underlying untreated mycobacterial or fungal infection.

Classification (two clinical forms)

Feature	Paradoxical IRIS	Unmasking IRIS
Underlying condition	Known, already-diagnosed (often partially treated) opportunistic infection / neoplasm	Previously undiagnosed , subclinical infection
What ART does	Causes worsening/flare of the existing, treated condition	“Unmasks” a latent infection that becomes clinically apparent
Typical example	Worsening lymphadenitis or new pulmonary infiltrates in a treated TB patient	New active TB or cryptococcal disease appearing after ART start
Inflammatory component	Prominent	Prominent, may mimic acute primary infection

- ▶ Beyond infections, ART may also **exacerbate pre-existing autoimmune conditions or trigger new ones** (e.g. *Graves’ disease*, sarcoidosis).

Epidemiology & risk factors

- ▶ Some form of IRIS occurs in **10–30%** of patients after starting ART (varies with setting); TB-associated IRIS occurs in **~10%** of HIV-infected TB patients.
- ▶ **Strongest risk factor:** starting ART at a very low **CD4+ count** (<50 cells/ μ L) together with a *precipitous drop in HIV-RNA*.
- ▶ The **earlier** ART is begun after starting treatment of the opportunistic infection, and the **lower the baseline CD4 count**, the **greater the risk** of IRIS.
- ▶ Disseminated / **extrapulmonary** disease and **advanced immunosuppression** increase risk.
- ▶ IRIS is largely confined to ART-treated HIV patients but analogous syndromes occur in **transplant recipients** (after reduction of immunosuppression), in **neutropenia recovery**, post-partum, and occasionally even in non-immunocompromised hosts (e.g. cryptococcosis).
- ▶ **Timing of onset:** anywhere from **2 weeks to 2 years** after ART; for TB-IRIS typically **1–3 months** after ART initiation.

Clinical spectrum (organism-specific manifestations)

Pathogen / condition	Characteristic IRIS presentation
Mycobacterium tuberculosis	Fever, enlarging lymphadenopathy, worsening pulmonary infiltrates, new pleural effusion; <i>CNS-TB → serious neurological deterioration, can be fatal</i>
Mycobacterium avium complex	Focal, often suppurative lymphadenitis or granulomatous masses
Cryptococcus neoformans	Recurrent meningitis-like picture, fever, headache, lymphadenopathy, raised ICP; hard to distinguish from relapse
CMV retinitis	Immune-recovery vitritis/uveitis
JC virus (PML)	Atypical/worsening course of progressive multifocal leukoencephalopathy
Kaposi sarcoma	Flare/worsening of lesions shortly after ART start
Hepatitis B/C	Flare of hepatitis (immune-mediated hepatic injury)
Autoimmune	<i>Graves' disease</i> , sarcoidosis, new autoimmune phenomena

- ▶ General manifestations from Harrison: localized lymphadenitis, prolonged fever, pulmonary infiltrates, hepatitis, raised intracranial pressure, uveitis, sarcoidosis and Graves' disease. The course can be protracted and severe cases may be **fatal**.

Diagnosis

- ▶ **There is no confirmatory diagnostic test** — IRIS is a **clinical diagnosis of exclusion** resting on case definitions that combine clinical and laboratory data.
- ▶ Essential first step: **exclude the alternatives** —
 - *failure of the antimicrobial therapy* (e.g. drug-resistant or inadequately treated TB),
 - *a new/second opportunistic infection*,
 - *drug toxicity or hypersensitivity*, and
 - *non-adherence / poor drug levels*.
- ▶ Supportive features: temporal link to ART, documented **fall in HIV-RNA and rise in CD4**, and an inflammatory (rather than purely infective) clinical picture.
- ▶ For cryptococcosis, a tissue biopsy may be required to distinguish inadequately treated infection from IRIS.

Management & timing of ART (prevention)

- ▶ **General principle:** *continue ART* wherever possible — IRIS reflects desirable immune recovery; stopping ART is reserved for life-threatening situations.
- ▶ **Mild–moderate paradoxical reactions:** symptomatic/supportive management; these do not worsen TB-treatment outcomes.
- ▶ **Severe reactions:** **glucocorticoids** to blunt inflammation while specific antimicrobial therapy continues. For severe TB-IRIS, **prednisolone for 4 weeks** (*1.5 mg/kg/day for 2 weeks, then half that dose for the remaining 2 weeks* — the Meintjes regimen) reduces hospitalisation and therapeutic procedures and hastens symptom relief, mediated by suppression of IL-6, IL-10, IL-12p40, TNF- α , IFN- γ and IP-10.
- ▶ **Optimising the timing of ART** is the key preventive strategy:

Co-infection	Recommended ART timing	Rationale
TB meningitis	Do NOT start ART within the first 8 weeks of anti-TB therapy	CNS-TB IRIS can cause fatal neurological deterioration
Cryptococcal meningitis	Start ART 4–6 weeks after starting antifungal therapy	Early ART increases IRIS and mortality
Cryptococcal antigenaemia (no active disease)	Pre-emptive fluconazole; start ART 2 weeks after antifungal therapy	Treat occult infection before immune recovery

- ▶ **Prophylactic dexamethasone is NOT recommended** in HIV-associated cryptococcosis — it is associated with **reduced fungal clearance and increased mortality**.
- ▶ Screen high-risk patients (CD4 <100–200/ μ L) with **serum cryptococcal antigen (CRAg)** before ART to detect occult infection and avert unmasking IRIS.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Timeline / mechanism schematic:** horizontal time-axis labelled “ART started”. Two crossing curves — one falling “HIV-RNA / viral load”, one rising “CD4+ T-cell count”. Mark the inflammatory peak (“IRIS: 2 weeks–2 years; TB-IRIS 1–3 months”) at the crossover. Side boxes labelled: *Antigen load (live organisms + dead-organism antigens) → Restored CD4 / Type IV hypersensitivity response → Cytokine surge (IL-6, TNF- α , IFN- γ , IP-10) → Tissue inflammation.*
- ▶ **Two-arm classification box:** central node “IRIS” branching to “Paradoxical (known, treated infection worsens)” and “Unmasking (previously undiagnosed infection appears)”, each with one example (TB lymphadenitis flare; new cryptococcal meningitis).

Clinical / Diagnostic significance

- ▶ Anticipate IRIS in any patient who deteriorates *after* starting ART, particularly with baseline CD4 <50/ μ L — recognising it avoids the dangerous reflex of stopping life-saving ART or escalating (unnecessary) second-line antimicrobials.
- ▶ Mandates a careful **work-up to exclude treatment failure and new OIs** before attributing deterioration to IRIS.
- ▶ Drives the **sequencing of therapy**: treat the opportunistic infection first, then introduce ART after an appropriate interval (immediately–2 weeks for most OIs if CD4 very low, but **defer 8 weeks in TB meningitis** and **4–6 weeks in cryptococcal meningitis**).
- ▶ Justifies **CRAg screening** and pre-emptive antifungal therapy in advanced HIV to prevent unmasking cryptococcal IRIS.
- ▶ Glucocorticoids are a double-edged tool — beneficial in severe paradoxical reactions but harmful as *prophylaxis* in cryptococcosis.

High-yield exam pointers

- ▶ IRIS = paradoxical worsening after ART due to *restored immunity*; **not** drug or treatment failure.
- ▶ Two forms: **paradoxical** (known infection flares) vs **unmasking** (latent infection revealed).
- ▶ Highest risk: CD4 <50/ μ L + steep fall in viral load; commonest with **TB and cryptococcosis**.
- ▶ Onset **2 weeks–2 years** post-ART (TB-IRIS **1–3 months**); incidence **10–30%** overall, **~10%** in HIV-TB.
- ▶ Mechanism = **type IV hypersensitivity-like** reaction; cytokines IL-6, TNF- α , IFN- γ , IP-10.
- ▶ **Diagnosis of exclusion** — rule out treatment failure, new OI, drug toxicity.
- ▶ Management = **continue ART** + supportive care; **glucocorticoids only for severe disease** (TB-IRIS: prednisolone 1.5 mg/kg/day $\times$ 2 wk, then half $\times$ 2 wk).

- ▶ Timing rules: TB meningitis → no ART in first 8 weeks; cryptococcal meningitis → ART at 4–6 weeks; prophylactic dexamethasone contraindicated in cryptococcosis.
- ▶ Other faces: CMV immune-recovery uveitis/vitreitis, MAC suppurative lymphadenitis, KS flare, hepatitis B/C flare, Graves' disease.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Human Immunodeficiency Virus Disease: AIDS and Related Disorders” (IRIS section + Table 208-12, Characteristics of IRIS); “Tuberculosis” (TB-IRIS, ART timing in TB meningitis, prednisolone regimen, cytokine profile); “Cryptococcosis” (cryptococcal IRIS, ART timing 4–6 weeks, dexamethasone caution, CRAg screening).
- ▶ **CMDT 2026** — “HIV Infection & AIDS” (Inflammatory Reactions / IRIS — diagnosis of exclusion, conservative management, corticosteroids for severe reactions, CMV/MAC/KS examples).



Immunization for travel in adults

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Travel immunization is the pre-travel administration of vaccines to protect the international traveller against infections encountered en route or at the destination, and to satisfy entry/exit regulations of host countries. About 30% of travellers report a travel-related illness, and vaccine-preventable infections (influenza/COVID-19 most common, then typhoid and hepatitis A) are an important, preventable subset. Because several vaccines are given as a **series** and all take roughly a week to induce protective immunity, travellers should ideally be referred to a travel clinic **at least 4–6 weeks before departure**, though even last-minute consultation provides benefit.

Framework: the pretravel consultation and the three vaccine categories

- ▶ The pretravel consultation has four pillars: (1) **trip risk assessment** (itinerary + traveller), (2) **immunizations**, (3) **prevention of arthropod-borne infection (malaria/vector)**, and (4) **prevention of gastrointestinal illness** — with shared decision-making on whether to travel.
- ▶ Travel vaccines are traditionally grouped into three (overlapping) categories:
 - **Routine** — those on the national child/adult schedule (e.g., MMR, Tdap, influenza, hepatitis B); travellers must simply be *up to date*, since these infections occur worldwide.
 - **Recommended** — not on the routine schedule but advised because of *anticipated risk* from the specific itinerary (e.g., typhoid, hepatitis A, Japanese encephalitis, rabies).

- **Required** — *mandated* by international regulation or by a specific country for entry/exit; proof is documented on the **International Certificate of Vaccination or Prophylaxis (ICVP, the “yellow card”)**. The prototype is **yellow fever**; cholera and meningococcal (Hajj/Umrah) requirements also exist.
- A traveller without proof or a documented **medical waiver** for a required vaccine may face entry barriers, vaccination on arrival, quarantine or other penalties.

Vaccines to consider for most destinations

Vaccine	Primary series in unvaccinated adults	Booster	Key travel point
Hepatitis A (Havrix, Vaqta)	2 doses 6–12 mo (Havrix) / 6–18 mo (Vaqta) apart	Not required after series	One of the commonest VPIs in travellers; a single dose protects healthy young adults before travel; consider Ig 0.1 mL/kg if >40 y or immunocompromised
Hepatitis B (recombinant; Heplisav-B)	3 doses 0,1,6 mo; Heplisav-B 2 doses 0,1 mo	Not after routine series	Important for long-term travellers, HCWs, sexual exposure; Twinrix accelerated schedule (days 0,7,21–30) if departing soon
Influenza + COVID-19	Per current seasonal recommendation	Seasonal	<i>Most common</i> VPIs in travel; give influenza even if local season has peaked (year-round risk in tropics)
Measles–mumps–rubella (MMR)	2 doses ≥28 days apart	None	Resurgent worldwide; ensure 2-dose evidence of immunity; immune if born before 1957 ; only MMR available for adults
Tetanus–diphtheria–pertussis (Td/Tdap)	Age-appropriate per schedule	Td q10y	Early tetanus booster (<10 y) for high-injury trips; diphtheria booster within 5 y if outbreak destination
Varicella	2 doses	—	Evidence of immunity needed; immune if born in US before 1980 or prior disease/zoster

Vaccine	Primary series in unvaccinated adults	Booster	Key travel point
Poliomyelitis (IPV)	3 doses if never vaccinated	Single lifetime adult booster	One IPV booster before travel to countries with wild-type or circulating vaccine-derived poliovirus in prior 12 months

Destination- or activity-specific travel vaccines

Vaccine	Schedule / type	Indication / pearl
Yellow fever (live attenuated)	1 dose; valid for life, from day 10	Sub-Saharan Africa & tropical S. America; <i>required</i> — see below
Typhoid	Vi capsular polysaccharide (injectable, 1 dose, booster 2 y) or oral live attenuated (4 doses 48 h apart, booster 5 y)	Highest risk South Asia; oral vaccine contraindicated if immunocompromised ; <i>no protection against paratyphoid</i>
Japanese encephalitis (IXIARO, inactivated Vero-cell)	2 doses, days 0 and 7–28	Risk <1 per million travellers but ↑ in long-term/rural/evening exposure in Asia & W. Pacific
Rabies (HDCV/PCECV, pre-exposure)	2 doses days 0 and 7 (revised 2022)	Endemic on all continents except Antarctica; 3rd dose (21 d–3 y) or titre check if >3-y risk; PrEP still needs urgent post-exposure boosters
Meningococcal ACWY (conjugate)	1 dose	African “meningitis belt” in dry season (Dec–June); required for Hajj/Umrah within preceding 3 y; conjugate preferred over polysaccharide
Cholera (Vaxchora, live oral)	1 oral dose	Efficacy ~90% at 10 days, 80% at 3 months; for outbreak areas/HCWs who cannot maintain hygiene
Tick-borne encephalitis (inactivated)	3 doses; 2 doses adequate for short-term travel	Forested Europe/Asia; <i>Ixodes</i> tick; also via unpasteurised dairy
Chikungunya (live, 2023)	1 dose, age ≥18 y	For increased-exposure travellers; contraindicated if immunocompromised
Dengue	No FDA-approved vaccine for travellers	Dengvaxia only for seropositive endemic residents; Qdenga (EU, age ≥4) may be considered

Yellow fever — the prototype “required” vaccine

- ▶ **Live attenuated vaccine**, available **only at state-authorized yellow-fever clinics**, recorded on the ICVP; valid for entry from **day 10** after administration and for the **lifetime** of the vaccinee — the 10-yearly booster requirement was **removed from the WHO International Health Regulations in 2016**.
- ▶ **Booster after 10 years is still advised** for: women pregnant during primary immunization, persons with HIV at the time of vaccination, post-HSCT recipients, and those at especially high risk (epidemics, prolonged stay, peak season).
- ▶ Requirement triggers: arrival from an endemic country within 10 days, or a transit stop ≥ 12 h in an endemic country.
- ▶ **Contraindications:** severe immunosuppression (immunosuppressive therapy, primary immunodeficiency, symptomatic HIV or $CD4 < 200/\mu L$), malignancy, thymus disorders, severe egg allergy. **Precautions:** age ≥ 60 y, pregnancy, breastfeeding, asymptomatic HIV with $CD4$ 200–499/ μL .
- ▶ **Adverse events:** mild fever/myalgia/lymphadenopathy/rash; rare serious events include anaphylaxis, neurologic disease (GBS, meningitis, encephalitis) and **yellow fever vaccine-associated viscerotropic disease (YEL-AVD)** (~ 0.3 per 100,000 doses, higher in the elderly/immunosuppressed).

Co-administration, special populations and general principles

- ▶ All routine travel vaccines may be given on the same day. Exceptions: **oral typhoid must be given ≥ 8 h after oral cholera**; and **live-virus vaccines** (yellow fever, MMR, live-attenuated influenza, varicella) should be given on the **same day or spaced ≥ 28 days apart** (otherwise repeat the second dose after ≥ 28 days).
- ▶ **Pregnancy:** live-virus vaccines (MMR, varicella, and yellow fever as a precaution) are generally **contraindicated**; inactivated vaccines (Tdap each pregnancy at 27–36 weeks, inactivated influenza, hepatitis B) are safe and recommended.
- ▶ **Immunocompromised:** avoid live vaccines (yellow fever, oral typhoid, live chikungunya, MMR, varicella) when severely immunosuppressed; risk of vaccine-virus dissemination. A true **contraindication** is anaphylaxis to the vaccine or a component; a precaution is moderate/severe acute illness.
- ▶ **Malaria is NOT vaccine-preventable in travellers** — prevention rests on **mosquito-bite avoidance** (DEET 20–50%, permethrin-treated clothing, insecticide-treated nets) plus **chemoprophylaxis** (atovaquone-proguanil, chloroquine/hydroxychloroquine, doxycycline, mefloquine, primaquine, tafenoquine — tailored to species and resistance) and early recognition of fever.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pretravel consultation flow box** with four labelled arms: *Risk assessment (Itinerary + Traveller) → Immunizations (Routine / Recommended / Required–ICVP) → Vector/Malaria prevention → GI-illness prevention.*
- ▶ **Yellow fever endemicity map (schematic)**: outline of *Africa* and *South America* shaded for **sub-Saharan Africa** and **tropical South America**, labelled “Yellow fever endemic / vaccine recommended”; annotate *ICVP valid from day 10, lifelong.*

Clinical / Diagnostic significance

- ▶ A focused **itinerary + traveller history** (destinations, season, rural vs urban, duration, accommodation, activities, pregnancy, immune status, drug interactions) drives vaccine selection and chemoprophylaxis choice.
- ▶ **Documentation matters medico-legally**: the ICVP/“yellow card” is the legal proof for required vaccines; medical waivers must be issued by authorised clinics.
- ▶ **Returning febrile traveller**: always consider **malaria** (leading cause of life-threatening infection in travellers) and typhoid/dengue; urge early evaluation — a key counselling point at the pretravel visit.
- ▶ Counsel on **rabies wound care** (immediate soap-and-water/povidone-iodine washing, urgent assessment for PEP = rabies immune globulin + vaccine series) and on **travellers’ diarrhoea** food/water precautions.

High-yield exam pointers

- ▶ Three categories: **Routine, Recommended, Required** — required = ICVP-documented (yellow fever prototype).
- ▶ Refer **4–6 weeks before travel**; vaccines need ~1 week for immunity.
- ▶ **Yellow fever**: single dose = lifelong protection; 10-yearly booster dropped by WHO (2016); YEL-AVD ~0.3/100,000.
- ▶ **Meningococcal ACWY required for Hajj/Umrah** within preceding 3 years; meningitis belt epidemics Dec–June.
- ▶ **Oral typhoid and oral cholera are live** → contraindicated in immunocompromised; give oral typhoid ≥8 h after oral cholera.
- ▶ **Live-virus vaccines**: same day or ≥28 days apart; contraindicated in pregnancy and severe immunosuppression.
- ▶ **Rabies pre-exposure**: 2 doses (days 0, 7) since 2022; still requires post-exposure boosters.
- ▶ Immunity benchmarks: **measles** — **born before 1957**; **varicella** — **US-born before 1980**.

- ▶ **Malaria has no traveller vaccine** — bite avoidance (DEET 20–50%, permethrin, nets) + chemoprophylaxis.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 130 "Health Recommendations for International Travel" (primary; Tables 130-1 and 130-3, Fig. 130-1) and Ch 129 "Immunization Principles and Vaccine Use" (general contraindications/precautions, pregnancy and immunocompromised principles). Coverage note: Harrison gives vaccine *types and schedules* but not granular antigen content/dosage in mL; chemoprophylaxis regimen specifics are deferred to Ch 231 (Malaria) and are summarised here only at the level stated in Ch 130. US-centric immunity criteria (birth-year cut-offs) are quoted verbatim from the text and should be adapted to local epidemiology.



Infections due to HACEK

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — HACEK is an acronym for a group of *fastidious, slow-growing, capnophilic* (CO₂-requiring) *gram-negative bacilli/coccobacilli* that are normal commensals of the **oral cavity and upper respiratory tract**. The members are *Haemophilus* species (classically *H. aphrophilus*, now reclassified), *Aggregatibacter* species (formerly *Actinobacillus actinomycetemcomitans* and *Haemophilus aphrophilus*), *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. Their clinical importance lies chiefly in being the principal **gram-negative cause of subacute infective endocarditis (IE)** on native and prosthetic valves; they also produce a spectrum of localised oral, skeletal, and abscess-forming infections. They account for ~0.8–6% of all IE (CMDT: <5%).

Microbiology and taxonomy of the HACEK group

- ▶ Common biology: fastidious, **slow-growing**, gram-negative; require an atmosphere **enriched with CO₂ (capnophilic)**; **do not grow on MacConkey/enteric media**; normal flora of the mouth.
- ▶ Taxonomy has been revised — the modern names differ from the original acronym:

Letter	Modern genus/species	Former name	Key disease niche
H	<i>Haemophilus parainfluenzae</i> (commonest <i>Haemophilus</i> in HACEK IE)	—	Subacute IE, polymicrobial abscess

Letter	Modern genus/species	Former name	Key disease niche
A	<i>Aggregatibacter actinomycetemcomitans</i> , <i>A. aphrophilus</i> , <i>A. paraphrophilus</i>	<i>Actinobacillus</i> ; <i>Haemophilus aphrophilus</i>	Commonest cause of HACEK IE; brain abscess; periodontitis
C	<i>Cardiobacterium hominis</i> (and <i>C. valvarum</i>)	—	Aortic-valve subacute IE
E	<i>Eikenella corrodens</i>	—	Human-bite/clenched-fist wounds; least common HACEK IE
K	<i>Kingella kingae</i>	—	Paediatric septic arthritis/osteomyelitis ; IE in older children/adults

- ▶ **HACEK bacteraemia is strongly predictive of underlying IE** (overall positive predictive value ~60%), but the association is organism-dependent: IE found in **62–100%** of *A. actinomycetemcomitans*, **17–55%** of *H. parainfluenzae*, **~50%** of *C. hominis*, but only **0–6%** of *Eikenella* bacteraemias.

Pathogenesis and routes of entry

- ▶ Reside as commensals in the **gingival crevice/oropharynx**; gain bloodstream access after **dental procedures, periodontal disease, or nasopharyngeal infection** — hence the typical history of recent dental work in a patient with valvular disease.
- ▶ *Eikenella corrodens* is inoculated through **human bites / clenched-fist** (“fight-bite”) injuries.
- ▶ *Kingella kingae* invasion is preceded by **upper respiratory tract infection or stomatitis** in ~80%; oropharyngeal colonisation peaks (≈5–10%) in the **first 3 years of life** and is higher in **daycare attenders**, explaining its age-restricted invasive disease (6 months–4 years) and reported child-to-child **outbreaks**.

HACEK infective endocarditis — clinical profile

- ▶ Predisposition: nearly always **pre-existing valvular disease or a prosthetic valve**; *Aggregatibacter* is linked to **prosthetic-valve endocarditis (PVE)** more than *Haemophilus*.
- ▶ Course is usually **subacute/indolent** (especially *Aggregatibacter* and *Cardiobacterium* — patients ill for weeks–months before diagnosis); *K. kingae* IE may be **more aggressive**.
- ▶ Compared with non-HACEK IE, HACEK IE occurs in **younger patients** and shows **more embolic, vascular and immunologic phenomena**.

- ▶ **Large vegetations** and **systemic embolism** are characteristic: major emboli in **28–71%** of series; echocardiographic vegetations seen in **up to 85%**.
- ▶ Valve localisation: *Aggregatibacter* and *Haemophilus* → **mitral**; *Cardiobacterium* → **aortic**.
- ▶ Complications: **congestive heart failure** (19–50% with *Haemophilus*), septic emboli (including **CNS emboli**), **mycotic aneurysms**, immune-complex glomerulonephritis, vasculitis, and renal failure.

Diagnosis

- ▶ **Alert the microbiology laboratory** when HACEK IE is suspected.
- ▶ Most clinically significant cultures turn **positive within the first week** using modern automated systems (BACTEC); studies have **not** shown that *prolonged incubation* improves recovery (CMDT: HACEK now usually grows within the standard 5-day incubation).
- ▶ Inoculating fluids (e.g., synovial fluid for *K. kingae*) into **aerobic blood-culture bottles** enhances recovery.
- ▶ **Molecular/rapid tools**: broad-range **16S rRNA gene PCR** (blood/valve tissue) and **MALDI-TOF mass spectrometry** on colonies improve speed and accuracy; **real-time PCR** is increasingly recovering *K. kingae* from culture-negative cases.
- ▶ HACEK organisms are listed among the “**typical**” IE **pathogens** that fulfil the **microbiologic major criterion** of the modified Duke / 2023 Duke-ISCVID criteria.
- ▶ Because of **slow growth**, **β-lactamase production may be missed** on susceptibility testing; Etest improves accuracy. Resistance is most common in *Haemophilus* and *Aggregatibacter*; in recent studies **ceftriaxone and levofloxacin were active against all isolates**.

Treatment of HACEK infections

Organism / setting	Preferred therapy	Alternatives / notes
HACEK IE (all five genera)	Ceftriaxone 2 g IV once daily	Favourable outcome in 80–90% ; NVE 4 weeks, PVE 6 weeks
β-lactam-intolerant	Levofloxacin 750 mg/day (data limited)	Fluoroquinolones not for patients <18 years
Alternative β-lactam	Ampicillin/sulbactam (3 g ampicillin q6h)	Amp/sulbactam resistance described in <i>Haemophilus</i> & <i>Aggregatibacter</i>
If β-lactamase excluded & susceptible	Penicillin 16–18 MU q4h or ampicillin 2 g q4h	Susceptibility hard to confirm due to slow growth

- ▶ **Surgery is usually NOT required** — unlike PVE from other gram-negative bacilli, HACEK IE is often cured by antibiotics alone.

- ▶ *Eikenella corrodens* is **resistant to clindamycin, metronidazole, and aminoglycosides** — relevant in bite-wound polymicrobial cover.
- ▶ **Prognosis is excellent**, significantly better than non-HACEK IE; 1-year mortality is lower than that of viridans-streptococcal IE.
- ▶ **Prophylaxis** (high-risk cardiac lesions before dental manipulation): **amoxicillin 2 g PO 1 h before**; if penicillin-allergic — cephalexin 2 g, azithromycin/clarithromycin 500 mg, or doxycycline 100 mg PO. This is directly relevant because HACEK organisms originate from the oral flora.

Organism-specific pearls (beyond endocarditis)

- ▶ ***Haemophilus parainfluenzae** — *commonest Haemophilus in HACEK IE; also pneumonia, meningitis, and brain/dental/pelvic/liver abscess; septicaemia often polymicrobial**.
- ▶ ***Aggregatibacter** — *commonest HACEK IE; A. actinomycetemcomitans co-isolated with Actinomyces israelii in soft-tissue abscesses; A. aphrophilus is an important cause of brain abscess** (10% of brain abscesses in one series) and bone/joint infection.
- ▶ ***Cardiobacterium hominis** ($\pm$ C. valvarum) — *aortic vegetations; presents with long-standing infection, embolisation, mycotic aneurysms**, immune-complex glomerulonephritis, vasculitis, arthritis.
- ▶ ***Eikenella corrodens** — *eponymous “corroding”/pitting of agar; human-bite wounds, head-and-neck and visceral abscesses, osteomyelitis, IUD-associated gynaecologic infection; usually part of mixed** infection.
- ▶ ***Kingella kingae** — *has surpassed S. aureus as the leading cause of septic arthritis and osteomyelitis in young children; bacteraemia can present with a petechial rash mimicking meningococcaemia**; adult/older-child IE is aggressive (arterial emboli, CVA, tricuspid insufficiency, cardiovascular collapse).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled heart with HACEK endocarditis**: draw a left heart in long-axis; label **mitral valve vegetation** (*Aggregatibacter*/*Haemophilus*), **aortic valve vegetation** (*Cardiobacterium*), **large friable vegetation** $\rightarrow$ **systemic/CNS embolus, mycotic aneurysm, and immune-complex glomerulonephritis** as peripheral consequences.
- ▶ **Flow box of HACEK pathway**: *Oral/upper-respiratory commensal $\rightarrow$ dental procedure / periodontitis / bite $\rightarrow$ transient bacteraemia $\rightarrow$ adherence to damaged or prosthetic valve $\rightarrow$ subacute vegetation $\rightarrow$ embolic + immunologic complications.* Label each arrow.

Clinical / Diagnostic significance

- ▶ Consider HACEK in any culture-negative or “fastidious-organism” subacute IE, particularly with poor dentition, recent dental work, prosthetic valve, large vegetations, or prominent embolic phenomena.
- ▶ Maintain the blood-culture incubation and **flag the lab**; add 16S rRNA PCR / MALDI-TOF when conventional cultures are negative.
- ▶ Differentiate from other culture-negative IE causes — *Coxiella burnetii*, *Bartonella*, *Tropheryma whippelii*, *Brucella*, nutritionally-variant streptococci (*Granulicatella*/*Abiotrophia*/*Gemella*) — which need **serology/special media**, not just longer incubation.
- ▶ A positive HACEK blood culture (especially *Aggregatibacter*, *Cardiobacterium*) should **prompt echocardiography** given the high predictive value for IE.

High-yield exam pointers

- ▶ HACEK = Haemophilus, Aggregatibacter (was *Actinobacillus*), *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae* — fastidious, CO₂-requiring, oral commensals.
- ▶ **Commonest gram-negative cause of subacute IE**; ~0.8–6% of all IE.
- ▶ **Aggregatibacter** = commonest HACEK IE and commonest in PVE; **Cardiobacterium** → aortic, **Aggregatibacter**/*Haemophilus* → mitral.
- ▶ HACEK bacteraemia PPV for IE ≈ 60%; highest with *A. actinomycetemcomitans*, lowest with *Eikenella*.
- ▶ **Large vegetations + frequent emboli** (28–71%); younger patients; vegetations on echo up to 85%.
- ▶ First-line therapy = ceftriaxone 2 g/day; NVE 4 weeks, PVE 6 weeks; often cured medically without surgery; excellent prognosis.
- ▶ *Eikenella* resists clindamycin, metronidazole, aminoglycosides; think of it in clenched-fist bite wounds.
- ▶ *Kingella kingae* = top cause of paediatric septic arthritis/osteomyelitis; inoculate joint fluid into blood-culture bottles; petechial rash mimics meningococcaemia.
- ▶ HACEK qualifies as a “typical” organism (major criterion) in the modified Duke / Duke-ISCVID criteria.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Infections Due to the HACEK Group and Miscellaneous Gram-Negative Bacteria” (Tamar F. Barlam) and “Infective Endocarditis” (etiology, modified Duke/Duke-ISCVID criteria, HACEK treatment regimens, antibiotic prophylaxis).

- **CMDT 2026** — “Bacterial & Chlamydial Infections” (Infective Endocarditis: HACEK organisms; culture-negative endocarditis) for current management and the classic acronym expansion.



Infective Endocarditis

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Infective endocarditis (IE) is microbial infection of the endocardial surface of the heart, most often the valves, whose prototypic lesion is the **vegetation** — a mass of platelets, fibrin, microorganisms and scant inflammatory cells. Infection may also involve the low-pressure side of a ventricular septal defect, mural endocardium damaged by aberrant jets or foreign bodies, or intracardiac devices; the analogous process on arteriovenous/arterio-arterial shunts (patent ductus, coarctation) is termed **infective endarteritis**. In developed countries the incidence is **~15 cases per 100,000 population/year** and is rising, with predisposition shifting from chronic rheumatic heart disease (still dominant in developing countries) towards injection drug use, degenerative valve disease and intracardiac devices.

Classification

IE is classified by temporal course, site, cause, or predisposing risk factor:

- **By tempo:** *Acute IE* — hectically febrile, rapidly destroys cardiac structures, seeds distant sites, fatal in weeks if untreated (β -haemolytic streptococci, *S. aureus*, pneumococci). *Subacute IE* — indolent, slowly progressive, rarely metastasises (viridans streptococci, enterococci, CoNS, HACEK).
- **By valve type:** Native-valve endocarditis (NVE), prosthetic-valve endocarditis (PVE — 16–30% of cases), transcatheter aortic valve replacement (TAVR)-PVE, and cardiovascular implantable electronic device IE (CIED-IE).
- **By setting:** Community-acquired, **health care-associated** (25–35% of NVE), IE in people who inject drugs (PWID).
- **PVE timing:** *Early* (<2 months post-surgery — nosocomial: *S. aureus*, CoNS, gram-negative bacilli, diphtheroids, fungi); *late* (>12 months — microbiology like community NVE). Risk is highest in the first year, higher for bioprosthetic than mechanical valves.

Etiology (microbiology)

- **Staphylococcus aureus** — now the **most common** overall cause; predominates in health care-associated IE (~52%) and PWID (often methicillin-resistant).

- ▶ **Viridans streptococci** (oral portal) — classic subacute NVE; *Streptococcus gallolyticus* (formerly *S. bovis*) arises from the gut and signals **colonic polyps/tumours**.
- ▶ **Enterococci** (genitourinary portal), **coagulase-negative staphylococci** (chief cause of PVE; usually methicillin-resistant), and the **HACEK** group — *Haemophilus*, *Aggregatibacter*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae* (upper-respiratory portal).
- ▶ **Culture-negative IE (5–15%)**: one-third to one-half due to prior antibiotics; remainder due to fastidious organisms — *Coxiella burnetii* (Q fever, predilection for prosthetic valves), *Bartonella* spp., *Tropheryma whippelii*, and nutritionally variant *Granulicatella*, *Abiotrophia*, *Gemella*. *Mycobacterium chimaera* has caused a global PVE outbreak from contaminated heater-cooler units.
- ▶ Mimics of culture-negative IE: atrial myxoma, marantic (non-bacterial thrombotic) endocarditis, antiphospholipid antibody syndrome.

Pathogenesis

- ▶ Intact endothelium resists most bacteria. **Endothelial injury** (high-velocity jets, low-pressure side of a lesion) → deposition of a platelet–fibrin thrombus = **nonbacterial thrombotic endocarditis (NBTE)**, the nidus for bacterial attachment during transient bacteraemia.
- ▶ Cardiac lesions prone to NBTE: mitral regurgitation, aortic stenosis, aortic regurgitation, VSD, complex congenital disease. NBTE also arises from hypercoagulable states (marantic endocarditis in malignancy; bland vegetations in SLE/antiphospholipid syndrome).
- ▶ Organisms adhere via **MSCRAMMs** (microbial surface components recognising adhesive matrix molecules) — fibronectin-binding proteins, clumping factor (*S. aureus*), FimA/glucans (streptococci). *S. aureus* can invade even **intact** endothelium via von Willebrand factor and fibronectin-binding proteins.
- ▶ Organisms deep in the vegetation are **metabolically inactive (nongrowing)** and relatively resistant to antibiotics — the rationale for prolonged, bactericidal, parenteral therapy.

Clinical features

Feature	Frequency
Fever	80–90%
Heart murmur	80–85%
New/worsened regurgitant murmur	20–50%
Arterial emboli	20–50%
Splenomegaly	15–50%
Neurologic manifestations	20–40%
Peripheral stigmata (Osler, Janeway, splinter, Roth)	2–15%

Feature	Frequency
Anaemia	70–90%
Elevated CRP	>90%

- ▶ **Cardiac:** new regurgitant murmur (valve/chordal destruction); congestive heart failure in 30–40% (chief surgical indication); paravalvular abscess (commonest with aortic valve) burrowing into the septum → **heart block**; coronary embolism (2%).
- ▶ **Peripheral stigmata:** ***Osler nodes** (*painful, immunologic, finger/toe pulps*), **Janeway lesions** (*painless, septic-embolic, palms/soles*), **Roth spots** (*retinal exudates*), *splinter/subungual haemorrhages, petechiae (palate, conjunctiva), clubbing**.
- ▶ **Embolic/metastatic:** stroke or encephalopathy (15–35%); renal/splenic infarcts; mycotic aneurysm; spondylodiscitis. *S. aureus*, vegetations >10 mm, and mitral anterior-leaflet involvement independently raise embolic risk; embolic rate falls sharply after effective therapy.
- ▶ **Immune-mediated:** diffuse hypocomplementaemic glomerulonephritis (immune-complex), positive rheumatoid factor, microscopic haematuria.
- ▶ **PWID:** 35–60% have isolated **tricuspid IE** — fever with faint/absent murmur, septic pulmonary emboli causing cough, pleuritic pain, nodular infiltrates.

Diagnosis — 2023 Duke-ISCVID criteria

Definite IE = 2 major or 1 major + 3 minor or 5 minor (clinical), or pathologic confirmation in a vegetation/abscess. **Possible IE** = 1 major + 1 minor or 3 minor.

Major criteria	Minor criteria
Positive blood cultures: typical IE organism in ≥2 sets (e.g. <i>S. aureus</i> , <i>S. lugdunensis</i> , <i>E. faecalis</i> , all streptococci except <i>S. pneumoniae</i> / <i>S. pyogenes</i> , <i>Granulicatella</i> / <i>Abiotrophia</i> / <i>Gemella</i> , HACEK); atypical organism in ≥3 sets	Predisposition (prior IE, IV drug use, prosthetic/repared valve, congenital disease, CIED, >mild regurgitation/stenosis, HCM)
Positive lab test: PCR for <i>Coxiella</i> / <i>Bartonella</i> / <i>T. whipplei</i> ; <i>C. burnetii</i> phase I IgG ≥1:800; <i>Bartonella</i> IgG ≥1:800	Fever >38.0°C
Imaging: echocardiography or cardiac CT showing vegetation, perforation, abscess, pseudoaneurysm, fistula, new dehiscence, or new regurgitation	Vascular phenomena (arterial/septic pulmonary emboli, mycotic aneurysm, intracranial/conjunctival haemorrhage, Janeway lesions)
FDG-PET/CT abnormal uptake on a prosthetic valve/graft/lead	Immunologic phenomena (glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor)
Direct evidence at heart surgery	Microbiologic evidence not meeting major criteria

- ▶ **Blood cultures (gold standard):** three two-bottle sets (10 mL/bottle) from separate venipunctures before antibiotics; in stable suspected subacute IE, withhold empirical therapy to allow uncontaminated cultures.
- ▶ **Echocardiography:** TTE misses vegetations <2 mm and is inadequate in ~20%; TEE detects vegetations in >90% — a negative TEE with high suspicion warrants repeat in 7–10 days. CTA is superior for pseudoaneurysm/abscess; FDG-PET/CT boosts sensitivity for PVE/TAVR-PVE, CIED and graft infection — CTA and PET findings now count as **major** criteria.
- ▶ Routine TEE is recommended in *S. aureus* bacteraemia because of the high prevalence of underlying IE (8–14%).

Management

Principles: all bacteria in the avascular, metabolically dormant vegetation must be killed → **prolonged, parenteral, bactericidal** therapy; duration is timed from the first negative blood culture. Manage with infectious-disease consultation, especially for *S. aureus*.

Organism	Representative regimen
Penicillin-susceptible streptococci (MIC ≤0.12)	Penicillin G or ceftriaxone 2 g/day × 4 wk (vancomycin if allergic)
Enterococci	Ampicillin + ceftriaxone, or ampicillin/penicillin + gentamicin × 4–6 wk
MSSA, native valve	Nafcillin/oxacillin/flucloxacillin (or cefazolin) × 4–6 wk; gentamicin not recommended
MRSA, native valve	Vancomycin or daptomycin (8–10 mg/kg/day) × 4–6 wk
Staphylococcal PVE	Vancomycin/antistaphylococcal penicillin + rifampin + gentamicin × 6–8 wk
HACEK	Ceftriaxone 2 g/day × 4 wk
<i>Coxiella burnetii</i>	Doxycycline + hydroxychloroquine ≥18 mo (24 mo if prosthetic)

- ▶ **Empirical:** acute IE → vancomycin + gentamicin/cefepime (covers MRSA, gram-negatives); subacute NVE → vancomycin + ceftriaxone.
- ▶ **Right-sided uncomplicated MSSA IE** may respond to a 2-week course; left-sided staphylococcal IE needs ≥6 weeks.
- ▶ **Rifampin** is essential in staphylococcal PVE (kills biofilm-embedded organisms) but is added only after bacteraemia clears, to avoid resistance.
- ▶ **CIED-IE:** antibiotics are **adjunctive to complete device removal** (percutaneous lead extraction preferred).

- ▶ **Anticoagulation:** neither anticoagulant nor antiplatelet therapy prevents emboli and both risk haemorrhagic transformation; reserve for independent indications (mechanical valve, AF) and reverse after acute stroke/haemorrhage.

Surgical indications (Table 133-6): moderate–severe CHF from valve dysfunction (commonest); paravalvular extension (abscess, fistula, heart block); persistent bacteraemia despite 7–10 days of therapy; lack of effective therapy (fungal, *Brucella*, multidrug-resistant gram-negatives); unstable dehiscence prosthesis; large (>10 mm) hypermobile vegetation with prior embolus and valve dysfunction; very large (>30 mm) vegetation. Surgery for NVE confers a survival benefit of ~27–55%, greatest with the most pressing indications.

Prevention

- ▶ Antibiotic prophylaxis is limited to **highest-risk lesions** (Table 133-9): prosthetic valves/material, prior IE, unrepaired cyanotic congenital disease (or repair with residual defect/within 6 months), LVAD/transplant valvulopathy — and **only** before procedures that manipulate gingiva/periapical tissue or perforate oral mucosa.
- ▶ **Regimen:** amoxicillin 2 g PO 1 h before procedure (ampicillin/cefazolin/ceftriaxone IV if NPO; doxycycline/azithromycin if penicillin-allergic). The AHA now **advises against clindamycin** (*C. difficile* risk). Good dental hygiene matters more than prophylaxis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Valve vegetation:** cross-section of a valve leaflet — label *vegetation* (platelets + fibrin + microorganisms), *endothelial injury site*, *underlying NBTE*, *regurgitant jet*, *paravalvular abscess*, *embolus shedding into bloodstream*.
- ▶ **Peripheral stigmata figure:** label *Osler nodes* (painful, finger pulps), *Janeway lesions* (painless, palms/soles), *splinter/subungual haemorrhages*, *Roth spots* (retina), *petechiae* (conjunctiva/palate), *clubbing*, *splenomegaly*.

Clinical / Diagnostic significance

- ▶ A new or changing regurgitant murmur with fever, or fever plus an IE-associated organism on blood culture, mandates echocardiography and the Duke-ISCVID work-up.
- ▶ *S. aureus* bacteraemia without an obvious focus is presumptive IE/CIED-IE until echocardiography proves otherwise.
- ▶ *S. gallolyticus* IE warrants **colonoscopy** to exclude colonic neoplasia.
- ▶ Persistent fever beyond 7 days on appropriate therapy demands a search for paravalvular/extracardiac abscess or embolic complication.
- ▶ Overall survival in developed countries is 80–85%; worse with prosthetic valves, *S. aureus*/resistant pathogens, neurologic complications and early PVE (40–50% mortality).

High-yield exam pointers

- ▶ **Vegetation** = platelets + fibrin + microorganisms + scant inflammatory cells; deep organisms are dormant → need prolonged bactericidal therapy.
- ▶ *****S. aureus* is now the commonest cause**** of IE overall; viridans streptococci classically cause subacute NVE.
- ▶ **HACEK** = *Haemophilus*, *Aggregatibacter*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*.
- ▶ **Osler nodes** = painful (immune); **Janeway lesions** = painless (septic emboli); **Roth spots** = retinal.
- ▶ Diagnosis by **2023 Duke-ISCVID criteria**: definite = 2 major / 1 major + 3 minor / 5 minor; CTA and FDG-PET/CT now count as major.
- ▶ TEE sensitivity >90% (vs TTE ~55–65%); repeat in 7–10 days if negative but suspicion high.
- ▶ PWID → **tricuspid** valve, *S. aureus* (often MRSA), septic pulmonary emboli.
- ▶ Staphylococcal PVE triple therapy includes **rifampin** (biofilm) + gentamicin.
- ▶ Prophylaxis only for high-risk lesions before dental/oral-mucosal procedures: **amoxicillin 2 g**; clindamycin no longer advised.
- ▶ Commonest surgical indication = **refractory heart failure** from valve dysfunction.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Infective Endocarditis" (microbiology, pathogenesis/NBTE-MSCRAMMs, 2023 Duke-ISCVID criteria, organism-specific regimens, surgical indications and timing, prophylaxis tables).
- ▶ CMDT 2026 — "Infective Endocarditis" (Bacterial & Chlamydial Infections): clinical findings, 2023 Duke-ISCVID summary, empirical and organism-specific treatment, role of surgery and anticoagulation.



Lepra Reactions

Asked in: Paper II May 2022 · Paper IV Nov 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — *Lepra (leprosy) reactions* are acute, immunologically mediated inflammatory episodes that interrupt the otherwise chronic, stable course of leprosy and may occur **before, during, or after** multidrug therapy (MDT). They are *medical emergencies* because they cause acute neuritis and nerve-function impairment; if not diagnosed and treated early they lead to permanent deformity, disability, and blindness. Two principal types are recognised — **Type 1 reaction** (T1R / **reversal reaction**), a delayed (cell-mediated) hypersensitivity event, and **Type 2 reaction** (T2R /

erythema nodosum leprosum, ENL), an immune-complex-mediated event — with *Lucio's phenomenon* as a third, distinct reactional state.

Overview & immunological basis

- ▶ Reactions reflect a sudden shift in the host immune response to *Mycobacterium leprae* antigens along the Ridley–Jopling spectrum (TT–BT–BB–BL–LL).
- ▶ Immunologic resistance is strongest at the tuberculoid (TT) pole and weakest at the lepromatous (LL) pole; the **unstable borderline groups (BT, BB, BL)** are most prone to reactions.
- ▶ Reactions can occur in untreated patients but are commonest after starting MDT; new reactions and nerve damage may appear **up to 3 years after completion** of therapy.
- ▶ The two types differ fundamentally in immunopathology — T1R = **Type IV (delayed) hypersensitivity** with upgrading cell-mediated immunity (CMI); T2R = **Type III (immune-complex) hypersensitivity / Arthus phenomenon**.

Type 1 Lepra Reaction (T1R / Reversal Reaction)

- ▶ A **delayed hypersensitivity reaction** associated with a *sudden alteration of CMI status* and a shift in the patient's position on the leprosy spectrum.
- ▶ Histologically marked by infiltration of lesions by **activated CD4+ T lymphocytes (especially T helper cells)**.
- ▶ Termed a “**reversal reaction**” because of the *upgrading* of CMI status; usually seen in the **borderline** portion of the spectrum (BT especially susceptible).
- ▶ **Skin**: existing lesions undergo *acute swelling and redness* (erythema and oedema of pre-existing patches/plaques), which may ulcerate.
- ▶ **Nerves**: painful, tender nerve trunks (*neuritis*) with consequent nerve damage and disfigurement; in severe T1R, **nerve abscesses** may form.
- ▶ “**Silent neuritis**” (“quiet nerve paralysis”): progressive sensory and/or motor impairment of hands, feet, and face *without* the usual inflammatory signs — easily missed, hence routine nerve assessment is essential.
- ▶ Less common features: arthralgia/arthritis; rarely fever, malaise, tenosynovitis, and oedema of the feet and hands.

Type 2 Lepra Reaction (T2R / Erythema Nodosum Leprosum)

- ▶ An **immune-complex-mediated syndrome** (antigen–antibody reaction involving complement) causing inflammation of skin, nerves, and other organs with systemic malaise — a **Type III hypersensitivity reaction (Coombs & Gell) / Arthus phenomenon**.
- ▶ Occurs in the **multibacillary (BL and LL)** end of the spectrum, mostly during MDT but also in untreated patients.

- ▶ **Skin:** crops of evanescent, *pink-to-red, tender, warm* maculopapular/papular/nodular or plaque lesions on the **outer aspects of thighs, legs, and face**; lesions blanch with light finger pressure and last a few days, changing colour pink/red → bluish/brownish (24–48 h) → dark over a week.
- ▶ Severe forms become vesicular, pustular, bullous, or necrotic and ulcerate — **erythema nodosum necroticans**.
- ▶ **Systemic / multi-organ involvement:** fever and constitutional symptoms, lymph-node enlargement, myositis, arthritis, synovitis, rhinitis, epistaxis, laryngitis, iridocyclitis and glaucoma, painful dactylitis, acute epididymo-orchitis, nephritis and renal failure, hepatosplenomegaly, anaemia, and — at a late stage — **amyloidosis**.
- ▶ **Severe T2R** includes swollen, painful, tender nerve trunks with sensory and motor deficits (i.e. it too causes neuritis).

Lucio's Phenomenon

- ▶ A distinct reactional state seen in **diffuse leprosy of Lucio and Latapí** (*"lepra bonita"*), occurring chiefly in Mexico and Central America; may be a variant of erythema nodosum necroticans.
- ▶ Pathology: **marked vasculitis with thrombosis** of superficial and deep dermal vessels → cutaneous haemorrhage and infarction.
- ▶ Lesions: slightly indurated, bluish-red, ill-defined, painful, rarely palpable plaques with an erythematous halo, usually on one limb; irregular/triangular shape, becoming purplish centrally with a *central haemorrhagic infarct* ± blister and an easily detached **necrotic eschar**, leaving an irregular ulcer that heals with a superficial scar.
- ▶ Patients remain **afebrile** throughout.

Comparison: Type 1 vs Type 2 reactions

Feature	Type 1 (Reversal)	Type 2 (ENL)
Immunology	Type IV / delayed (cell-mediated) hypersensitivity	Type III / immune-complex (Arthus)
Mechanism	Upgrading of CMI; CD4+ T-cell infiltration	Antigen–antibody complexes + complement
Spectrum affected	Borderline (BT, BB, BL)	Multibacillary (BL, LL)
Skin lesions	Acute erythema & swelling of <i>existing</i> lesions	<i>New</i> crops of tender erythematous nodules
Systemic upset	Usually mild	Prominent — fever, malaise, multi-organ
Neuritis	Common and often severe	Occurs, mainly in severe T2R
Drug of choice	Oral prednisolone (glucocorticoid)	Thalidomide / high-dose prednisolone

Treatment of lepra reactions

- ▶ **General:** identify and treat early; assess nerve function; reassure regarding non-contagiousness; continue MDT through the reaction.
- ▶ **Type 1 reaction:** oral short-acting **glucocorticoids** are the treatment of choice — **prednisolone 1 mg/kg/day once daily (max 60–80 mg)**; WHO programmes commonly use an initial dose of **40 mg**, tapered slowly by **5 mg every 2 weeks over ~20 weeks** (better outcomes and lower relapse than the older 12-week regimen). Review every 2 weeks with nerve assessment; reactions often flare again as the dose falls to <10–20 mg.
- ▶ **Type 2 reaction (ENL):**
 - *Mild, first episode (localised nodules):* aspirin and **pentoxifylline**.
 - *Rapid control:* **thalidomide** is the most effective drug (rapidly suppresses skin signs, neuritis, and iritis); **100–200 mg once or twice daily**, tapered and stopped after 1–2 weeks in acute first episodes; maintenance **50 mg/day** for severe recurrent ENL. *Strictly contraindicated in pregnancy* (teratogenic) — use only in women of child-bearing age after counselling, a negative pregnancy test, and strict contraception.
 - *Where thalidomide is restricted:* **high-dose oral prednisolone**, quickly tapered over 2–3 weeks to zero or a low maintenance dose; ENL is usually transient (resolving in ~2 weeks).
 - *Recurrent ENL:* **high-dose clofazimine** — 300 mg/day for 1 month → 200 mg/day for 1 month → 100 mg/day maintenance (maximal effect takes several weeks; GI side-effects and skin discolouration with prolonged use).
- ▶ **Silent neuropathy / neuritis without skin signs:** managed as for T1R — **high-dose prednisolone** is the drug of choice; nerve-decompression surgery is of unproven benefit (no RCT evidence).
- ▶ **Nerve-recovery prognosis:** good if steroids are started soon after onset of nerve-function impairment; some recovery possible up to 6 months, but impairment persisting >6 months rarely benefits from steroids.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Ridley–Jopling spectrum bar** (left = TT, right = LL): label *TT – BT – BB – BL – LL*; mark a bracket over BT–BB–BL as “Type 1 (reversal) reaction zone” and a bracket over BL–LL as “Type 2 (ENL) reaction zone”; annotate “high CMI / paucibacillary” at the TT end and “low CMI / multibacillary” at the LL end.
- ▶ **Comparison schematic of skin lesions:** (a) T1R — *existing* plaque becoming red and swollen; (b) T2R — *new* crop of tender erythematous nodules on the leg. Labels: “Type IV hypersensitivity (T1R)”, “Type III / immune complex (T2R)”, “neuritis – tender thickened nerve”.

Clinical / Diagnostic significance

- ▶ Reactions are the *leading cause of nerve damage and disability* in leprosy; recognition prevents permanent deformity and blindness.
- ▶ **Neuritis** (tender, thickened nerve trunks with sensory/motor loss) is the key emergency component of both reactions — palpate the **greater auricular, ulnar, radial, radial cutaneous, median, lateral popliteal, posterior tibial, sural, and superficial peroneal nerves** at every visit.
- ▶ Eye involvement in T2R (iridocyclitis, glaucoma) is sight-threatening and demands urgent treatment.
- ▶ Differentiate ENL nodules from the lesions of T1R, cellulitis, and vasculitis; necrotic ulcerating lesions raise the possibility of erythema nodosum necroticans or Lucio's phenomenon.
- ▶ Monitor for steroid- and thalidomide-related toxicity; counsel rigorously on thalidomide teratogenicity.

High-yield exam pointers

- ▶ **T1R = reversal reaction = Type IV (delayed/CMI) hypersensitivity**, borderline spectrum, *upgrading* CMI, CD4+ T-cell infiltration.
- ▶ **T2R = ENL = Type III (immune-complex/Arthus) hypersensitivity**, BL/LL spectrum, *new* tender nodules + systemic features.
- ▶ T1R inflames *pre-existing* lesions; ENL produces *new* crops of nodules.
- ▶ **Prednisolone 1 mg/kg/day** is first-line for T1R; **thalidomide 100–200 mg/day** is the most effective drug for ENL (teratogenic — pregnancy contraindicated).
- ▶ **Silent neuritis** = progressive nerve impairment without inflammatory signs — treat as T1R with steroids.
- ▶ **Lucio's phenomenon** = vasculitis/thrombosis with cutaneous infarction in diffuse (Lucio–Latapí) leprosy; patient afebrile.
- ▶ Reactions can occur **before, during, or after** MDT, up to **3 years** after completing treatment — MDT is continued during a reaction.
- ▶ Erythema nodosum necroticans = necrotic/ulcerating severe ENL; late ENL complication = **amyloidosis**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 184 "Leprosy" (sections: *Leprosy Reactions; Treatment of Leprosy Reactions; Treatment and Prognosis of Nerve Function Impairment; Ridley–Jopling Classification*). Coverage note: the chapter fully supports both reaction types, Lucio's phenomenon, and management; the explicit "Type IV" and "multibacillary BL/LL" labels for T1R/T2R respectively are standard textbook immunology consistent with the chapter's description (delayed CMI for T1R; immune-complex/Type III for T2R).



Leptospirosis

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Leptospirosis is a globally important **zoonotic** spirochaetal infection caused by pathogenic *Leptospira* species, transmitted to humans chiefly through contact with water, soil or animal tissue contaminated by the urine of infected reservoir hosts (especially rats). It produces a wide clinical spectrum from asymptomatic/anicteric febrile illness to fulminant multi-organ disease; the classic severe form — the triad of **jaundice, acute kidney injury and haemorrhage** — is termed **Weil's syndrome**. Severe pulmonary haemorrhage is an increasingly recognised, highly lethal presentation. An estimated ~1 million severe cases occur annually with a mean case-fatality of nearly 10%.

Aetiologic agent & microbiology

- ▶ *Leptospira* are spirochaetes of order **Spirochaetales**, family **Leptospiraceae**. Traditional dichotomy: pathogenic *L. interrogans* (sensu lato) and free-living *L. biflexa* (sensu lato).
- ▶ Modern phylogenetic (core-genome) analysis defines **64 species** — **17 pathogenic**, **21 intermediate**, **26 non-pathogenic (saprophytic)**.
- ▶ For clinical/epidemiologic purposes, **serologic** classification is used: pathogenic leptospires are divided into **>260 serovars** arranged in **26 serogroups** by antigenic (LPS) composition.
- ▶ Morphology: coiled, thin, highly motile organisms with **hooked ends** and **two periplasmic (axial) flagella**; **6–20 µm long**, **~0.1 µm diameter**. Stain poorly — visualised by **dark-field microscopy** and **silver impregnation** of tissue.
- ▶ Fastidious: require special media and **weeks to months** to grow in culture. Double-membrane cell wall rich in lipoproteins; **LPS has relatively low endotoxic potency**, yet protective humoral immunity is **serovar-specific anti-LPS antibody**.

Epidemiology & transmission

- ▶ Worldwide distribution; greatest in **tropics/subtropics** (warm, humid climate, poor sanitation favour survival). Most cases in **men**, peaking in **summer–autumn** (temperate) and the **rainy/monsoon season** (tropics).
- ▶ **Reservoir**: almost all mammals; **rodents** — **especially rats** — **are the most important**. Leptospires colonise the host renal tubule symbiotically and are shed in urine for years.
- ▶ Characteristic **serovar–host associations**: *Icterohaemorrhagiae* and *Copenhageni* — rats; *Grippityphosa* — voles; *Hardjo* — cattle; *Canicola* — dogs; *Pomona* — pigs.
- ▶ **Transmission**: direct contact with infected animal urine/blood/tissue, or (more commonly) environmental exposure — **water is the key vehicle** (leptospires survive months in moist conditions). Outbreaks follow **floods**, recreational freshwater activity (triathlons, rafting, mud-runs), and sporting events.

- ▶ **High-risk occupations:** veterinarians, agricultural/rice-field workers, sewage and abattoir workers, fishing-industry workers; also urban slum/unhoused populations exposed to rat urine. Also a recognised **traveller's disease**.

Pathogenesis

- ▶ **Portal of entry:** cuts, abraded skin, or mucous membranes (conjunctival, oral).
- ▶ **Leptospiraemic phase:** highly motile organisms proliferate, cross tissue barriers and **disseminate haematogenously to all organs**, evading complement-mediated killing and phagocytosis. An exaggerated **pro-inflammatory** response correlates with mortality.
- ▶ **Immune phase:** appearance of antibody coincides with clearance from blood, but organisms persist in **kidney, liver, lung, heart and brain**; leptospires are then shed in **urine**.
- ▶ **Kidney:** acute tubular damage + **interstitial nephritis** → interstitial oedema and acute tubular necrosis; dysregulated tubular transporters cause impaired Na⁺ absorption, **K⁺ wasting and polyuria** (non-oliguric hypokalaemic renal failure).
- ▶ **Liver:** focal hepatocellular necrosis (widespread necrosis unusual), inflammation, disruption of intercellular junctions and **bile-canalicular plugging/leakage** → jaundice with relatively preserved synthetic function.
- ▶ **Haemorrhage:** widespread petechiae/haemorrhages; **thrombocytopenia** (platelet consumption), consumptive coagulopathy/DIC, and **endothelial-cell activation** (raised soluble E-selectin, von Willebrand factor) increasing vascular permeability — histology shows endothelial swelling **without overt vasculitis or necrosis**.

Clinical features — biphasic course

- ▶ **Incubation:** usually 1–2 weeks (range 2–30 days). Disease is classically **biphasic**: an acute leptospiraemic phase (fever 3–10 days, organism culturable/PCR-positive in blood) followed by an immune phase (antibodies appear, leptospires shed in urine). Severe disease may be monophasic and fulminant.

Feature	Mild (anicteric) leptospirosis	Severe (icteric) leptospirosis — Weil's syndrome
Frequency	~99% of infections; often unrecognised	~1% of infections
Onset	Abrupt flu-like illness	May be indistinguishable initially, then rapidly progressive
Hallmarks	Fever, chills, intense frontal/retro-orbital headache (dengue-like), conjunctival suffusion, myalgia of	Triad — jaundice + acute kidney injury + haemorrhage; pulmonary haemorrhage; hypotension/shock

Feature	Mild (anicteric) leptospirosis	Severe (icteric) leptospirosis — Weil's syndrome
	calves/back/abdomen, nausea/vomiting	
CNS	Aseptic meningitis (commoner in children); usually benign	Altered sensorium, leptospiral meningitis
Course/mortality	Self-limited over 7–10 (4–30) days; low mortality	Case-fatality 5–40% (CMDT); multi-organ failure

- ▶ **Conjunctival suffusion** (redness without exudate) and severe **calf myalgia** are characteristic clues.
- ▶ **Pulmonary haemorrhage** (cough, chest pain, respiratory distress, haemoptysis ± jaundice) is a major, often lethal presentation and may not be apparent until intubation.
- ▶ **Jaundice** occurs in 5–10%; can be deep/orange-tinged but rarely reflects fulminant hepatic necrosis; tender hepatomegaly.
- ▶ **AKI** common — oliguric or non-oliguric; **hypokalaemia, hyponatraemia, and urinary magnesium loss** (uniquely associated with leptospiral nephropathy). Dialysis can be life-saving; renal recovery is the rule in survivors.
- ▶ **Other:** myocarditis with non-specific ST–T changes/arrhythmias (poor prognostic sign), pancreatitis (raised amylase), rhabdomyolysis (raised CK), and late **autoimmune uveitis** (chronic sequela).
- ▶ **Poor prognostic factors:** age >40 years, altered mental status, acute renal failure, respiratory insufficiency, hypotension, and arrhythmias.

Investigations & diagnosis

- ▶ **Supportive non-specific findings:** leukocytosis with left shift, raised CRP/procalcitonin/ESR; **thrombocytopenia** (platelets $\leq 100 \times 10^9/L$) correlating with bleeding and renal failure; raised bilirubin with only **moderate** aminotransferase/ALP rise; **elevated serum CK** (helps distinguish from viral hepatitis, where CK is normal); coagulation markers of DIC in pulmonary haemorrhage ($\uparrow$ PT/PTT/D-dimer, $\downarrow$ fibrinogen).
- ▶ **Non-oliguric hypokalaemic renal insufficiency** is characteristic of early disease; urine shows leukocytes, erythrocytes, casts, mild proteinuria.
- ▶ **CSF (if meningitic):** pleocytosis (few to >1000 cells/ μL), early polymorphonuclear then lymphocytic predominance; protein normal/mildly raised, glucose normal.
- ▶ **Definitive diagnosis** — isolation of the organism, positive PCR, seroconversion, or a rising titre:

- **Microscopic agglutination test (MAT)** — reference standard (live antigen panel); a single titre of 1:200–1:800 with strong clinical evidence, or preferably a ≥ 4 -fold rise between acute and convalescent sera. Identifies presumptive serogroup.
 - **ELISA** — broadly reacting antigen; plus commercial **rapid lateral-flow/agglutination** tests for resource-limited settings.
 - Antibodies usually undetectable until the **second week**; serology is insensitive in the first ~5 days.
 - **PCR (real-time)** — confirms diagnosis during the **first 5 days** of illness, detecting leptospiral DNA in blood, urine, CSF and aqueous humour — its key advantage over serology.
- **Imaging:** chest radiograph shows **patchy bilateral alveolar infiltrates** (alveolar haemorrhage, lower-lobe predominant), pleural-based densities, or ARDS-pattern ground-glass.

Differential diagnosis

- **Febrile/myalgic phase:** influenza, SARS-CoV-2, **dengue**, **chikungunya**, malaria, **typhoid**, scrub typhus/rickettsioses, viral hepatitis, acute HIV.
- **Haemorrhagic/renal presentation:** dengue haemorrhagic fever, **hantavirus** (HFRS/HCPs), yellow fever, and other viral haemorrhagic fevers. Co-infection (e.g. with dengue/rickettsiae) occurs — test for these when leptospirosis is suspected.

Treatment

- **General principle:** start antibiotics **early** (especially in severe disease, as soon as the diagnosis is *considered*) — benefit diminishes once organ damage is established. Leptospire are susceptible to β -lactams, cephalosporins, aminoglycosides and macrolides, but **not** to vancomycin, rifampicin, metronidazole or chloramphenicol. Resistance has not been reported.

Indication	Regimen (7 days)
Mild	Doxycycline 100 mg PO bid or Amoxicillin 500 mg PO tid or Ampicillin 500 mg PO tid (azithromycin 500 mg OD $\times 3$ days an alternative; doxycycline/azithromycin preferred where rickettsioses co-endemic)
Moderate/severe	Penicillin G 1.5 million units IV/IM q6h or Ceftriaxone 2 g/day IV or Cefotaxime 1 g IV q6h or Doxycycline 200 mg IV load then 100 mg IV q12h
Chemoprophylaxis	Doxycycline 200 mg PO once weekly or Azithromycin 250 mg PO once/twice weekly

- Randomised trials show **no significant difference** between penicillin, ceftriaxone, cefotaxime and doxycycline for severe disease (a 2024 meta-analysis found no clear survival benefit for any single antibiotic).

- ▶ **Supportive care is essential and can be life-saving:** aggressive fluid/electrolyte resuscitation in non-oliguric renal dysfunction; **early haemodialysis/peritoneal dialysis** for oliguric renal failure (reduces mortality, usually needed only briefly); **lung-protective low-tidal-volume ventilation** for pulmonary haemorrhage/ARDS. Evidence for **glucocorticoids** and **desmopressin** in pulmonary involvement is contradictory.
- ▶ A **Jarisch–Herxheimer reaction** may occur within hours of starting therapy.

Prevention

- ▶ Avoid exposure to contaminated water/soil and animal urine/tissue; use protective **footwear, eyewear and clothing**; targeted **rodent control**.
- ▶ **Pre-/post-exposure doxycycline** for well-defined short-term exposure (e.g. monsoon flooding) — efficacy disputed; a 2024 meta-analysis did not show reduced infection or mortality.
- ▶ **Vaccines:** animal (veterinary) bacterin vaccines must match local serovars; human bacterin vaccines (Japan, China, Cuba, France) give short-term serovar-specific immunity with significant side effects and limited availability.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Biphasic natural history (timeline):** x-axis weeks 1–4 then months–years. Mark **Incubation period (2–30 days)** → **Acute/leptospiroemic phase (fever; Leptospira in blood & CSF)* → *Immune/convalescent phase (antibody rise; Leptospira in urine; uveitis, interstitial nephritis)*. Overlay curves for **leptospiroemia**, **antibody titre (MAT)**, and **specimen windows for blood culture/PCR (early) vs urine PCR/culture and serology (late)**. Labels: Leptospiroemia, Leptospiruria & immunity, Fever, Antibody titre*.
- ▶ **Weil's syndrome triad (Venn/triangle):** three overlapping circles labelled **Jaundice (liver)**, **Acute kidney injury (kidney)**, **Haemorrhage (pulmonary/GI/skin)** with central label **Weil's syndrome**.

Clinical / Diagnostic significance

- ▶ Suspect leptospirosis in any **febrile illness with myalgia, conjunctival suffusion and an exposure history** (flood/freshwater/occupational/animal contact), particularly post-monsoon in endemic India.
- ▶ The combination of **jaundice + AKI + thrombocytopenia/haemorrhage** with only modestly raised transaminases but **high CK** strongly favours leptospirosis over viral hepatitis.
- ▶ **Non-oliguric hypokalaemic AKI** and **urinary magnesium loss** are near-pathognomonic renal clues.
- ▶ Use **PCR in the first 5 days** and **paired MAT serology** thereafter — do not withhold empirical antibiotics awaiting serology.

High-yield exam pointers

- ▶ Cause: *Leptospira interrogans* (sensu lato); >260 serovars in 26 serogroups; hooked-ended motile spirochaete seen on **dark-field**.
- ▶ Main reservoir = **rats**; serovar *Icterohaemorrhagiae/Copenhageni* causes severe disease; **water-borne**, monsoon/flood-associated.
- ▶ **Weil's syndrome** = jaundice + AKI + haemorrhage; **pulmonary haemorrhage** is a leading cause of death.
- ▶ **Conjunctival suffusion** + **calf myalgia** = classic bedside clues; headache is **frontal/retro-orbital** (dengue-like).
- ▶ Diagnosis: **MAT** (≥ 4 -fold rise / titre 1:200–1:800) is reference; **PCR** best in first 5 days; antibodies appear in **week 2**.
- ▶ Renal hallmark: **non-oliguric hypokalaemic** renal insufficiency; **CK elevated** (normal in viral hepatitis).
- ▶ Treatment: **IV penicillin / ceftriaxone / cefotaxime** (severe) or **oral doxycycline/amoxicillin/azithromycin** (mild) $\times 7$ days; early **dialysis** and **lung-protective ventilation** are life-saving.
- ▶ Prophylaxis: **doxycycline 200 mg weekly** for short-term high-risk exposure (efficacy disputed). Watch for **Jarisch–Herxheimer** reaction.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Leptospirosis" (Goeijenbier & Wagenaar) — aetiology, pathogenesis, clinical syndromes, diagnosis, Table 189-1 treatment/chemoprophylaxis.
- ▶ CMDT 2026 — "Spirochetal Infections: Leptospirosis" — anicteric vs icteric (Weil syndrome) classification, laboratory criteria, current drug regimens, 2024 meta-analyses on antibiotic and prophylaxis efficacy.



Mechanisms of Antibiotic Drug Resistance

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Resistance* is the reduction in or loss of an antibacterial agent's effect on a bacterium, and the bacterial properties or alterations that produce this reduced activity are termed *resistance mechanisms*. It is quantified in the laboratory by the **minimal inhibitory concentration (MIC)** — the lowest drug concentration that inhibits growth under standardised conditions — which, compared against regulatory **breakpoints**, classifies an isolate as susceptible, intermediate, or resistant. Resistance may be **intrinsic** (a natural property of the species) or **acquired** (via mutation or gene

transfer), and bacteria frequently carry combinations of mechanisms conferring **multidrug resistance (MDR)**.

Genetic basis — how resistance arises and spreads

- ▶ **Chromosomal mutation** — spontaneous point mutations during DNA replication, selected under antibiotic pressure (e.g. *rpoB* for rifampin, *gyrA/parC* for quinolones, ribosomal mutations).
- ▶ **Acquisition of new genes by horizontal transfer** — usually on self-replicating **plasmids** or other mobile elements (**transposons**, gene cassettes) carrying one or several resistance genes, so a single plasmid can confer multidrug resistance.
- ▶ **Transformation** — uptake of fragments of environmental DNA from related species and direct recombination into the chromosome; important in *Streptococcus pneumoniae* and *Neisseria gonorrhoeae* (generates **mosaic PBP** genes).
- ▶ **Origin and selection** — many resistance genes originated in antibiotic-**producer** organisms (self-protection) and were later mobilised onto plasmids; antimicrobial exposure in humans, animals and the environment then **selects** resistant strains. Initial fitness costs are often offset over time by **compensatory mutations**, allowing resistant strains to persist even without ongoing drug pressure.

The three broad mechanistic categories

All resistance mechanisms fall into three groups (Harrison, Table 150-1; Fig. 150-1):

Category	Strategy	Representative examples
1. Altered / bypassed target	Modify or substitute the drug's binding site so binding falls	Altered PBPs (MRSA <i>mecA</i> /PBP2a, mosaic PBPs); d-Ala-d-Lac in VRE; <i>gyrA/parC</i> mutations; <i>rpoB</i> ; ribosomal methylation; bypass DHFR/DHPS
2. Altered access to target	Reduce uptake (porin loss) or increase active efflux	Loss of OprD/porins (carbapenems); MexXY, broad-spectrum multidrug efflux pumps
3. Drug inactivation / modification	Enzymatically destroy or chemically modify the drug	β -lactamases (ESBL, AmpC, carbapenemases); aminoglycoside-modifying transferases; chloramphenicol acetyltransferase

Mechanism by drug class

- ▶ **β -Lactams (penicillins, cephalosporins, monobactams, carbapenems):** Three routes — (a) β -lactamase degradation of the β -lactam ring (commonest in gram-negatives, concentrated in the

periplasmic space); (b) **altered PBP targets**; (c) **reduced porin diffusion**. β -Lactamase classes: *plasmid* enzymes inactivating penicillins/early cephalosporins; **extended-spectrum β -lactamases (ESBLs)** that also degrade ceftriaxone, cefotaxime, ceftazidime, aztreonam (some also cefepime); **AmpC** (chromosomal in *Enterobacter*; inducible/derepressed, degrades most cephalosporins except cefoxitin/cefepime); and **carbapenemases** that destroy nearly all β -lactams — *Klebsiella pneumoniae* carbapenemase (KPC), **New Delhi metallo- β -lactamase (NDM)**, originally Indian subcontinent), and **OXA-48**. PBP-mediated resistance: **mosaic PBPs** (penicillin-resistant pneumococcus, gonococcus, meningococcus) and **PBP2a** encoded by *mec* in MRSA (a bypass transpeptidase of low affinity; only **ceftaroline** binds PBP2a). β -Lactamase **inhibitors** — clavulanate, sulbactam, tazobactam, avibactam, vaborbactam, relebactam, durlobactam — restore activity; only *avibactam*, *vaborbactam*, *relebactam* inhibit AmpC and KPC-type carbapenemases (but **not** metallo-enzymes such as NDM).

- ▶ **Glycopeptides (vancomycin, teicoplanin)**: Acquisition of **van** gene cassettes in enterococci (VRE) replaces the terminal d-Ala-d-Ala of the peptidoglycan stem peptide with d-Ala-d-Lac, which vancomycin binds with **1000-fold lower affinity**; *van* genes are transposon/plasmid-borne and have rarely transferred to *S. aureus* (true VRSA). **VISA** (intermediate resistance) arises instead from stepwise chromosomal mutations producing a thickened, poorly cross-linked cell wall that traps vancomycin at decoy d-Ala-d-Ala termini away from the synthesis site.
- ▶ **Aminoglycosides (gentamicin, tobramycin, amikacin, plazomicin)**: Mainly plasmid-encoded **aminoglycoside-modifying enzymes** adding acetyl, adenylyl or phosphate groups (amikacin/plazomicin spared by most); **16S rRNA methylases** confer resistance to *all* aminoglycosides including plazomicin; ribosomal-protein mutation (streptomycin); MexXY **efflux** in *Pseudomonas*.
- ▶ **Tetracyclines & glycylcyclines**: Plasmid-mediated **active efflux** and **ribosomal protection proteins** (*TetM/TetO*). Newer agents (tigecycline, eravacycline, omadacycline) evade common mechanisms but can be lost to broad-spectrum efflux overexpression.
- ▶ **Macrolides/lincosamides/streptogramins (MLS)**: Acquired **Erm methylases** modify the 23S rRNA binding site (the **MLSB** phenotype, inducible or constitutive); plus **efflux** pumps and, for streptogramins/chloramphenicol, drug-modifying enzymes. 23S rRNA mutational resistance is commoner in organisms with few rRNA gene copies (mycobacteria, *H. pylori*, *Treponema*).
- ▶ **Oxazolidinones (linezolid, tedizolid)**: 23S rRNA mutations (more in enterococci) and the plasmid **Cfr methylase** (cross-resistance with chloramphenicol/lefamulin).
- ▶ **Quinolones**: Chromosomal **target mutations** in DNA gyrase and topoisomerase IV; **efflux** overexpression; and acquired plasmid genes — *qnr* (target protection), *aac(6')-Ib-cr* (modifies ciprofloxacin/norfloxacin), and efflux determinants — that also enrich for higher-level resistance and link to multidrug-resistance plasmids.

- ▶ **Rifamycins (rifampin, rifabutin, rifapentine):** A **single mutation in the β subunit of RNA polymerase (rpoB) gives high-level resistance — hence rifamycins are always used in combination**.
- ▶ **Sulfonamides & trimethoprim:** Plasmid-acquired **resistant DHPS** and **resistant DHFR** that *bypass* inhibition of the native enzymes; resistance to co-trimoxazole needs both.
- ▶ **Polymyxins (colistin, polymyxin B):** Mutations reducing the **negative charge of LPS**, and the transferable plasmid **mcr-1** (and variants) encoding a phosphoethanolamine transferase that masks the LPS target.
- ▶ **Daptomycin / metronidazole / nitrofurantoin:** Daptomycin — multigene mutations altering membrane charge; metronidazole — loss of activating nitroreductase / *nim* genes; nitrofurantoin — stepwise loss of nitroreductase activity.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **“Gram-negative bacterium showing antibiotic targets and resistance mechanisms”** (after Harrison Fig. 150-1). Draw the cell with **outer membrane + porin, periplasmic space, inner membrane, ribosome, DNA, and a resistance plasmid**. Label: *Loss of porins* → carbapenem resistance; *β -lactamases in periplasmic space*; *Overexpressed transmembrane efflux pump* (β -lactams, quinolones, aminoglycosides, tetracyclines, chloramphenicol); *Altered iron-uptake pathway (cefiderocol)*; *Bypass targets — trimethoprim (DHFR), sulfonamides (DHPS)*; *Antibiotic-modifying enzymes (aminoglycosides, ciprofloxacin)*; *Ribosomal mutation/methylation (tetracyclines, oxazolidinones, aminoglycosides)*; *Target mutations (DNA gyrase, topoisomerase IV)*; *LPS modification (polymyxins)*.
- ▶ **Simple flow box:** *Three categories of resistance — (1) Altered/bypassed target* → (2) *Reduced uptake / increased efflux* → (3) *Drug inactivation* — each with one example arrow.

Clinical / Diagnostic significance

- ▶ **Laboratory detection:** MIC by broth/agar microdilution, disk diffusion, or **E-test** (gradient strip) interpreted against breakpoints; phenotypic tests for ESBL, AmpC and carbapenemase; molecular detection of *mecA*, *vanA/B*, KPC/NDM/OXA, *mcr*.
- ▶ **Empiric vs definitive therapy:** Because prevalence varies by geography and institution, empirical choice should follow the **local antibiogram**; therapy must then be **de-escalated** to the *narrowest-spectrum* agent for the *shortest effective duration* once susceptibilities return.
- ▶ **Apparent treatment failure** despite “susceptible” report — consider undrained pus/foreign body, poor drug penetration (CNS, intracellular sites), superinfection, emergence of resistance on therapy, polymicrobial infection, impaired host defences, or non-infective causes (drug fever).

- ▶ **Salvage agents for MDR gram-negatives:** ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, **cefiderocol** (siderophore cephalosporin taken up via iron transport, stable to many β -lactamases including carbapenemases), and polymyxins.
- ▶ **Combination therapy** is used for synergy and to *prevent emergence of resistance* (classically rifampin, antitubercular regimens), not merely for broad coverage.

High-yield exam pointers

- ▶ Three mechanistic categories: **target alteration/bypass**, **reduced access (porin loss/efflux)**, **drug inactivation**.
- ▶ **MRSA** = **mecA** $\rightarrow$ **PBP2a** (bypass transpeptidase); **ceftaroline** is the anti-MRSA β -lactam.
- ▶ **VRE** = **van genes** $\rightarrow$ **d-Ala-d-Lac** (1000 $\times$ lower vancomycin affinity); **VISA** = **thickened cell wall**, not van.
- ▶ **ESBL** spares carbapenems; **carbapenemases** = **KPC, NDM, OXA-48**; avibactam/vaborbactam/relebactam cover KPC but **not** NDM (metallo-).
- ▶ **Rifampin resistance = single rpoB mutation** $\rightarrow$ never use as monotherapy.
- ▶ **Quinolone resistance** = gyrA/parC mutations + efflux + plasmid *qnr* / *aac(6')-Ib-cr*.
- ▶ **Colistin resistance** = **plasmid mcr-1** (phosphoethanolamine transferase on LPS).
- ▶ **16S rRNA methylase** defeats *all* aminoglycosides, including plazomicin.
- ▶ CDC 2019: **>2.8 million** resistant infections, **~35,900 deaths/year**; **urgent threats** — CRE, carbapenem-resistant *Acinetobacter*, drug-resistant *N. gonorrhoeae*, *C. difficile*, *Candida auris*. Countered by the **five core actions** and a **One Health** approach.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Bacterial Resistance to Antimicrobial Agents” (definitions, MIC/breakpoints, genetic basis, the three mechanistic categories, per-class mechanisms, β -lactamase/inhibitor detail, CDC 2019 threats and core actions); and “Treatment and Prophylaxis of Bacterial Infections” (principles of combination therapy and stewardship).
- ▶ **CMDT 2026** — “Common Problems in Infectious Diseases & Antimicrobial Therapy” (susceptibility testing/MIC, antibiogram-guided empirical therapy, de-escalation, causes of apparent treatment failure).

♦ ♦ ♦

Melioidosis

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Melioidosis (*Whitmore's disease*) is a potentially fatal infection caused by *Burkholderia pseudomallei*, a gram-negative, facultative intracellular saprophyte of soil and surface

water in the tropics. It is geographically restricted chiefly to **Southeast Asia and northern Australia**, with sporadic cases from India, China and other tropical zones. Among the pseudomonads, *B. pseudomallei* is one of the most virulent species: host compromise is **not** a prerequisite for disease, the clinical spectrum runs from asymptomatic infection to fulminant septicaemia, and the organism's capacity for intracellular survival permits prolonged **latency and late reactivation** (the so-called “*Vietnamese time-bomb*”).

Etiology & microbiology

- ▶ **Organism:** *Burkholderia pseudomallei* — a non-lactose-fermenting, oxidase-positive, motile gram-negative bacillus of the genus *Burkholderia* (formerly *Pseudomonas*).
- ▶ A **facultative intracellular** pathogen that replicates within polymorphonuclear leukocytes (PMNs) and macrophages; survival is aided by a **polysaccharide capsule**.
- ▶ A close relative, *B. mallei*, causes **glanders** (an equine zoonosis) — covered in the same chapter and a frequent comparison point (see below).
- ▶ **Environmental reservoir:** soil and water; the organism is a *primary pathogen* (unlike opportunistic *P. aeruginosa* and *Stenotrophomonas*). Humans are **never colonised without being infected**.
- ▶ A recognised **potential agent of biological warfare**, which has stimulated interest in vaccine development; it is handled as a high-consequence select agent and has caused point-source outbreaks (e.g. contaminated *aromatherapy spray*).

Epidemiology & risk factors

- ▶ **Endemic zones:** Southeast Asia (notably Thailand) and tropical northern Australia; occasional cases in India and China. Should be suspected in **returning travellers and military personnel** from endemic regions — symptoms may appear only later because of latency.
- ▶ **Routes of acquisition** — three principal portals:
 - *Percutaneous inoculation* through skin abrasions (the commonest route; rice-paddy and soil exposure).
 - *Inhalation* of contaminated aerosols/dust (associated with severe pneumonic and septicaemic disease, e.g. during monsoon/heavy rains).
 - *Ingestion* of contaminated water.
- ▶ **Person-to-person transmission is rare.**
- ▶ **Predisposing host factors** (present in many, though not all, patients): **diabetes mellitus** (the single most important association), **chronic renal failure**, **alcohol abuse**, and other chronic illness.
- ▶ A significant cause of **fatal community-acquired pneumonia and septicaemia** in endemic areas, with reported mortality as high as **44% (Thailand)**.

Pathogenesis

- ▶ After inoculation/inhalation, *B. pseudomallei* is taken up by phagocytes but **survives intracellularly**, escaping killing within PMNs and macrophages.
- ▶ The **polysaccharide capsule** and a functional **type III secretion system** (which mediates intracellular survival and cell-to-cell spread) are key virulence determinants.
- ▶ Intracellular persistence underlies the characteristic **latency** and ability to relapse months to years after primary exposure.
- ▶ Infection provokes a **florid inflammatory/granulomatous (abscess-forming) response**; haematogenous dissemination, most often in debilitated hosts, seeds multiple deep organs and produces the highly lethal septicaemic forms.

Clinical manifestations

B. pseudomallei causes a **wide spectrum**, from asymptomatic infection to multifocal abscesses, pneumonia and disseminated septic disease. The major recognised forms:

Clinical form	Key features
Acute pulmonary (commonest diagnosed form)	Ranges from mild illness with upper-lobe infiltrates on chest film to severe necrotizing pneumonia ; high fever, cough
Chronic pulmonary	<i>Mimics pulmonary tuberculosis</i> — chronic cough, fever, haemoptysis, night sweats , cavitary lung disease
Cutaneous / localised	Skin ulceration with associated lymphangitis and regional lymphadenopathy
Septicaemic / disseminated	Spread from lung or skin (esp. in debilitated patients) → bacteraemia with multi-organ abscesses (liver, spleen, prostate, kidney) and septic shock; high mortality
Neurological (CNS) melioidosis	Endemic in South Asia and Australia; encephalomyelitis / brain abscess / meningitis
Latent / reactivation	Quiescent infection reactivating later, often when host defences fall

Diagnosis / investigations

- ▶ **Definitive diagnosis is by culture**, which is the gold standard — *B. pseudomallei* isolated from blood, sputum, pus/abscess aspirate, urine or wound swab confirms the disease (isolation from any site is diagnostic, as humans are not colonised).
- ▶ The organism is a non-fermenting, **oxidase-positive** gram-negative rod; on Gram stain it classically shows **bipolar (“safety-pin”) staining**, and it grows well on selective Ashdown’s agar (wrinkled colonies). [*microbiology details: standard, see Coverage note*]

- ▶ **Imaging** to map deep abscesses: chest radiograph (upper-lobe infiltrates / cavitation), and ultrasound or CT of liver, spleen, prostate and kidneys to detect visceral abscesses; MRI for suspected CNS disease.
- ▶ Screen for and assess **underlying diabetes and renal impairment**, which modify prognosis and management.
- ▶ **Differential diagnosis**: pulmonary tuberculosis (the chronic cavitary form is a classic mimic), other causes of community-acquired pneumonia, and disseminated pyogenic abscesses.

Treatment

Treatment is prolonged and deliberately divided into **two sequential phases** — an IV *intensive* (*eradication-initiation*) phase to control sepsis, followed by a long oral *eradication* phase to clear intracellular organisms and **prevent relapse**.

Phase	Regimen (Harrison, Table 170-2)	Duration
Intensive (IV)	Ceftazidime 2 g IV q6h <i>or</i> meropenem 1 g IV q8h <i>or</i> imipenem 500 mg IV q6h	≥2 weeks; 4–8 weeks (Australian guidelines) for severe infection, osteomyelitis and CNS disease
Eradication (oral)	Trimethoprim-sulfamethoxazole (TMP-SMX) 1600/320 mg PO q12h	≥3 months (12 weeks)

- ▶ The intensive IV phase must be **lengthened** for deep-seated disease (severe sepsis, osteomyelitis, neurological melioidosis), and large abscesses require **drainage** alongside antibiotics.
- ▶ The prolonged oral eradication course is essential because intracellular persistence causes **relapse** if treatment is curtailed.
- ▶ *B. pseudomallei* is **intrinsically resistant** to many agents (e.g. aminoglycosides, many early penicillins/cephalosporins) — empirical “sepsis” regimens that omit ceftazidime/carbapenems may fail; susceptibility is to advanced penicillins, ceftazidime and carbapenems.
- ▶ **Glanders (B. mallei)** is treated with the same drugs for the same duration as melioidosis (and is additionally susceptible to the macrolides azithromycin and clarithromycin).

Melioidosis vs glanders (companion comparison)

Feature	Melioidosis (<i>B. pseudomallei</i>)	Glanders (<i>B. mallei</i>)
Reservoir	Environmental — soil & water	Not environmental ; persists only in equine hosts
Acquisition	Inoculation / inhalation / ingestion	Contact with infected horses; respiratory secretions highly infectious; at-risk = horse

Feature	Melioidosis (<i>B. pseudomallei</i>)	Glanders (<i>B. mallei</i>)
		handlers, equine butchers, veterinarians
Distribution	SE Asia, N Australia, India, China	Africa, Asia, South America (eradicated from Europe/N America)
Capsule	Major virulence factor	Critical virulence determinant
Treatment	Ceftazidime/carbapenem → TMP-SMX	Same as melioidosis (+ azithromycin/clarithromycin susceptible)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis / portals-of-entry schematic:** a central soil-and-water reservoir with three arrows to a human — labels: *Percutaneous inoculation, Inhalation, Ingestion* → *B. pseudomallei* (facultative intracellular) → uptake & survival in macrophage/PMN (capsule, Type III secretion system) → branching to *Localised skin ulcer + lymphangitis, Acute/chronic pneumonia, Haematogenous dissemination* → *multi-organ abscesses (liver, spleen, prostate, kidney) + septicaemia*, and a dashed loop labelled *Latency / relapse*.
- ▶ **Two-phase treatment timeline bar:** Label segment 1 *Intensive IV phase — ceftazidime / meropenem (≥2 wks; 4–8 wks if severe/osteomyelitis/CNS)*; Label segment 2 *Oral eradication phase — TMP-SMX ≥3 months (prevents relapse)*.

Clinical / Diagnostic significance

- ▶ Consider melioidosis in any febrile patient from an endemic area — especially a diabetic — presenting with community-acquired pneumonia, sepsis, or multifocal abscesses; it is a **great mimic of tuberculosis** and of pyogenic abscess disease.
- ▶ **Isolation of the organism from any clinical specimen is diagnostic** — alert the microbiology laboratory, both for biosafety (select agent) and because the organism may be misidentified by automated systems.
- ▶ Therapeutic success hinges on choosing the **right drug class** (ceftazidime/carbapenem, not aminoglycosides) and **completing the long eradication course** — incomplete therapy leads to relapse.
- ▶ Search systematically for **occult visceral abscesses** (prostate, liver, spleen) and treat underlying **diabetes/renal disease**, as these influence outcome.

High-yield exam pointers

- ▶ **Melioidosis = Whitmore's disease**, caused by *Burkholderia pseudomallei*, a **facultative intracellular gram-negative saprophyte of soil and water**.

- ▶ **Endemic in SE Asia (esp. Thailand) and northern Australia**; sporadic in India/China — suspect in returning travellers/soldiers.
- ▶ **Diabetes mellitus** is the dominant predisposing factor; renal failure and alcohol abuse also predispose; *host compromise is not essential*.
- ▶ Three portals: **inoculation, inhalation, ingestion**; person-to-person spread is rare.
- ▶ **Acute pulmonary disease** is the commonest form; **chronic cavitary pneumonia** mimics TB; septicaemic disease carries mortality up to 44%.
- ▶ Virulence: **polysaccharide capsule + type III secretion system** → intracellular survival, **latency and relapse**.
- ▶ **Diagnosis = culture (gold standard)**; isolation from any site is significant.
- ▶ **Treatment = two phases**: intensive IV **ceftazidime/meropenem** ≥2 wks → oral **TMP-SMX** ≥3 months; drain abscesses; *intrinsically resistant to aminoglycosides*.
- ▶ Closely related **B. mallei** → **glanders** (equine zoonosis); both are **potential bioterrorism (select) agents**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Infections Due to *Pseudomonas*, *Burkholderia*, and *Stenotrophomonas* Species” (*Burkholderia pseudomallei*/melioidosis and *B. mallei*/glanders sections, incl. Table 170-2 antibiotic regimens); “Acute Meningitis” (CNS melioidosis as a regional cause); and the genomic-epidemiology chapter (point-source *B. pseudomallei* aromatherapy-spray outbreak).
- ▶ **CMDT 2026** — antimicrobial-spectrum/treatment tables listing *B. pseudomallei* (melioidosis) and *B. mallei* (glanders).
- ▶ **Coverage note**: Harrison covers the etiology, epidemiology, pathogenesis, clinical spectrum and staged treatment of melioidosis well, but does not detail laboratory morphology. The **bipolar “safety-pin” Gram appearance**, growth on **Ashdown's selective agar**, the eponym **Whitmore's disease**, and the **“Vietnamese time-bomb”** latency nickname are universally accepted standard microbiology/clinical facts added for completeness and are not verbatim from the cited chapters.



Multidrug-Resistant Tuberculosis (MDR-TB)

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Multidrug-resistant tuberculosis (MDR-TB) is disease caused by a strain of *Mycobacterium tuberculosis* resistant *at least* to **isoniazid (H)** and **rifampin (R)** — the two most efficacious first-line bactericidal drugs. It represents one end of a spectrum that ranges from rifampin-

resistant (RR) through pre-XDR to extensively drug-resistant (XDR) TB. Because the two most potent drugs are lost and co-resistance to other first-line agents (e.g., ethambutol) is common, MDR-TB requires longer, more toxic, costlier and individualised regimens. Drug resistance almost invariably follows effective **monotherapy** (provider error, poor adherence, malabsorption, or poor-quality/crushed drugs).

Definitions & resistance spectrum

Category	Resistance pattern (Harrison 22e)
RR-TB	Resistant to rifampin ($\pm$ other drugs); rifampin resistance is an excellent <i>proxy</i> for MDR-TB
MDR-TB	Resistant at least to isoniazid AND rifampin
Pre-XDR-TB	MDR/RR-TB strain <i>additionally</i> resistant to any fluoroquinolone
XDR-TB	MDR-TB + resistance to any fluoroquinolone AND at least one additional Group A drug (i.e., bedaquiline or linezolid)

- ▶ **Primary resistance** = patient infected from the outset by a resistant strain; **acquired resistance** = develops in the infecting strain during inadequate treatment.
- ▶ *Mono-resistance to rifampin is rare and is managed as MDR-TB.*

Epidemiology & risk factors

- ▶ Of an estimated **10.8 million** new TB cases in 2023, **~400,000** were RR/MDR-TB — **3.2% of new** and **16% of previously treated** cases. Only ~189,000 were enrolled on treatment, reflecting limited culture/DST capacity.
- ▶ Geography: **>50% of all MDR/RR-TB occurs in India (27%), Russian Federation (7.4%), Indonesia (7.4%), China (7.3%) and the Philippines (7.2%)**; the former Soviet states have the highest *proportion* among new cases (up to one-third).
- ▶ **Risk factors:** presenting from an area where $\geq 5\%$ of incident cases are MDR, **prior TB treatment**, treatment default/failure/relapse, and contact with a known MDR case.
- ▶ The **vast majority of XDR-TB remains undiagnosed** because reliable DST and laboratory capacity are lacking in low-income settings.

Molecular basis of drug resistance

Resistance is due to **spontaneous chromosomal mutations** (no plasmid transfer); knowing the target genes underpins rapid molecular DST.

Drug	Gene(s)	Encoded target / note
Isoniazid	<i>katG</i> , <i>inhA</i> (also <i>kasA</i> , <i>ndh</i>)	Catalase-peroxidase; enoyl-ACP (keto-enoyl) reductase
Rifampin	<i>rpoB</i>	β -subunit of RNA polymerase (core region; mostly missense)
Pyrazinamide	<i>pncA</i>	Pyrazinamidase (activates prodrug); mutated in 72–98%
Ethambutol	<i>embB</i> (codon 306 in 50–70%)	Arabinosyltransferase
Fluoroquinolones	<i>gyrA</i> , <i>gyrB</i>	DNA gyrase
Bedaquiline	<i>atpE</i> ; <i>Rv0678/mmpR</i> , <i>pepQ</i>	ATP synthase subunit c; efflux-pump repressor → <i>cross-resistance with clofazimine</i>
Linezolid	23S rRNA, <i>rplC</i> (L3), <i>rplD</i> (L4)	50S ribosomal subunit

Diagnosis — rapid drug-susceptibility testing (DST)

- ▶ Universal DST is the WHO standard of care: every initial isolate should be tested at least to rifampin (proxy for MDR); expanded testing to isoniazid, fluoroquinolones and key second-line drugs is mandatory once RR-TB is found.
- ▶ Rapid molecular tests (preferred first test):
 - Xpert MTB/RIF & Xpert MTB/RIF Ultra — detect *M. tuberculosis* and *rpoB* (rifampin resistance) simultaneously.
 - Truenat MTB-Rif Dx — portable, battery-operated; rifampin resistance sensitivity ~84%, specificity ~97%.
 - Line probe assays (LPAs) — DNA-strip tests detecting *rpoB*, *katG*, *inhA*; second-line LPAs are the recommended initial test for fluoroquinolone / injectable resistance in confirmed RR/MDR-TB.
- ▶ Phenotypic culture-based DST (MGIT liquid ~3 weeks; solid Löwenstein-Jensen ≥8 weeks) is still needed for drugs/mutations not covered by molecular tests and to monitor emerging resistance.
- ▶ Whole-genome sequencing (WGS) and targeted next-generation sequencing (tNGS) give comprehensive resistance profiles; tNGS can be run directly on sputum.

WHO drug grouping (for longer regimens) & treatment regimens

WHO priority grouping (Table 183-3):

Group	Drugs	Rule
A (use all three)	Levofloxacin/moxifloxacin; bedaquiline; linezolid	All three included; ≥ 3 retained if bedaquiline stopped
B (≥ 1 included)	Clofazimine; cycloserine/terizidone	Add a 2nd if a Group A drug cannot be used
C (complete the regimen)	Ethambutol, delamanid, pyrazinamide, imipenem- cilastatin/meropenem, amikacin (or streptomycin), ethionamide/prothionamide, PAS	Used when A/B insufficient

- **Kanamycin and capreomycin are NO LONGER recommended** (worse failure/relapse); injectables are now largely avoided. All-oral regimens are preferred.

Recommended all-oral regimens (2022–2024 WHO):

Regimen	Composition & duration	Use
BPaLM (<i>preferred</i>)	Bedaquiline + Pa pretomanid + Linezolid 600 mg + Moxifloxacin $\times 6$ months	MDR/RR or pre-XDR, age ≥ 14 y, any HIV status; <i>drop Mfx if documented fluoroquinolone resistance</i> (= BPaL)
BDLLfxCfz	Bedaquiline + delamanid + linezolid 600 + levofloxacin + clofazimine $\times 6$ months	Non-inferior alternative; usable in children, adolescents, pregnant/breast-feeding women
9-month all-oral	BLMZ, or BLLfxCfzZ, or BDLLfxZ	No fluoroquinolone resistance & no prior exposure to B/D/L
Longer individualised	≥ 3 Group A + ≥ 1 Group B (add C as needed); ≥ 18 –20 months (15–17 months after culture conversion)	Complex patterns including XDR-TB

- **BPaLM** achieves treatment success $\sim 90\%$ (TB-PRACTECAL, Nix-TB, ZeNix). It is **avoided in disseminated, CNS and osteoarticular TB and in pregnancy/breast-feeding** (incomplete pretomanid safety data).
- Landmark trials: **STREAM stage-1** (9-month “Bangladesh” regimen), **Nix-TB/ZeNix** (BPaL, linezolid dose-finding), **TB-PRACTECAL** (24-week BPaLM non-inferior with fewer serious adverse events), **endTB** and **BEAT-TB**.
- **Surgery** (lobectomy/wedge resection) may be added for localised disease with adequate pulmonary reserve.

Monitoring, key drug toxicities & special situations

- ▶ **QT-prolonging drugs** — bedaquiline, delamanid, clofazimine, fluoroquinolones: baseline + serial ECG; do **not** use if QTc >500 ms or history of ventricular arrhythmia.
- ▶ **Bedaquiline**: 400 mg/day × 2 weeks then 200 mg thrice-weekly; FDA **black-box warning** (QT prolongation; excess mortality 11.4% vs 2.5% in one trial); CYP3A4-metabolised — rifampin/efavirenz lower its levels.
- ▶ **Linezolid**: 600 mg once daily; optic & peripheral neuropathy, **myelosuppression/pancytopenia**, lactic acidosis, serotonin syndrome (weak MAO inhibitor).
- ▶ **Clofazimine**: reversible orange-brown skin/secretion discoloration; very long t_{1/2} (~70 days). **Cycloserine**: seizures, psychosis, depression. **Amikacin** (if used): serial **audiometry**.
- ▶ **HIV co-infection**: integrase inhibitor **dolutegravir/raltegravir at double dose** (not bictegravir/cabotegravir/elvitegravir) or efavirenz; advanced immunosuppression (CD4 <100/μL) raises failure/relapse risk.
- ▶ **Programmatic essentials**: DOT/patient support, informed consent, monthly bacteriologic monitoring, active drug-safety monitoring, infection-control measures.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Concentric/Venn classification of drug resistance**: outermost ring “RR-TB (rifampin-R)” → inner “MDR-TB (H + R resistant)” → “Pre-XDR (MDR + any fluoroquinolone-R)” → core “XDR (+ bedaquiline or linezolid-R)”. Label each with its defining drug(s).
- ▶ **Diagnostic-to-treatment algorithm**: *Sputum* → Xpert MTB/RIF Ultra → *Rifampin resistance detected (RR-TB)* → **second-line LPA / phenotypic DST (fluoroquinolone)** → branch to “BP_aLM (6 mo)”, “9-month all-oral”, or “Longer ≥18-mo individualised (XDR)”. Labels: *Group A / B / C drugs, DST, culture conversion*.

Clinical / Diagnostic significance

- ▶ A single **rifampin-resistance** result on Xpert should trigger a full second-line DST and an MDR regimen — never treat presumptively as drug-susceptible.
- ▶ Empirical MDR therapy is justified in a high-likelihood patient (failure/default, MDR contact) while confirmatory DST is awaited.
- ▶ Avoid repeated empirical **fluoroquinolone** courses for “community-acquired pneumonia” — they delay TB diagnosis and **breed fluoroquinolone resistance**.
- ▶ Prevention of resistance = ≥2 quality-assured bactericidal drugs to which the strain is susceptible, **fixed-dose combinations**, supervised therapy, and completion of the full course.

High-yield exam pointers

- ▶ MDR = resistant to at least H + R; XDR adds fluoroquinolone + bedaquiline/linezolid resistance.

- ▶ Rifampin resistance (*rpoB*) is the molecular proxy for MDR — basis of Xpert MTB/RIF.
- ▶ Isoniazid resistance: *katG* / *inhA*; pyrazinamide: *pncA*; ethambutol: **embB306**; fluoroquinolone: *gyrA*; bedaquiline: *atpE* / **Rv0678** (cross-resistant to clofazimine).
- ▶ Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid (memorise — most heavily weighted).
- ▶ BPaLM × 6 months is now the preferred MDR/RR regimen (age ≥14 y); BPaL if fluoroquinolone-resistant.
- ▶ Kanamycin and capreomycin are no longer recommended.
- ▶ Mandatory ECG monitoring for QT-prolonging anti-TB drugs; linezolid → cytopenias & neuropathy; bedaquiline → black-box QT/mortality warning.
- ▶ India carries 27% of the world's MDR/RR-TB burden.

SOURCE & COVERAGE

Harrison 22e — Ch 183 “Tuberculosis” (epidemiology, definitions, diagnosis/DST, WHO drug groups & regimens, monitoring) + Ch 186 “Antimycobacterial Agents” (drug mechanisms, resistance genes, doses, MDR definition, BPaLM/trials). Coverage note: All specifics (definitions, gene names, regimen compositions, doses, QT cut-off, epidemiology) are drawn from these two chapters; RNTCP/NTEP (India)–specific programmatic nomenclature is not in Harrison and is therefore not quoted.



Neurocysticercosis

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Neurocysticercosis (NCC) is the term for involvement of the **brain, spinal cord, or cerebrospinal fluid (CSF)** by the **larval (cysticercus) stage of the pork tapeworm Taenia solium**. It follows ingestion of *T. solium* eggs, in which humans act as the intermediate (dead-end) host. NCC is the single most important cause of acquired epilepsy in the developing world and in immigrants from endemic regions, and is highly prevalent in India, Latin America, sub-Saharan Africa, China and Southeast Asia*. Globally an estimated 20 million people carry cysticerci, ~400,000 develop neurological symptoms and ~50,000 die each year.

Aetiology, life cycle and pathogenesis

- ▶ ***T. solium* causes two distinct human infections* — taeniasis (*adult tapeworm in the gut, acquired by eating undercooked pork containing cysticerci*) and cysticercosis (*tissue larval infection, acquired by ingesting eggs*). Humans are the only definitive host; the pig is the usual intermediate host*.

- ▶ **Route to cysticercosis** — faecal–oral ingestion of eggs from a **human tapeworm carrier**. Eggs are sticky and found under the carrier’s fingernails; **autoinfection** can occur (carrier ingests own ova). Hence cysticercosis can occur even in people who never eat pork, including vegetarians, if exposed to a carrier’s faeces.
- ▶ **Pathogenesis** — Ingested eggs release **oncospheres** that penetrate the intestinal wall and disseminate haematogenously to tissues, preferentially the **CNS, skeletal muscle, subcutaneous tissue and eye**. The oncosphere matures into a fluid-filled **cysticercus** (single invaginated scolex) over ~60–90 days.
- ▶ ***Worm morphology (helps distinguish from *T. saginata*)** — *scolex bears an armed rostellum with two rows of hooklets plus four suckers; mature tapeworm up to 3 m with up to 1000 proglottids; each gravid proglottid has 8–12 uterine branches (vs 15–30 in *T. saginata**) and releases ~50,000 immediately-infective eggs.*
- ▶ **Symptom generation** — clinical effects depend on **location, number, size and viability** of cysts and, critically, on the **host inflammatory response** to a degenerating cyst. A live (vesicular) cyst evades immunity and may stay silent; symptoms typically arise when the larva **degenerates** and provokes oedema and gliosis.

Classification and clinical manifestations

NCC is classified by **anatomical location and parasite viability** (Harrison Fig. 242-1), which dictates presentation and treatment.

Location / form	Key features	Typical clinical picture
Parenchymal (viable cyst)	Round cyst 5–20 mm, often with visible scolex	Seizures (commonest); usually benign course
Single enhancing lesion	Solitary degenerating cyst with ring/disc enhancement + perilesional oedema	New-onset focal seizures (classic <i>Indian</i> presentation — solitary cysticercus granuloma)
Parenchymal calcification	Old, dead, calcified larva	Recurrent seizures, especially if perilesional oedema/enhancement
Intraventricular	Thin-walled cyst, fluid isodense to CSF	Obstructive hydrocephalus , raised ICP, <i>Bruns’ syndrome</i>
Subarachnoid / basal (racemose)	Grape-like proliferating cysts up to 6 cm, no scolex	Chronic meningitis, arachnoiditis , vasculitis/strokes, communicating hydrocephalus — most aggressive form
Spinal / ocular	Cord or subretinal/vitreous cysts	Progressive myelopathy; visual loss

- ▶ **Seizures** are the most frequent manifestation — focal, focal with secondary generalisation, or generalised — driven by inflammation of parenchyma surrounding the cyst.
- ▶ **Headache** accompanies virtually all CNS forms.
- ▶ **Hydrocephalus** results from CSF-flow obstruction by ventricular cysts and/or inflammation, or from **communicating hydrocephalus due to arachnoiditis**; raised-ICP features include headache, vomiting, dizziness, ataxia, papilloedema and visual loss.
- ▶ ***Bruns' syndrome** — *intermittent acute hydrocephalus precipitated by head movement/position change, the mobile ventricular cyst acting as a ball valve**.
- ▶ **Racemose cysticercosis** — proliferating clusters of cysts at the base of the brain → altered consciousness and death if untreated.
- ▶ **Extra-neural disease** — muscle (asymptomatic **cigar-shaped calcifications**), painless **subcutaneous nodules**, and ocular disease (subretinal/vitreous cyst, or ptosis from extra-ocular muscle involvement).

Diagnosis — imaging, serology, CSF and Del Brutto criteria

- ▶ **Neuroimaging is the primary diagnostic tool.** A cystic lesion containing an eccentric **mural scolex** (“dot-in-hole” appearance) is pathognomonic. Parenchymal cysts are 5–20 mm and round; subarachnoid cysts may reach 6 cm and be lobulated.
- ▶ **CT vs MRI** — CT is superior for calcified lesions; MRI is superior for small cysts, the scolex, enhancement, and ventricular/subarachnoid cysts (best seen on FIESTA / 3D-CISS sequences). Performing both is ideal.
- ▶ **Serology** — the enzyme-linked immunoelectrotransfer blot (EITB) using *lentil-lectin-purified glycoprotein* antigens is >99% sensitive and specific in patients with **multiple** cysts; sensitivity falls with **single lesions or calcifications** (may be seronegative). **Serum is more sensitive than CSF.** Crude-antigen ELISAs have high false-positive/negative rates and **should be avoided.** Antigen-detection (monoclonal antibody) and real-time PCR aid diagnosis/follow-up of extraparenchymal disease.
- ▶ **CSF** — lymphocytic, neutrophilic or **eosinophilic pleocytosis**; raised protein; glucose usually normal **but may be markedly reduced** (mimics tuberculous/fungal meningitis in basal disease).
- ▶ **Revised Del Brutto diagnostic criteria (2017)** — diagnosis is graded *definitive* or *probable* by combining the following, after excluding mimics:

Tier	Criteria
Absolute	Histology of parasite; subretinal cysticercus on funduscopy; conclusive scolex-in-cyst on neuroimaging

Tier	Criteria
Neuroimaging — major	Cystic lesions without scolex; typical enhancing lesions; multilobulated subarachnoid cysts; typical parenchymal calcifications
Neuroimaging — confirmative	Resolution of cysts after cysticidal drugs; migration of ventricular cyst on serial imaging
Neuroimaging — minor	Obstructive hydrocephalus or abnormal basal-leptomeningeal enhancement
Clinical/exposure — major	Positive EITB antibody or cysticercal antigen; cysticercosis outside CNS; household <i>T. solium</i> contact
Clinical/exposure — minor	Symptoms suggestive of NCC; residence in/origin from an endemic area

- ****Indian validated criteria — in a patient from an endemic area with a single enhancing lesion, seizures, a normal examination and no systemic disease, a round lesion 5–20 mm without midline shift* is almost always NCC (the solitary cysticercus granuloma*).**

Management

Principle: treat the **complications first** (seizures, raised ICP, hydrocephalus); **antiparasitic therapy is never an emergency** and must never be started while ICP is elevated or before ocular disease is excluded.

Problem	Approach
Seizures	Antiseizure drugs; taper after 6 months in single-lesion disease if imaging normalises and seizure-free; after 2 years in multilesional disease if lesions resolve without calcification. Calcified lesions = higher recurrence risk.
Viable parenchymal cysts	Albendazole 15 mg/kg/day for 8–28 days (CMDT: 10–15 mg/kg/day; may escalate to 30 mg/kg/day). For >2 cysts, add praziquantel 50 mg/kg/day (combination superior).
Subarachnoid / giant cysts	Prolonged or combination antiparasitics plus prolonged glucocorticoids for arachnoiditis/vasculitis; shunt if hydrocephalus.
Anti-inflammatory cover	High-dose glucocorticoids during all antiparasitic therapy — dexamethasone 0.1–0.4 mg/kg/day or prednisone 60 mg/day. Methotrexate / TNF inhibitors as steroid-sparing agents for prolonged courses.
Hydrocephalus / intraventricular cyst	Reduce ICP first; neuroendoscopic/surgical cyst removal (lateral & 3rd ventricle endoscopically; 4th

Problem	Approach
	ventricle by posterior microdissection). Avoid antiparasitics before surgery (they make cysts friable). VP shunt if removal impossible; antiparasitics + steroids reduce shunt failure.
Diffuse cerebral oedema (cysticercotic encephalitis)	Glucocorticoids are the mainstay; antiparasitic drugs are contraindicated.
Ocular / spinal	Drug-induced inflammation may cause irreversible damage; intraocular disease → surgery ; spinal disease → combined medical + surgical.

- ▶ **Drug interaction pearl** — corticosteroids **lower** praziquantel levels but **raise** albendazole levels, favouring albendazole when steroids are co-administered.
- ▶ **Taeniasis (gut carrier)** — single-dose **praziquantel 10 mg/kg** (or niclosamide 2 g); praziquantel may rarely trigger CNS inflammation if cryptic cysticercosis coexists.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Label the T. solium life cycle (cause of taeniasis vs cysticercosis):* Human definitive host → gravid proglottids/eggs in faeces → Pig (intermediate host) ingests eggs → oncosphere → cysticercus in pig muscle → undercooked pork eaten by human → adult tapeworm (taeniasis); *AND the cysticercosis loop:* Human ingests eggs (faecal–oral/autoinfection) → oncosphere → cysticercus in CNS/muscle/eye → neurocysticercosis. *Mark the scolex with hooklets** on the larva.
- ▶ **Axial MRI/CT cartoon labelling:** *vesicular cyst with eccentric scolex (“dot-in-hole”), ring-enhancing single lesion with perilesional oedema, intraventricular cyst causing hydrocephalus, and a parenchymal calcified nodule.*

Clinical / Diagnostic significance

- ▶ **Leading infective cause of adult-onset focal epilepsy** in endemic India — any young adult from an endemic area with new focal seizures and a normal exam should have neuroimaging for a solitary cysticercus granuloma.
- ▶ **Basal/subarachnoid NCC with low-glucose, lymphocytic CSF closely mimics tuberculous meningitis** — a crucial differential in Indian practice; EITB serology and characteristic imaging help separate them.
- ▶ **Calcified NCC** is the commonest imaging finding in endemic regions and a marker of remote infection; perilesional oedema around a calcification can cause **recurrent seizures**.
- ▶ **Public-health link** — household screening of a tapeworm carrier (the egg source) prevents new cases; control needs mass chemotherapy of humans and pigs, meat inspection, sanitation, and the **pig vaccine licensed in India**.

High-yield exam pointers

- ▶ NCC = larval *T. solium* in CNS; acquired by ingesting **eggs** (faecal–oral), *not* by eating pork — even vegetarians can get it.
- ▶ **Seizure = commonest manifestation**; NCC = top cause of acquired epilepsy in the developing world.
- ▶ “Dot-in-hole” scolex sign is diagnostic; CT best for calcification, MRI best for scolex/cysts (FIESTA/3D-CISS).
- ▶ EITB (immunoblot) >99% sensitive/specific for multiple cysts; single/calcified lesions may be seronegative; serum > CSF.
- ▶ **Del Brutto 2017 criteria** = absolute + neuroimaging (major/confirmative/minor) + clinical/exposure (major/minor).
- ▶ ***Bruns’ syndrome*** = positional intermittent obstructive hydrocephalus from a mobile ventricular ball-valve cyst.
- ▶ Always give glucocorticoids with antiparasitics; never give antiparasitics with raised ICP or in cysticercotic encephalitis.
- ▶ Albendazole is first-line; add praziquantel for >2 viable cysts; manage seizures/hydrocephalus before killing the parasite.

SOURCE & COVERAGE

- ▶ Harrison’s Principles of Internal Medicine, 22e — “Cestode Infections” (Taeniasis solium & Cysticercosis; Revised Diagnostic Criteria Table 242-1; Fig. 242-1) and “Seizures and Epilepsy” (NCC as a cause of acquired epilepsy).
- ▶ CMDT 2026 — “Protozoal & Helminthic Infections” (Cysticercosis: epidemiology, racemose form, treatment regimens, steroid–antiparasitic interaction).
- ▶ *Coverage note*: The corpus is solid on aetiology, the Del Brutto criteria, imaging and management. It classifies NCC by **location and viability** (parenchymal/intraventricular/subarachnoid/calcified) rather than by the named four-stage radiological evolution (*vesicular* → *colloidal-vesicular* → *granular-nodular* → *nodular-calcified*); that staging is universally accepted standard neurology and is reflected here in descriptive terms faithful to the source.



Nipah Virus Infection

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Nipah virus* (NiV) is a highly virulent, enveloped negative-sense RNA virus of the family **Paramyxoviridae**, genus **Henipavirus** (alongside *Hendra virus*), first recognised in

humans in 1998–99. It is a bat-borne zoonosis that causes a severe **acute encephalitis with prominent respiratory involvement** and a very high case-fatality rate ($\approx 67\text{--}92\%$). It is a classic *emerging infectious disease* — the Malaysian emergence in 1998 was driven by deforestation and intensive pig farming — and is a recurrent public-health threat in South and Southeast Asia (Malaysia, Singapore, Bangladesh, India). It must be handled at **biosafety level 4 (BSL-4)** and is a *WHO R&D Blueprint priority pathogen* for which there is no licensed human vaccine or proven specific therapy.

Etiology and Virology

- ▶ **Family Paramyxoviridae, genus Henipavirus**; the two prototype species are Nipah virus and Hendra virus — the most lethal members of the family. Named after Sungai Nipah* village, Malaysia, the site of the index outbreak.
- ▶ **Enveloped, non-segmented, negative-sense single-stranded RNA virus**; pleomorphic.
- ▶ Two key surface glycoproteins: **G (attachment) glycoprotein** and **F (fusion) glycoprotein**. The G protein binds host cell-surface receptors **ephrin-B2 and ephrin-B3**, which are highly expressed on **neurons and vascular endothelium** — explaining the dual neuro-vascular tropism.
- ▶ F-protein-mediated cell–cell fusion produces multinucleated **syncytia**, a hallmark cytopathic effect.
- ▶ Unusually **broad host range** (bats, pigs, horses, humans) and the ability to infect both CNS and respiratory epithelium underlie its severity.

Epidemiology and Transmission

- ▶ **Natural reservoir**: fruit bats of the genus *Pteropus* (flying foxes), which are persistently infected but asymptomatic.
- ▶ **Geography**: cases concentrated in **Malaysia, Singapore, Bangladesh and India**; a distinct *Malaysian strain* and a more virulent, more transmissible *Bangladesh/India strain* are recognised.
- ▶ **Transmission routes (well documented)**: *pig-to-human*, *cow-to-human*, *human-to-human*, and **nosocomial** spread. Consumption of **raw date-palm sap** contaminated by bat saliva/excreta is the principal vehicle in Bangladesh/India; close contact with respiratory secretions of cases (and caregiving) drives person-to-person and hospital clusters.

Outbreak setting	Vehicle / amplifier	Key features
Malaysia 1998–99 / Singapore	Intermediate amplifying host = pigs; abattoir workers	First recognition; linked to deforestation + intensive pig farming (Harrison); predominantly encephalitis
Bangladesh (e.g., 2010–14 cluster: 14 cases, 8 fatal)	Raw date-palm sap; person-to-person	Higher CFR, more human-to-human and nosocomial transmission

Outbreak setting	Vehicle / amplifier	Key features
India (West Bengal, Kerala)	Date-palm sap / bat contact; hospital clusters	Recurrent seasonal outbreaks; high mortality

- Incubation period is typically 4–14 days (occasionally longer).
- High case-fatality rate (67–92%) — far exceeding most arboviral encephalitides.

Pathogenesis

- After mucosal/respiratory entry, the virus targets **endothelial cells and neurons** via ephrin-B2/B3 receptors.
- Produces a **systemic vasculitis** with endothelial syncytia, vasculitis-induced thrombosis, ischaemia and microinfarction — most marked in the **CNS** (and also lung, heart, kidney).
- Combined **direct neuronal infection** plus **vasculitic microinfarcts** generates the characteristic disseminated, multifocal encephalitic picture.
- Respiratory tract infection produces an **acute respiratory distress syndrome (ARDS)**-like illness and facilitates aerosol/droplet person-to-person spread.

Clinical Features

- Spectrum ranges from **asymptomatic/mild** infection to **fulminant encephalitis** and ARDS; the dominant syndrome is **acute febrile encephalitis**.

Phase / syndrome	Manifestations
Prodrome	Fever, headache, myalgia, vomiting, sore throat — non-specific
Acute encephalitis	Altered sensorium, encephalopathy , cranial nerve palsies , dystonia , segmental myoclonus, areflexia, hypotonia, seizures; brain-stem signs carry a grave prognosis
Respiratory	Cough, atypical pneumonia, ARDS — a key distinguishing feature from arboviral encephalitides; aids transmission
Autonomic/vascular	Tachycardia, hypertension, features of disseminated vasculitis
Late / relapsing	Relapsing or late-onset encephalitis weeks–months after recovery (≈ 3.4 – 7.5%), due to recrudescence of latent CNS infection

- **Neurologic sequelae** (cranial nerve palsies, persistent encephalopathy, dystonia, cognitive/behavioural deficits) persist in ≈ 15 – 32% of survivors.

Diagnosis

- ▶ **Strong epidemiological clues are essential:** travel/residence in an endemic area, **date-palm sap** ingestion, contact with sick pigs/bats, or contact with a known case; consider NiV in any **cluster of severe encephalitis with respiratory features** in South/Southeast Asia.
- ▶ **Laboratory confirmation (CMDT):**
 - ELISA — IgM/IgG antibody detection in **serum and CSF**.
 - RT-PCR — viral RNA in **urine and respiratory secretions** (note: **not reliably detected in blood**); CSF and throat/nasal swabs are also used.
 - **Virus isolation / immunohistochemistry** on tissue — performed only under BSL-4 containment.
- ▶ **CSF:** features of viral encephalitis (mild–moderate pleocytosis, raised protein, normal glucose).
- ▶ **Neuroimaging:** MRI typically shows **multiple small (2–7 mm) disseminated subcortical and deep white-matter T2/FLAIR hyperintensities** corresponding to microinfarcts (a relatively characteristic pattern).
- ▶ **Differential diagnosis** (per Harrison): Japanese encephalitis, herpes simplex and other viral encephalitides, cerebral malaria, leptospirosis, scrub typhus, bacterial meningoencephalitis — empirical **acyclovir** and antibacterials should cover treatable mimics until NiV is confirmed.

Management and Prevention

- ▶ **No proven specific antiviral therapy; care is largely supportive** — ICU-level management of encephalitis (seizure control, raised intracranial pressure, SIADH) and of respiratory failure/ARDS (oxygen, mechanical ventilation).
- ▶ **Ribavirin** was used in the Malaysian outbreak with a *possible* reduction in mortality, but benefit is unproven; **remdesivir** and the experimental human monoclonal antibody **m102.4** (targets the G-glycoprotein ephrin-binding site) are investigational/compassionate-use agents.
- ▶ **Infection prevention and control (critical):** strict **contact + droplet (and airborne for aerosol-generating procedures)** precautions, isolation of cases, PPE for caregivers, safe handling/burial practices, and BSL-4 handling of specimens — nosocomial amplification is a recurring feature of outbreaks.
- ▶ **Public-health prevention:** avoid raw date-palm sap (cover collection pots/use bamboo skirts), avoid contact with sick pigs/bats and bat-bitten fruit, surveillance of *Pteropus* populations, and rapid outbreak containment with contact tracing and quarantine.
- ▶ **No licensed human vaccine** (a recombinant Hendra-G subunit equine vaccine exists for horses; human candidates are in trials).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Nipah virus transmission cycle (label):** *Pteropus* fruit-bat reservoir → contamination of **date-palm sap and fruit** (Bangladesh/India route) and infection of **pigs (amplifying host)**

(Malaysia route) → **human** infection → **human-to-human / nosocomial** spread; annotate **ephrin-B2/B3 receptor** tropism for **neurons + endothelium**.

- ▶ **Virion structure (label):** envelope, G (attachment) glycoprotein, F (fusion) glycoprotein, helical nucleocapsid with **negative-sense ssRNA**, matrix protein.

Clinical / Diagnostic significance

- ▶ NiV is the **most lethal paramyxovirus** and a model **One-Health emerging zoonosis** — its emergence illustrates how **ecological disruption** (deforestation, intensive farming, **sap harvesting**) precipitates spillover.
- ▶ Suspect NiV in **clustered, rapidly progressive encephalitis with respiratory illness** in endemic regions; early suspicion enables containment and prevents nosocomial catastrophe.
- ▶ Diagnostic pearl: **PCR is positive in urine/respiratory secretions but not blood**; paired serum + CSF ELISA confirms the diagnosis.
- ▶ Survivors require **neurological follow-up** for late/relapsing encephalitis and persistent deficits.

High-yield exam pointers

- ▶ **Family Paramyxoviridae, genus Henipavirus**; sister virus = **Hendra**; named after *Sungai Nipah*, Malaysia (1998).
- ▶ **Reservoir* = *Pteropus fruit bats*; *pigs* = *amplifying host* (Malaysia); *raw date-palm sap** (Bangladesh/India).
- ▶ Receptors **ephrin-B2/B3** → **neuro-vascular tropism**; pathology = **endothelial syncytia + vasculitis** → **microinfarcts**.
- ▶ Syndrome = **acute encephalitis + respiratory illness**; signs include **cranial nerve palsies, segmental myoclonus, dystonia, brain-stem involvement**.
- ▶ **CFR 67–92%**; neurologic sequelae **15–32%**; relapsing/late encephalitis **3.4–7.5%**.
- ▶ **Dx:** ELISA (serum + CSF) and RT-PCR (**urine/respiratory secretions, NOT blood**); MRI = multiple small disseminated lesions; handle at **BSL-4**.
- ▶ **Rx:** supportive ICU care; ribavirin/remdesivir/**m102.4 mAb** investigational; **no licensed human vaccine**.
- ▶ **Prevention:** droplet/contact isolation, avoid raw sap & sick animals; a **WHO priority/Blueprint pathogen** with pandemic potential.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Emerging and Re-Emerging Infectious Diseases” (Nipah as an emerging zoonosis; Malaysia 1998 emergence linked to deforestation + intensive pig farming; Hendra/Nipah listed); “Acute Meningitis and

Encephalitis” chapter (Nipah, a Paramyxoviridae, as a cause of Southeast-Asian encephalitis outbreaks); “Arthropod-Borne and Rodent-Borne Virus Infections” (Nipah in the encephalitis differential).

- ▶ **CMDT 2026** — “Viral & Rickettsial Infections” (Nipah under paramyxoviruses): first described 1999; geography; fruit-bat reservoir; Bangladesh date-palm-sap cluster (14 cases, 8 fatal); pig-/cow-/human-/nosocomial transmission; CFR 67–92%; neurologic sequelae 15–32%; relapses 3.4–7.5%; ELISA (serum/CSF) and PCR (urine/respiratory secretions, not blood) diagnosis.
- ▶ **Coverage note:** The corpus covers Nipah only briefly — Harrison treats it as an emerging-disease/encephalitis example and CMDT provides the main clinical paragraph; there is **no dedicated Nipah chapter**. Standard, universally-accepted virology and management details not explicitly in the corpus but added for completeness and accuracy: genus *Henipavirus* and ephrin-B2/B3 receptors; G/F glycoproteins and syncytia; *Pteropus* genus; incubation 4–14 days; MRI microinfarct pattern; ribavirin/remdesivir/m102.4 and the absence of a licensed human vaccine; BSL-4 and WHO-priority-pathogen status; and Indian (West Bengal, Kerala) outbreaks.



Preventive strategies for antibiotic resistance in multidisciplinary intensive care units

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Antimicrobial resistance (AMR)* is the reduction or loss of an antibacterial agent’s activity, arising from spontaneous chromosomal **mutation** or **horizontal acquisition** of resistance genes (plasmids, transposons, transformation). The multidisciplinary ICU is the hospital’s *epicentre of resistance* because it concentrates the three drivers of resistance simultaneously — intense **antibiotic selection pressure**, a dense reservoir of **colonised/infected hosts** (high colonisation pressure), and abundant opportunities for **cross-transmission** via invasive devices and the hands of staff. Prevention is therefore not a single measure but a coordinated, institution-wide programme resting on **two complementary pillars** — **antimicrobial stewardship** (rational prescribing) and **infection prevention and control** (interrupting transmission) — backed by surveillance and a *One Health* perspective. The CDC estimates >2.8 million resistant infections and 35,900 deaths annually in the United States, underscoring the stakes.

Why the ICU breeds resistance (the rationale to target)

- ▶ **Selection pressure:** broad-spectrum empirical regimens, prolonged courses and unnecessary antibiotics select resistant strains and “bystander” organisms; prior antibiotic exposure, prior

resistant infection and prior hospitalisation each raise the odds of harbouring a resistant pathogen.

- ▶ **Colonisation pressure:** the proportion of patients on a ward who are colonised is itself a risk factor for spread; antibiotic-altered microbiota become readily colonised by **multidrug-resistant organisms (MDROs)**, which then act as silent reservoirs.
- ▶ **Cross-transmission:** transmitted on hands, shared equipment (stethoscopes, glucometers, ultrasound, BP cuffs), contaminated environment, plumbing and water.
- ▶ **Devices and breached barriers:** central lines, urinary catheters, endotracheal tubes and surgical wounds are portals of entry — catheter-associated bloodstream infection alone *triples* in-hospital mortality risk, and ventilator-associated pneumonia (VAP) occurs in up to 10% of ventilated patients.
- ▶ **The MDRO targets:** CDC *urgent* threats — carbapenem-resistant *Acinetobacter*, *Candida auris*, *Clostridioides difficile*, **carbapenem-resistant Enterobacterales (CRE)** and drug-resistant *N. gonorrhoeae*; *serious* threats include ESBL-producing Enterobacterales, VRE, MDR *Pseudomonas aeruginosa*, MRSA and drug-resistant *S. pneumoniae*. Key enzymes: **ESBLs**, **AmpC**, and carbapenemases **KPC**, **NDM** (originally Indian subcontinent) and **OXA-48**; plasmid-borne colistin resistance via *mcr-1*.

Pillar 1 — Antimicrobial stewardship (ASP)

*Stewardship promotes the appropriate drug, dose, route and duration, with four goals: (1) improve patient care, (2) preserve antibiotics by curbing resistance, (3) reduce adverse effects (e.g. *C. difficile*), and (4) control cost.* Mandated/supported by **CDC** core elements, **The Joint Commission** Medication Management Standards, CMS Conditions of Participation and the 2015 **National Action Plan for Combating Antibiotic-Resistant Bacteria**.

- ▶ **Multidisciplinary team:** infectious-disease physician + clinical pharmacist with ID training (core dyad), plus clinical microbiologist, infection-prevention practitioner, hospital epidemiologist and information-systems specialist.

Strategy	What it involves
Prospective audit + feedback	ID physician/pharmacist reviews broad-spectrum orders (carbapenems) or costly agents (daptomycin, ceftazidime-avibactam) and recommends alternatives
Formulary restriction	Limited set of agents on formulary to curb indiscriminate use
Preauthorisation	Approval required before using restricted agents — via CPOE criteria or ID consultation

Strategy	What it involves
De-escalation / streamlining	Narrow therapy once culture & susceptibility known; stop the “anti-pseudomonal/anti-MRSA” drug if not recovered
Dose optimisation (PK/PD)	Use pharmacokinetic-pharmacodynamic targets (e.g. extended β -lactam infusions, AUC/MIC)
IV-to-oral conversion	Switch when patient stable and gut absorbing
Antibiotic time-out / shortest duration	Reassess at 48–72 h; use the shortest effective course (shorter courses select less resistance)
Diagnostic stewardship	Avoid culturing asymptomatic bacteriuria; restrict unnecessary tests to prevent inappropriate treatment
Guidelines, indication documentation, education	Local pathways, documenting indication, ongoing prescriber education

- The “Four Moments of Antibiotic Decision-Making” (a practical bedside frame): (1) *Does this patient have an infection that needs antibiotics?* (2) *Have appropriate cultures been taken before starting?* (3) *After a few days — can antibiotics be stopped, narrowed, or switched IV-to-oral?* (4) *What duration is truly necessary?*
- **ICU/VAP-specific algorithm (6 steps):** (1) start broad-spectrum empirically to cover MDR GNB/MRSA; (2) **stop** if infection becomes unlikely; (3) **narrow** once the organism is identified; (4) **optimise** by PK/PD; (5) **switch to monotherapy on days 3–5**; (6) **shorten duration** (a short, fixed course e.g. ~7–8 days for most VAP). Quantitative lower-respiratory cultures (BAL $\geq 10^4$ CFU/mL or tracheal aspirate $\geq 10^5$ CFU/mL) with a de-escalation algorithm increase antibiotic-free days without harming outcome.
- **Rapid diagnostics & biomarkers:** rapid molecular detection of organisms/resistance (multiplex PCR, MALDI-TOF) shortens time to appropriate therapy and to de-escalation; **procalcitonin-guided** cessation reduces antibiotic exposure in the ICU (*PRORATA* trial) and is a recognised adjunct.

Pillar 2 — Infection prevention and control (interrupt transmission)

- **Hand hygiene** before/after every patient contact — alcohol-based hand rub, but **soap-and-water (mechanical removal)** for *C. difficile* and norovirus (spores/non-enveloped virus resist alcohol).
- **Standard precautions** for all patients + **transmission-based precautions:** **contact** (gown + gloves) for MDROs and *C. difficile*; **droplet** and **airborne** (N95 + negative-pressure room, ≥ 12 air changes/h) as indicated.
- **Daily 2% chlorhexidine gluconate bathing** of ICU patients with central lines — standard of care to prevent bloodstream infection.

- ▶ **Environmental cleaning** of high-touch surfaces and shared equipment; **sporicidal (bleach)** cleaning and adjunctive **UV-C** for tenacious pathogens; dedicated disinfectants and screening of transfers for *C. auris*; **water-safety/management plans** (*Legionella*, NTM, MDR gram-negatives in drains).
- ▶ **Device-care bundles** (the single highest-yield ICU intervention) — see table — plus the cardinal rule: *insert devices only when essential and review the need for each device daily*.

Bundle	Key evidence-based elements
CLABSI	Hand hygiene; maximal sterile barrier ; chlorhexidine-alcohol skin prep; ultrasound-guided insertion; prefer subclavian (femoral most infection-prone); all-inclusive kit + checklist; scrub-the-hub; disinfectant caps; chlorhexidine-impregnated dressings; daily chlorhexidine baths; daily review of line need
VAP	Avoid intubation (HFNO/NIV); head-of-bed 30–45° ; daily oral care/tooth-brushing; aseptic respiratory-equipment care (no tap-water rinsing); minimise sedation , early mobilisation, early enteral feeding, daily extubation-readiness (spontaneous breathing trials)
CAUTI	Catheterise only when strictly necessary; aseptic insertion + closed drainage; minimise manipulation; daily review of need ; alternatives — bladder scan, condom/intermittent catheter
SSI	Treat infection pre-op; prophylaxis within 1 h before incision and stop after closure ; clip (not shave) hair; chlorhexidine-alcohol antisepsis; nasal mupirocin decolonisation in <i>S. aureus</i> carriers for high-risk surgery

- ▶ **Active surveillance & cohorting**: screen high-risk transfers/long-term-care admissions for MDROs/*C. auris*, isolate pending results, cohort staff and patients during outbreaks; reduce colonisation pressure.
- ▶ **C. difficile control**: because antibiotic exposure is the chief cause, *stewardship is the first-line preventive measure* — restricting **fluoroquinolones and clindamycin** reduces incidence; add contact isolation, soap-and-water hand hygiene and bleach disinfection.
- ▶ **Selective digestive/oropharyngeal decontamination (SDD/SOD)**: may reduce HAP and mortality, but routine use is *limited by concern over selecting resistance* and remains context-dependent.

Institutional, surveillance and One Health measures

- ▶ **Surveillance & tracking:** laboratory-based + automated electronic surveillance; mandatory reporting (e.g. NHSN), expressed as **standardised infection ratios**; produce a periodic **antibiogram** to guide empirical therapy to *local* susceptibility data.
- ▶ **Outbreak response:** molecular typing — **whole-genome sequencing** (gold standard) — to confirm clonality and trace plasmid-borne resistance genes; case definition, case-finding, control measures, communication.
- ▶ **Regional/interfacility communication** of MDRO status on transfer; **CDC five core actions** — (1) infection prevention & control, (2) tracking & data, (3) antibiotic use & access (stewardship), (4) vaccines/therapeutics/diagnostics, (5) environment & sanitation via the **One Health** approach (agriculture, animal antibiotic use, environmental reservoirs).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **“Two-pillar prevention framework”:** a central box *Preventing AMR in the ICU* feeding two columns — **Antimicrobial Stewardship** (label: audit-and-feedback, formulary restriction, preauthorisation, de-escalation, PK/PD dosing, IV-to-oral, antibiotic time-out, shortest duration, diagnostic stewardship) and **Infection Prevention & Control** (label: hand hygiene, contact/droplet/airborne precautions, CLABSI/VAP/CAUTI/SSI bundles, chlorhexidine bathing, environmental + water safety, active surveillance/isolation) — both resting on a base bar labelled *Surveillance • Antibiogram • Outbreak investigation (WGS) • One Health*.
- ▶ **“Chain of transmission interrupted”:** Reservoir (colonised patient/environment/device) → Hands of HCW / shared equipment → Susceptible patient; mark the break-points — *hand hygiene, contact precautions, environmental cleaning, device removal*.

Clinical / Diagnostic significance

- ▶ **Empirical-to-targeted transition:** appropriate early empirical cover saves lives in septic ICU patients, but must be paired with mandatory cultures *before* antibiotics and prompt **de-escalation** once susceptibilities return — this is where resistance is actually contained.
- ▶ **Local data drive choice:** the institutional antibiogram and individual risk factors (prior antibiotics, prior MDRO, length of stay) determine the empirical regimen; rapid diagnostics shorten the window of unnecessary broad-spectrum exposure.
- ▶ **Bundle compliance is auditable:** process measures (hand-hygiene compliance, line-insertion checklist adherence) and outcome measures (CLABSI/VAP/CAUTI rates, hospital-onset *C. difficile*) feed quality improvement and reimbursement.
- ▶ **Stewardship pays clinically:** demonstrated reductions in *C. difficile*, improved susceptibility patterns and lower cost without worse outcomes.

High-yield exam pointers

- ▶ AMR prevention in the ICU = **two pillars**: *Antimicrobial Stewardship + Infection Prevention & Control*, on a base of *surveillance/One Health*.
- ▶ **Three core ASP strategies**: prospective audit + feedback, formulary restriction, preauthorisation.
- ▶ **Four Moments of Antibiotic Decision-Making**; ASP goals = better care, less resistance, fewer adverse effects, lower cost.
- ▶ **VAP 6-step strategy**: start broad → stop if unlikely → narrow → PK/PD optimise → **monotherapy** day 3–5 → **shorten duration**.
- ▶ **Shorter courses select less resistance**; de-escalate on cultures; consider **procalcitonin-guided** stop (*PRORATA*).
- ▶ **Device bundles** + “insert only if essential, review daily”; **daily 2% chlorhexidine** baths prevent CLABSI; HOB 30–45° for VAP.
- ▶ **Hand hygiene** is the single most effective IPC measure — but **soap-and-water** for *C. difficile*/norovirus; **contact precautions** for MDROs.
- ▶ **Stewardship is first-line prevention of *C. difficile*** — restrict **fluoroquinolones + clindamycin**.
- ▶ CDC **urgent** threats: CR-*Acinetobacter*, *C. auris*, *C. difficile*, CRE, drug-resistant gonorrhoea; carbapenemases KPC/NDM/OXA-48.
- ▶ CDC **five core actions** + **One Health**; outbreak typing by **whole-genome sequencing**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Bacterial Resistance to Antimicrobial Agents” (mechanisms, CDC threats table & five core actions, One Health); “Treatment and Prophylaxis of Bacterial Infections” (antimicrobial stewardship strategies, ASP team, prophylaxis); “Infections Acquired in Health Care Facilities” (device bundles, transmission-based precautions, chlorhexidine bathing, surveillance, *C. difficile*/*C. auris*).
- ▶ **CMDT 2026** — “Common Problems in Infectious Diseases & Antimicrobial Therapy” (antimicrobial stewardship, *Four Moments of Antibiotic Decision-Making*, selective digestive decontamination).
- ▶ **Murray & Nadel’s Textbook of Respiratory Medicine** — “Ventilator-Associated Pneumonia” (ICU 6-step antimicrobial management, quantitative-culture de-escalation, PK/PD, monotherapy on days 3–5, duration, procalcitonin/PRORATA, rapid diagnostics).
- ▶ *Coverage note*: the corpus covers stewardship and infection control fully; explicit ICU-specific stewardship detail is consolidated chiefly from the Murray VAP chapter (the general texts treat it more briefly, as the spec anticipated). Procalcitonin/PRORATA and short fixed VAP courses are standard, source-supported ICU practice.



Progressive Multifocal Leucoencephalopathy

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Progressive multifocal leucoencephalopathy (PML) is a subacute, usually fatal **demyelinating disease of the central nervous system** caused by lytic reactivation of the **JC virus** (a human polyomavirus) in profoundly immunosuppressed patients. It is the **only known clinical manifestation of JC virus infection** and characteristically produces *multifocal, non-enhancing* white-matter lesions that coalesce over time. In Harrison's it is described chiefly as a **late opportunistic infection of AIDS** (seen in ~1–4% of AIDS patients) and, in the multiple sclerosis chapter, as the **principal serious risk of natalizumab** and certain other disease-modifying therapies (DMTs).

Etiology & Pathogenesis

- ▶ **Causative agent:** JC virus, a ubiquitous **human polyomavirus** (double-stranded DNA, non-enveloped). The eponym derives from the initials of the index patient (*John Cunningham*).
- ▶ **High background seroprevalence:** ~80% of the **general adult population** have antibodies to JC virus, indicating prior (usually childhood, asymptomatic) infection. The virus then remains **latent** (kidney/lymphoid tissue).
- ▶ **Restricted replication in health:** <10% of **healthy adults** show any evidence of ongoing viral replication — disease requires a permissive immunosuppressed state.
- ▶ **Reactivation:** Loss of immune surveillance permits viral reactivation, haematogenous spread to the CNS, and **lytic infection of oligodendrocytes**, producing demyelination.
- ▶ **Pathology:** Lesions begin as **small foci of demyelination in subcortical white matter** that progressively **coalesce**. The **cerebral hemispheres, cerebellum, and brainstem** may all be involved.
- ▶ **Why immunomodulators raise risk:** Natalizumab blocks the **$\alpha 4 \beta 1$ integrin (adhesion molecule)**, *preventing lymphocytes from binding endothelial cells and entering the CNS* — the resulting loss of intrathecal immune surveillance permits unchecked JC virus replication, the mechanistic basis of its PML risk.

Predisposing immunosuppressed states (who gets PML)

Setting	Key points (per source)
Advanced HIV/AIDS	A late manifestation of AIDS ; occurs in ~1–4% of AIDS patients; one of the few opportunistic infections that continues to occur despite widespread ART
Natalizumab (Tysabri) for MS	Anti- $\alpha 4 \beta 1$ integrin MAb; major risk is PML (~0.4%); give only if serum JC virus antibodies are absent (~50% of patients); repeat JCV antibody testing every 6 months on treatment

Setting	Key points (per source)
Dimethyl/diroximel fumarate for MS	Rare PML cases, associated with persistent lymphopenia
Cladribine (Mavenclad) for MS	Lymphocytotoxic; infection risk including PML
Other (standard)	Haematological malignancy, transplant/chemotherapy, other potent immunosuppression — <i>see Coverage note</i>

Clinical features

- ▶ **Tempo:** Subacute, protracted course with **multifocal neurologic deficits**, *with or without* changes in mental status.
- ▶ **Focal signs:** Hemiparesis, **visual field defects** (hemianopia), **ataxia**, **aphasia**, and **sensory deficits** — reflecting the multifocal white-matter involvement.
- ▶ **Seizures:** Occur in ~20% of patients.
- ▶ **Notable negatives:** Headache, fever, nausea and vomiting are rarely seen — their presence should prompt a search for an alternative diagnosis (e.g., toxoplasmosis, lymphoma).
- ▶ **Course:** Relentless progression; cognitive and focal deficits accumulate.

Investigations & Diagnosis

- ▶ **MRI brain (key investigation):**
 - Multiple, NON-enhancing white-matter lesions that may coalesce.
 - Predilection for the occipital and parietal lobes.
 - T2-weighted: signal hyperintensity; T1-weighted: diminished (low) signal.
 - Absence of mass effect and absence of enhancement help distinguish PML from enhancing/space-occupying lesions.
- ▶ **CSF JC virus DNA (PCR):** Diagnostic sensitivity ~76%, specificity close to 100% — a positive CSF JCV PCR in the right clinical/MRI context is effectively confirmatory.
- ▶ **Brain biopsy:** Reserved for atypical cases (definitive demonstration of demyelination with oligodendroglial inclusions) — *standard practice; see Coverage note*.
- ▶ **CD4 count / HIV viral load** in PML complicating HIV, as these carry prognostic weight (below).

Differential diagnosis (HIV CNS lesions)

Feature	PML	CNS toxoplasmosis	Primary CNS lymphoma
Enhancement	Non-enhancing	Ring-enhancing (eccentric <i>target sign</i>)	Enhancing (often homogeneous)

Feature	PML	CNS toxoplasmosis	Primary CNS lymphoma
Number/site	Multifocal, white matter , occipito-parietal	Multiple, deep + grey–white junction/basal ganglia	Single or few, periventricular
Mass effect	Minimal/absent	Present (oedema)	Present
Confirmatory test	CSF JCV DNA PCR	Response to anti-toxoplasma Rx; serology	CSF EBV DNA; biopsy

Treatment & Prognosis

- ▶ No specific antiviral therapy exists for PML; agents such as **cidofovir** have failed to show clear benefit.
- ▶ Cornerstone = restore immunity / remove the trigger:
 - In HIV: initiate/optimize ART to reconstitute CD4 immunity.
 - In drug-induced PML: **stop the offending DMT** (and, for natalizumab, consider plasma exchange to accelerate drug clearance — *standard; see Coverage note*).
- ▶ Immune reconstitution inflammatory syndrome (IRIS): Paradoxical worsening of PML can follow ART initiation as an immune-reconstitution phenomenon — a key management caveat.
- ▶ Prognosis (HIV-associated):
 - Pre-ART era: most patients died **within 3–6 months** of symptom onset.
 - With ART: dramatically improved — **median survival ~2 years**, and survival >15 years has been reported; however, **only ~50%** of HIV-PML patients show neurologic improvement.
 - Favourable predictors: **baseline CD4+ count >100/μL** and ability to maintain HIV viral load <500 copies/mL. Baseline HIV-1 viral load itself has **no independent predictive value**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Axial T2/FLAIR MRI brain schematic (PML lesions).** Labels to mark: *Asymmetric subcortical white-matter hyperintensity; Parieto-occipital predilection; Coalescing demyelinating foci; Involves subcortical U-fibres; NON-enhancing on post-contrast T1; T1-hypointense / T2-hyperintense; No/minimal mass effect; Grey matter relatively spared.*
- ▶ **Pathogenesis flow diagram.** Boxes/arrows: *Latent JC virus (kidney/lymphoid tissue) → Severe immunosuppression (HIV with low CD4 / natalizumab / fumarate / cladribine) → Viral reactivation → Haematogenous spread to CNS → Lytic infection of oligodendrocytes → Multifocal demyelination → Progressive multifocal neurological deficits.*

Clinical / Diagnostic significance

- ▶ **AIDS-defining illness:** PML is an AIDS-defining opportunistic infection; its appearance signals **advanced immunosuppression** and warrants ART optimisation.
- ▶ **Pharmacovigilance for DMTs:** **JC virus antibody stratification** is mandatory before and during **natalizumab** therapy — JCV-seronegative patients are preferred candidates; rising JCV index, prior immunosuppressant use, and longer treatment duration raise risk.
- ▶ **“Non-enhancing white-matter lesions + focal deficits + immunosuppression”** is the classic triad that should trigger CSF JCV PCR.
- ▶ **Watch for IRIS** when starting ART in a patient with (or at risk of) PML — neurologic worsening may be inflammatory rather than progressive infection.
- ▶ **MRI + CSF JCV DNA PCR** can often avoid the need for brain biopsy.

High-yield exam pointers

- ▶ **JC virus = human polyomavirus;** PML is its **ONLY clinical manifestation**; ~80% adults are seropositive.
- ▶ **Occurs in ~1–4% of AIDS patients;** a late AIDS manifestation; persists despite ART.
- ▶ **MRI:** multiple **NON-enhancing** white-matter lesions, **occipito-parietal**, **T2-hyperintense / T1-hypointense**.
- ▶ **CSF JC virus DNA PCR:** sensitivity ~76%, specificity ~100%.
- ▶ ~20% have seizures; headache/fever/vomiting are **rare** (suggest another diagnosis).
- ▶ **No specific therapy;** **cidofovir ineffective** — treat by **immune reconstitution (ART) / stopping the culprit DMT**.
- ▶ **Natalizumab PML risk ~0.4%** — give only if **JCV antibody negative**; retest q6 months.
- ▶ **Prognosis:** pre-ART death in **3–6 months**; with ART median survival ~2 years; better if **CD4 >100/μL** and **VL <500 copies/mL**.
- ▶ **ART can cause paradoxical worsening = PML-IRIS.**

SOURCE & COVERAGE

Harrison’s Principles of Internal Medicine, 22e (2025) — **Ch 208 “Human Immunodeficiency Virus Disease: AIDS and Related Disorders”** (JC virus/PML epidemiology, clinical features, MRI, CSF JCV PCR, ART/prognosis, IRIS) and **Ch 455 “Multiple Sclerosis”** (Table 455-6: natalizumab/fumarate/cladribine PML risk and JCV antibody stratification). **Coverage note (spec.gap = true):** Harrison 22e has **no dedicated PML chapter**; content is distributed across the HIV chapter (which cross-refers to Ch 142 on polyomaviruses, *not supplied here*) and the MS-therapeutics chapter. Items added as **universally accepted standard internal medicine but NOT explicitly stated in the two supplied chapters** are flagged in-text: the *John Cunningham* eponym expansion; **oligodendrocyte** as the lytically infected target cell; **brain biopsy** as the definitive test;

plasma exchange to clear natalizumab; and non-HIV immunosuppressed settings (haematologic malignancy, transplant/chemotherapy). The differential-diagnosis comparison draws on toxoplasmosis (eccentric target sign, ring enhancement) and CNS lymphoma descriptions within Ch 208.



Pyrexia of Unknown Origin (PUO / Fever of Unknown Origin)

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Pyrexia of unknown origin (PUO), more often termed *fever of unknown origin* (FUO), denotes a **prolonged febrile illness that defies diagnosis despite intensive, structured evaluation**. The term should be reserved for such illnesses — most fevers either resolve spontaneously or declare a cause once distinguishing features appear. FUO is not a single disease but a final common presentation of an atypical manifestation of a common disorder far more often than a rare exotic disease. The diagnostic challenge lies in disciplined pursuit of *potentially diagnostic clues* rather than indiscriminate testing.

Diagnostic criteria — classic vs current definition

- ▶ The original Petersdorf and Beeson (1961) definition: illness of ≥ 3 weeks' duration, fever $\geq 38.3^{\circ}\text{C}$ ($\geq 101^{\circ}\text{F}$) on two occasions, with diagnosis uncertain despite 1 week of inpatient evaluation.
- ▶ Harrison's **current (modern) definition** retains time/temperature thresholds but mandates a standardised minimum workup and excludes the immunocompromised:

Criterion	Requirement
Temperature	Fever $\geq 38.3^{\circ}\text{C}$ ($\geq 101^{\circ}\text{F}$) on at least two occasions
Duration	Illness of at least 3 weeks
Host	No known immunocompromised state
Investigation	Diagnosis uncertain after thorough history, examination and the obligatory investigations (see below)

- ▶ **Inflammation of unknown origin (IUO)** — identical to FUO *except the temperature criterion*: persistently raised CRP/ESR for ≥ 3 weeks in an immunocompetent patient with a **normal body temperature** and no explanation despite the same obligatory workup. IUO and FUO share the **same causes and the same workup**.
- ▶ For perspective, normal mean oral temperature is $\sim 36.6^{\circ}\text{C}$; *fever* is a pyrogen-driven upward shift of the hypothalamic set point (mediated by pyrogenic cytokines IL-1, IL-6, TNF), distinct

from hyperthermia (uncontrolled heat gain, set point unchanged, unresponsive to antipyretics).

Hyperpyrexia = fever $>41.5^{\circ}\text{C}$.

Classification — categories of FUO

The classic Durack–Street four-category scheme separates the immunocompetent “classic” patient from special hosts, each with a distinct differential and threshold (durations per CMDT 2026):

Category	Defining features
Classic FUO	≥ 3 weeks, fever $\geq 38.3^{\circ}\text{C}$, immunocompetent, undiagnosed after the obligatory workup
Hospital-associated (nosocomial) FUO	Fever in a hospitalised patient from a process not present/incubating on admission ; cultures negative; undiagnosed despite appropriate evaluation (≥ 3 days, including ≥ 2 days culture incubation)
Neutropenic FUO	Fever with <500 neutrophils/ μL ; cultures negative; undiagnosed after 3 days — <i>fungal and occult bacterial infection</i> dominate
HIV-associated FUO	Confirmed HIV, febrile ≥ 4 weeks as outpatient or ≥ 3 days as inpatient; undiagnosed after 3 days (≥ 2 days incubation) — <i>mycobacterial/opportunistic infection</i> dominate

- Special scenarios with unique differentials: FUO in solid-organ transplant recipients (CMV, fungi, nocardiosis, *P. jirovecii*, mycobacteria) and FUO in the returning traveller (malaria, enteric fever, leishmaniasis, rickettsioses).

Etiology — broad categories

The five working categories (CMDT) and their geographic skew (Harrison):

Category	Key examples
Infections	Extrapulmonary/miliary tuberculosis, infective/culture-negative endocarditis, occult abscess (hepatic, splenic, subphrenic, pelvic, renal), diverticulitis, vertebral osteomyelitis/spondylodiscitis; brucellosis, Q fever (<i>Coxiella burnetii</i>), Whipple disease (<i>Tropheryma whippelii</i>), EBV/CMV, malaria, leishmaniasis, HIV seroconversion
Noninfectious inflammatory diseases (NIIDs)	Adult-onset Still's disease, large-vessel vasculitis / giant cell arteritis, polymyalgia rheumatica, SLE, polyarteritis nodosa, cryoglobulinemia, sarcoidosis; autoinflammatory syndromes (familial Mediterranean fever, VEXAS, Schnitzler's)

Category	Key examples
Malignancy	Malignant lymphoma (most common neoplastic cause), leukaemia, renal cell carcinoma, hepatic tumours, atrial myxoma, Castleman disease
Miscellaneous	Drug fever, factitious/fraudulent fever, granulomatous hepatitis, subacute thyroiditis, recurrent pulmonary emboli, alcoholic hepatitis
Undiagnosed	~Half of cases (higher in Western cohorts — “the FVO paradox”); most resolve spontaneously

- **Geography matters:** infection (esp. **tuberculosis** — up to half of infective FVO) predominates in Asia/Middle-East; **NIIDs predominate in Western cohorts** (up to one-third). In adults >65 years, multisystem immune diseases (GCA, PMR, sarcoid, RA) cause 25–30%.
- **Eponym pearls:** *VEXAS* — somatic UBA1 variants, elderly males, vacuoles in myeloid precursors. *Schnitzler’s* — urticaria + bone pain + monoclonal gammopathy. *Marantic (nonbacterial thrombotic) endocarditis* — paraneoplastic. Common **drug-fever** culprits: allopurinol, carbamazepine, lamotrigine, phenytoin, sulfasalazine, furosemide, sulfonamides, minocycline, vancomycin, β -lactams, isoniazid; fever subsides **within ~72 h** of stopping the drug.

Diagnostic approach — obligatory workup and PDC-driven strategy

- **Obligatory minimum investigations** (define the patient as true FVO): ESR and CRP; full blood count with differential and platelets; haemoglobin, electrolytes, creatinine, total protein, ALP, ALT, AST, LDH, creatine kinase, ferritin; ANA and rheumatoid factor; serum protein electrophoresis; urinalysis; **blood cultures (n = 3)**; urine culture; **chest radiograph**; **abdominal ultrasonography**; and TST or IGRA. (CMDT additionally lists HIV antibody/antigen and TSH.)
- **Hunt for Potentially Diagnostic Clues (PDCs)** — all localising signs, symptoms and abnormalities pointing to a diagnosis — through *repeated* history and examination. History: fever pattern/duration, drugs, travel (remote and recent), animal/occupational exposures, sexual and family history, country of origin. Examination: eyes/**fundoscopy**, lymph nodes, **temporal arteries**, liver, spleen, skin and mucosae, surgical scars.
- **Stop confounders early:** discontinue **antibiotics and glucocorticoids** before further testing (they mask cultures and shrink nodes); withdraw all drugs/supplements to exclude **drug fever**; exclude **factitious fever** (self-induced) and **fraudulent fever** (manipulated thermometer) by simultaneous multi-site temperature measurement and by noting **pulse–temperature dissociation**.
- **Targeted, PDC-guided testing only:** “screening” serologies/febrile agglutinins are low-yield and discouraged without a clue. Hold blood cultures long enough for fastidious HACEK organisms; use special media when *Legionella*, *Bartonella*, *Histoplasma* or nutritionally-variant streptococci are suspected. Headache → CSF examination (HSV-2, *Cryptococcus*, *M. tuberculosis*). For

suspected **miliary TB**, **liver biopsy** for acid-fast smear, culture and PCR has the highest yield.

Cryoglobulins are a useful low-cost screen.

- ▶ **Yield of invasive tests:** bone-marrow biopsy 15–25% (higher in HIV); liver biopsy 10–15% — pursue any abnormal finding aggressively (rash → skin biopsy; node → excision biopsy + culture).

Imaging — role of 18F-FDG-PET/CT

- ▶ **18F-FDG-PET/CT is the pivotal functional imaging test** when PDC-guided tests are unrevealing. FDG accumulates in high-glycolysis tissue — **malignant cells and activated leukocytes** — so it images infection, sterile inflammation **and** malignancy (an advantage in FUO, where all three are possible). It localises the metabolic focus to direct biopsy/culture.
- ▶ **Diagnostic yield ~50%** (Harrison meta-analyses); CMDT cites yields of **84–98%** for underlying cause. Perform it **during active inflammation** (raised CRP/ESR or while febrile) for best yield; **postpone glucocorticoids** until after the scan (they rapidly quench FDG uptake in vasculitis and lymphoma).
- ▶ **Alternatives** when PET/CT is unavailable: **67Ga-citrate scintigraphy** (yield ~21–54%) or **111In-/99mTc-labelled leukocyte scintigraphy** (~8–31%); whole-body MRI is a promising emerging option.
- ▶ **Giant cell arteritis** is found in up to 17% of elderly FUO patients; PET/CT detects large-vessel involvement, but **temporal artery biopsy is still recommended in patients ≥55 years** (small-calibre temporal vessels and high cerebral FDG can confound PET).

Treatment, prognosis and the role of therapeutic trials

- ▶ **Treat the established cause** — empirical therapy is generally *avoided*; it can mask infection/lymphoma and abolish culture yield. **Empirical therapy is justified only when the patient is haemodynamically unstable, septic, neutropenic or deteriorating**, or with strong suspicion of TB or sight-threatening GCA.
- ▶ **Therapeutic trials** (used selectively): antituberculous therapy (reassess at **6 weeks** — no response argues against TB); NSAIDs (often dramatic in Still's disease); **colchicine** (prevents FMF and recurrent pericarditis attacks); glucocorticoids (impressive in **GCA/PMR**, but only after lymphoma/infection excluded); **IL-1 inhibition with anakinra** (recombinant IL-1Ra blocking IL-1 α and IL-1 β) for autoinflammatory FUO with serositis, high ferritin and high CRP.
- ▶ **Prognosis is favourable** in undiagnosed FUO: fever resolves spontaneously in ~75% of undiagnosed patients; long-term mortality is $\leq 8\%$. A **normal PET/CT predicts spontaneous resolution**. A **second opinion at an FUO expert centre** yields a diagnosis in over half of previously unexplained cases.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm for FUO** (flow chart): *Fever* $\geq 38.3^{\circ}\text{C}$ + *illness* ≥ 3 weeks + *immunocompetent* → **History + examination + obligatory investigations** → *Stop antibiotics/glucocorticoids; exclude thermometer manipulation and drug fever* → branch: **PDCs present** → guided tests → diagnosis; **PDCs absent/misleading** → cryoglobulins + fundoscopy → **^{18}F -FDG-PET/CT** → *Abnormal* → confirm by biopsy/culture; *Normal* → repeat history/examination, PDC-driven invasive testing → *Stable* → follow up for new PDCs / NSAID vs *Deteriorating* → further tests / therapeutic trial.
- ▶ **Etiologic pie/box with labels**: **Infections, Noninfectious inflammatory diseases (NIIDs), Malignancy, Miscellaneous, Undiagnosed** — annotated with the geographic contrast (TB-rich Asia vs NIID-rich West).

Clinical / Diagnostic significance

- ▶ The single highest-value manoeuvre is the **repeated, meticulous history and examination** to extract PDCs — FUO is usually an atypical presentation of a *common* disease.
- ▶ **Tuberculosis (especially miliary/extrapulmonary)** is the most important treatable infectious cause in India and the tropics; a negative TST/IGRA does **not** exclude it.
- ▶ **Giant cell arteritis** must be actively sought in any elderly FUO with raised ESR/CRP, headache or visual symptoms — it is treatable and sight-threatening.
- ▶ Always re-examine for **endocarditis (including culture-negative/HACEK), occult abscess, lymphoma and drug fever** — the four “must-not-miss” recurring culprits.
- ▶ Discontinuing antibiotics/steroids and timing PET/CT to active inflammation materially change diagnostic yield.

High-yield exam pointers

- ▶ **Petersdorf–Beeson 1961**: ≥ 3 weeks, fever $\geq 38.3^{\circ}\text{C}$ (101°F) $\times 2$, undiagnosed after **1 week inpatient** evaluation.
- ▶ Modern definition adds a **mandatory minimum workup** and excludes the **immunocompromised**; IUO = FUO with a *normal temperature*.
- ▶ **Four categories**: classic, nosocomial, neutropenic ($<500/\mu\text{L}$), HIV-associated (4 wks OP / 3 days IP).
- ▶ Five etiologic classes: **infection, malignancy, NIID/autoimmune, miscellaneous, undiagnosed** (~50%).
- ▶ **Lymphoma** = commonest malignant cause; **TB/endocarditis** = commonest infective causes; **GCA/Still's/SLE/sarcoid** lead the NIIDs.
- ▶ **^{18}F -FDG-PET/CT** is the key functional scan; do it during active inflammation; hold steroids until after.

- ▶ **Drug fever** resolves within ~72 h of stopping the culprit; suspect with eosinophilia/DRESS.
- ▶ **Empirical therapy is the exception** (instability, neutropenia, suspected TB, GCA with visual loss); most undiagnosed FUO resolves spontaneously, mortality ≤8%.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Fever of Unknown Origin”; and “Fever” (definition, fever vs hyperthermia, pyrogenic cytokines).
- ▶ **CMDT 2026** — “Common Problems in Infectious Diseases & Antimicrobial Therapy: Fever of Unknown Origin” (categories, age/duration considerations, laboratory/imaging/biopsy yields, current management).
- ▶ *Coverage note:* The spec lists no dedicated subspecialty textbook for this topic; the Durack–Street four-category framework is named per standard internal-medicine teaching (Harrison 22e details the classic/IUO definitions and the structured PET/CT-based approach; CMDT 2026 supplies the explicit nosocomial/neutropenic/HIV thresholds). All numbers, eponyms and criteria were verified against these chapters.



Rationale, pre-requisites and contraindications to short course MDR TB regimen. Name the drugs and the duration of use

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Multidrug-resistant tuberculosis (MDR-TB) is disease caused by a strain of *M. tuberculosis* resistant at least to **isoniazid and rifampin**, the two most potent first-line bactericidal drugs; rifampin-resistant TB (RR-TB) is treated identically. A **short-course MDR-TB regimen** is an all-oral course of **6–9 months** that has now replaced the older 18–24-month, injectable-containing regimens. The flagship is the **6-month BPaLM regimen** (bedaquiline, pretomanid, linezolid, moxifloxacin), recommended by WHO since 2022 and incorporated into the 2024 guidance for MDR/RR-TB.

Resistance categories that frame the regimen choice

Term	Resistance pattern
RR-TB	Resistance to rifampin (managed as MDR)
MDR-TB	Resistance to isoniazid + rifampin
Pre-XDR-TB	MDR/RR-TB plus resistance to any fluoroquinolone

Term	Resistance pattern
XDR-TB	MDR-TB + fluoroquinolone resistance + resistance to ≥1 other Group A drug (bedaquiline or linezolid)

- ▶ India alone carries ~27% of the global MDR/RR-TB burden; resistance arises by spontaneous point mutations (*rpoB* → rifampin in 95%; *katG/inhA* → isoniazid; *gyrA/gyrB* → fluoroquinolones), and almost always follows effective **monotherapy** or poor adherence.

Rationale for a short-course, all-oral regimen

- ▶ **Traditional regimens were unacceptable:** ≥18–24 months, dominated by toxic injectable agents (kanamycin, capreomycin, amikacin) causing **ototoxicity and nephrotoxicity**, with poor tolerability, high default rates and cure in only ~50–60%.
- ▶ **Evidence base for shortening:** a 2018 individual-patient meta-analysis of >12,000 patients linked **better outcomes to linezolid, bedaquiline, clofazimine, carbapenems and later-generation fluoroquinolones**, and **worse outcomes to kanamycin and capreomycin** — which were therefore dropped.
- ▶ **Landmark trials:** the STREAM-1 trial validated a 9–12-month shorter (“Bangladesh”) regimen (~90% success); Nix-TB and ZeNix established **BPaL** (bedaquiline–pretomanid–linezolid, ~89% favourable outcomes) for highly resistant TB and showed **linezolid 600 mg** caused far fewer adverse events than 1200 mg; TB-PRACTECAL proved the 24-week **BPaLM** regimen **non-inferior** with **fewer serious adverse events** than the 9–20-month standard of care; **BEAT-Tuberculosis** validated **BDLLfxCfz**.
- ▶ **Programmatic advantages:** all-oral therapy removes painful injections, **lowers pill burden**, improves adherence and completion, shortens the period of infectiousness (interrupting transmission), is more **cost-effective**, and reduces amplification of further resistance.

Name the drugs and the duration of use

WHO/Harrison now endorse **four approaches** to MDR/RR-TB; all-oral regimens are preferred, and the choice depends on disease severity, drug-resistance pattern and prior treatment.

Regimen	Component drugs	Duration
BPaLM (preferred)	Bedaquiline + Pa (pretomanid) + Linezolid 600 mg + Moxifloxacin	6 months (drop moxifloxacin → BPaL if fluoroquinolone resistance documented)
BDLLfxCfz	Bedaquiline + Delamanid + Linezolid 600 mg + Levofloxacin + Clofazimine	6 months (Lfx or Cfz may be omitted per FQ-DST; usable in children & pregnancy)
9-month all-oral	BLMZ, or BLLfxCfzZ, or BDLLfxZ	9 months (when FQ-susceptible, no prior 2nd-line exposure)

Regimen	Component drugs	Duration
Longer individualised	Group A (Lfx/Mfx, bedaquiline, linezolid) + ≥1 Group B (clofazimine, cycloserine/terizidone) ± Group C	≥18–20 months (XDR-TB / complex resistance)

Component drug detail (BPALM):

- ▶ **Bedaquiline** — diarylquinoline; inhibits mycobacterial ATP synthase; dose **400 mg once daily** ×2 weeks, then **200 mg thrice weekly** for ~6 months; CYP3A4-metabolised, very long $t_{1/2}$ (>14 days); carries an FDA **black-box warning** (QT prolongation, mortality signal).
- ▶ **Pretomanid** — nitroimidazole **prodrug** inhibiting mycolic-acid synthesis; **200 mg once daily**; main risk **hepatotoxicity**.
- ▶ **Linezolid** — oxazolidinone binding the 50S ribosome; **600 mg once daily** (better tolerated than 1200 mg); toxicities — **myelosuppression, optic and peripheral neuropathy, lactic acidosis, serotonin syndrome** (weak MAOI).
- ▶ **Moxifloxacin** — fluoroquinolone inhibiting DNA gyrase/topoisomerase IV; **400 mg once daily** in BPALM; QT prolongation.
- ▶ (BDLLfxCfz adds **delamanid 100 mg twice daily** and **clofazimine** — a riminophenazine causing reversible **orange–brown skin/fluid discolouration**, $t_{1/2}$ ~70 days.)

Pre-requisites before starting a short-course regimen

- ▶ **Confirmed RR/MDR-TB** by rapid molecular DST (e.g., Xpert MTB/RIF) — rifampin resistance at minimum.
- ▶ **Baseline fluoroquinolone DST** — mandatory; decides whether moxifloxacin/levofloxacin is retained (it directs BPALM vs BPAL, and BDLLfxCfz composition).
- ▶ **No prior exposure (or <1 month)** to the regimen's novel drugs (bedaquiline, pretomanid, linezolid for BPALM; bedaquiline, delamanid, linezolid for BDLLfxCfz) — unless susceptibility is confirmed.
- ▶ **Eligible age & disease form**: BPALM for patients ≥14 years, all forms **except** disseminated, CNS and osteoarticular TB (BDLLfxCfz extends to children and pregnant/breastfeeding women).
- ▶ **Baseline cardiac assessment**: ECG/QTc and serum electrolytes (K^+ , Mg^{2+} , Ca^{2+}) — patients on QT-prolonging drugs (bedaquiline, delamanid, clofazimine, fluoroquinolones) need on-treatment ECG monitoring.
- ▶ **Baseline organ-function screen**: LFTs (hepatotoxic drugs), **full blood count** (linezolid marrow suppression), **visual acuity & colour vision** (linezolid optic neuritis), renal function, **HIV test** and **pregnancy test**.
- ▶ **Informed consent** and enrolment in active TB drug-safety monitoring (aDSM).

- ▶ **Adherence support** — directly observed therapy (DOT) or **video-observed therapy (VOT)**, social/nutritional support, plus pyridoxine where neuropathy risk is high.

Contraindications and cautions

- ▶ **Pregnancy and breastfeeding** — a contraindication to BPaLM (pretomanid safety data incomplete); use BDLLfxCfz or a bedaquiline-based 9-month/longer regimen instead (avoid thioamides, bedaquiline and delamanid where data are lacking in pregnancy).
- ▶ **Disseminated, CNS (meningeal) and osteoarticular TB** — excluded from BPaLM; require longer, individualised therapy.
- ▶ **QTc >500 ms or a history of ventricular arrhythmia** — do **not** give the QT-prolonging agents (bedaquiline, delamanid, clofazimine, fluoroquinolones).
- ▶ **Significant prior exposure (>1 month)** to, or documented resistance to, the regimen's core drugs.
- ▶ **Age <14 years** for BPaLM (choose a child-appropriate regimen).
- ▶ **Severe drug intolerance/allergy** to a core agent, and clinically significant **drug–drug interactions** (e.g., strong CYP3A4 inducers lowering bedaquiline, serotonergic drugs with linezolid).
- ▶ Injectable agents **kanamycin and capreomycin must not be used**; amikacin is reserved (≥ 18 years, with audiometry) only when oral options fail.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Resistance ladder (vertical steps)**: label RR-TB (*rifampin-R*) → MDR-TB (*isoniazid + rifampin-R*) → Pre-XDR (MDR + *fluoroquinolone-R*) → XDR (MDR + FQ-R + *bedaquiline/linezolid-R*).
- ▶ **BPaLM 6-month timeline (horizontal bar)**: labels — *Baseline (Day 0): DST + FQ-DST, ECG/QTc, LFT, CBC, vision, HIV, pregnancy test*; four parallel drug bars — *Bedaquiline 400 mg OD ×2 wk → 200 mg thrice-weekly, Pretomanid 200 mg OD, Linezolid 600 mg OD, Moxifloxacin 400 mg OD (omit if FQ-resistant → BPaL)*; bracket 26 weeks (*extend if culture-positive at month 4*); footer *Monthly monitoring: sputum culture, ECG, CBC, vision & neuro review*.

Clinical / Diagnostic significance

- ▶ **Universal upfront DST**, especially for rifampin and fluoroquinolones, is the single most important determinant of regimen selection and prevents inadvertent under-treatment.
- ▶ **Sputum culture (liquid)** is the standard for monitoring; Xpert MTB/RIF and serial chest X-rays are **not** suitable for response monitoring (they detect non-viable bacilli / lag behind).
- ▶ **QTc surveillance** during treatment is essential because several agents are additively cardiotoxic; correct hypokalaemia/hypomagnesaemia.

- ▶ Linezolid demands monthly FBC, vision and neurological review; dose reduction or interruption mitigates marrow suppression and optic/peripheral neuropathy.
- ▶ Persistent culture positivity at month 4 (or extensive cavitation) flags slow responders who may need **regimen extension or re-evaluation for amplified resistance** and surgery in localised disease.

High-yield exam pointers

- ▶ MDR-TB = resistance to at least isoniazid + rifampin; XDR = MDR + fluoroquinolone + a second Group A drug (bedaquiline/linezolid).
- ▶ BPaLM = Bedaquiline + Pretomanid + Linezolid (600 mg) + Moxifloxacin for 6 months — the preferred short-course regimen; becomes BPaL if fluoroquinolone-resistant.
- ▶ Bedaquiline 400 mg OD ×2 wk then 200 mg thrice-weekly; linezolid 600 mg OD; pretomanid 200 mg OD; moxifloxacin 400 mg OD.
- ▶ **Pre-requisites:** confirmed RR/MDR-TB, baseline FQ-DST, no prior drug exposure, age ≥14, baseline ECG/LFT/CBC/vision, informed consent, aDSM.
- ▶ **Contraindications:** pregnancy/breastfeeding (BPaLM), CNS/osteoarticular/disseminated TB, QTc >500 ms, prior exposure/resistance, age <14.
- ▶ **All-oral and injectable-free** — kanamycin/capreomycin abandoned for worse outcomes and toxicity.
- ▶ **Group A** = levofloxacin/moxifloxacin, bedaquiline, linezolid (always in longer regimens); **Group B** = clofazimine, cycloserine/terizidone.
- ▶ Treatment success with short-course all-oral regimens approaches ~**89–90%** (Nix-TB/ZeNix/TB-PRACTECAL).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Tuberculosis” (drug-resistant TB definitions, the four WHO approaches, BPaLM/BDLLfxCfz/9-month regimens, Group A/B/C drugs, pre-requisites, contraindications and monitoring) and “Antimycobacterial Agents” (drug mechanisms, doses, adverse effects; STREAM-1, Nix-TB, ZeNix, TB-PRACTECAL trial detail).
- ▶ **CMDT 2026** — “Pulmonary Disorders” (current management of drug-resistant TB; isoniazid- and pyrazinamide-mono-resistant regimens; bedaquiline–pretomanid–linezolid reference).

Coverage note: The corpus fully supports the regimens, drugs, doses, pre-requisites and contraindications above. The specific WHO operational rule that BPaLM may be **extended from 26 to 39 weeks** in patients still culture-positive at month 4 is standard WHO programmatic

guidance and is stated here as such, as the precise extension figure is not given verbatim in the chapters read.



Rhino-Orbital-Cerebral Mucormycosis

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Mucormycosis is a group of life-threatening, highly angioinvasive and relentlessly progressive infections caused by fungi of the order **Mucorales** (subphylum *Mucoromycotina*). The **rhino-orbital-cerebral (ROCM)** form is the most common presentation worldwide and classically affects patients with **uncontrolled diabetes mellitus, especially diabetic ketoacidosis (DKA)**. It begins in the paranasal sinuses and spreads contiguously/haematogenously to the orbit and brain, producing the characteristic black necrotic eschar and cavernous-sinus thrombosis. Mortality remains high; outcome depends on early polyene therapy, aggressive surgical debridement and rapid reversal of the predisposing state.

Etiology and Predisposing Factors

- ▶ The Mucorales comprise **seven families** that cause human disease. ***Rhizopus oryzae and R. delemar** (family *Mucoraceae*) are by far the most common causes. *Apophysomyces elegans* is an important agent in India, and *Mucor irregularis** in China.
- ▶ Mucormycosis incidence is **higher in India than most other countries even before the COVID-19 pandemic**; during the pandemic it occurred commonly as a co-infection in hospitalised COVID-19 patients, driven by high-dose corticosteroids combined with the high background prevalence of diabetes.

Family	Representative genera/species
Mucoraceae	<i>Rhizopus oryzae</i> , <i>R. delemar</i> , <i>R. microsporus</i> , <i>Rhizomucor</i> , <i>Mucor</i> , <i>Actinomucor</i>
Lichtheimiaceae	<i>Lichtheimia</i> (formerly <i>Mycocladius</i> / <i>Absidia</i>)
Cunninghamellaceae	<i>Cunninghamella</i>
Saksenaceae	<i>Saksenaea</i> , <i>Apophysomyces</i>
Mortierellaceae, Thamnidaceae, Syncephalastraceae	<i>Mortierella</i> , <i>Cokeromyces</i> , <i>Syncephalastrum</i>

- ▶ **Key predisposing factors:** uncontrolled diabetes mellitus / DKA (→ ROCM specifically); defects in phagocytic function (**neutropenia**, high-dose **corticosteroids**); **elevated free iron** (e.g., deferoxamine therapy in iron-overloaded dialysis patients); solid-organ or **haematopoietic stem-cell transplant (HSCT)**; haematological malignancy.

- ▶ Patients on **itraconazole** or **voriconazole** prophylaxis may be at increased risk; breakthrough disease is also reported with **posaconazole**, **isavuconazole** or **echinocandin** prophylaxis.
- ▶ *Important caveat:* the **majority of diabetics presenting with mucormycosis are NOT acidotic**, and many have **no prior diagnosis of diabetes** — presentation may be the first recognition of **hyperglycaemia** (often unmasked by recent glucocorticoids).

Pathogenesis — the Iron / GRP78 / CotH Axis

- ▶ The Mucorales are ubiquitous environmental fungi; infection follows inhalation of spores into the sinuses in a susceptible host.
- ▶ **Free iron is the central virulence determinant.** In DKA, acidosis causes **dissociation of iron from sequestering proteins**, enhancing fungal survival and virulence. The ketoacid β -**hydroxybutyrate** upregulates host and fungal receptors mediating adherence and tissue penetration.
- ▶ **Deferoxamine** acts as a fungal **xenosiderophore** — it chelates iron for the host but delivers it directly to the Mucorales, historically causing rapidly fatal disseminated disease.
- ▶ Even without acidosis, **hyperglycaemia** promotes infection by ≥ 4 mechanisms: (1) **hyperglycation of iron-sequestering proteins** (disrupts iron sequestration); (2) **upregulation of GRP78**, a mammalian receptor that binds Mucorales and enables tissue penetration; (3) poorly characterised **defects in phagocyte function**; (4) enhanced expression of **CotH**, a Mucorales-specific invasin that mediates host-cell invasion by binding GRP78.
- ▶ The hallmark is **angioinvasion** $\rightarrow$ **vascular thrombosis** $\rightarrow$ **tissue infarction and necrosis**, which also impairs antifungal drug delivery to the infected site.

Clinical Features and Stage-wise Progression of ROCM

- ▶ Patients with **diabetes/DKA** typically develop the **rhino-orbital-cerebral form** and only rarely pulmonary or disseminated disease.
- ▶ **Early symptoms are non-specific:** eye or facial pain, **facial numbness**, followed by **conjunctival suffusion**, periocular swelling and **blurry vision**.
- ▶ Periorbital skin takes on a **dusky, subacute appearance** — in contrast to the acute, bright-red periocular changes of **bacterial orbital cellulitis**.
- ▶ **Fever may be absent in up to half** of cases; the WBC count is usually elevated as long as marrow function is intact.
- ▶ **Sino-orbital spread:** untreated infection spreads from the **ethmoid sinus** $\rightarrow$ **orbit**, causing compromise of extraocular-muscle function, **proptosis** and **chemosis**.
- ▶ **Intracranial / cavernous-sinus spread:** from the orbit the fungus extends contiguously or haematogenously to the **frontal lobe**, and via venous drainage to the **cavernous sinus**. **Contralateral eye involvement with bilateral proptosis, chemosis, vision loss and ophthalmoplegia is ominous and suggests cavernous-sinus thrombosis.**

- ▶ **Local tissue evolution:** infected tissue may look **normal** initially (hence “blind” biopsy of normal-appearing sinus is warranted when suspicion is high) → **erythematous** (± oedema) → **violaceous** → **black necrotic eschar**. Extension into the mouth produces painful necrotic ulceration of the **hard palate** — a *late* finding indicating extensive, well-established disease.
- ▶ *Note:* progression is **variable, not always fulminant** — death may occur in days, or progression may take months, depending on host immunity, inoculum and species virulence.

Diagnosis

- ▶ **A high index of suspicion is essential** — autopsy series show **up to half of cases are diagnosed only post-mortem**.
- ▶ **Definitive diagnosis:** positive culture from a **sterile site** (needle aspirate, tissue biopsy, pleural fluid) or histopathological evidence of **invasive disease**. Biopsy with histopathology is the most sensitive and specific modality.
- ▶ **Characteristic histology:** broad/wide ($\geq 6\text{--}30\ \mu\text{m}$), thick-walled, **ribbon-like, aseptate** (pauciseptate) hyphae that **branch at right angles** ($\approx 90^\circ$). Best stained with PAS or H&E; methenamine silver may not stain optimally.

Feature	Mucorales	Aspergillus / Fusarium / Scedosporium
Septation	Aseptate / pauciseptate	Septate
Hyphal width	Broad, ribbon-like ($6\text{--}30\ \mu\text{m}$)	Thin
Branching angle	Wide, $\sim 90^\circ$ (right angle)	Acute ($\sim 45^\circ$)

- ▶ **Culture caveats:** positive in **<50%** of cases — long filamentous hyphae are killed by tissue **homogenisation**, so alert the lab and place **minced tissue sections** (not homogenate) on media; incubate at both **room temperature and 37°C** . Mucorales are not fastidious and grow within **48–96 h**. Species identification requires culture (not histology).
- ▶ **Imaging:** sinusitis on CT/MRI is often **indistinguishable from bacterial sinusitis**, and bony erosion into the orbit is **rarely seen on CT even when clinically present**. MRI is **more sensitive** ($\sim 80\%$) for orbital and CNS disease. Imaging routinely **underestimates** extent — high-risk patients should undergo **endoscopy and/or surgical exploration with biopsy**.
- ▶ **PCR of Mucorales-specific targets** is useful but **not FDA-approved**. Because therapy must often start empirically, **begin a lipid polyene as soon as suspicion is reasonable** while confirmation is awaited.

Differential Diagnosis

- ▶ **Other invasive moulds:** aspergillosis, scedosporiosis, fusariosis, dematiaceous (brown-pigmented) fungi — distinguishing them matters because **polyenes treat Mucorales whereas**

expanded-spectrum triazoles treat most septate moulds, and voriconazole actually exacerbates mucormycosis.

- ▶ **Entomophthoromycoses** (*Basidiobolus*, *Conidiobolus*) — histologically similar but distinguished by culture; also treated with polyenes, so urgent differentiation is unnecessary.
- ▶ **Bacterial orbital cellulitis / cavernous-sinus thrombosis** (most commonly *Staphylococcus aureus*, also streptococci and gram-negatives).
- ▶ ***Klebsiella rhinoscleromatis*** (indolent facial rhinoscleroma).
- ▶ ***Tolosa-Hunt syndrome** — *painful ophthalmoplegia, ptosis, headache and cavernous-sinus inflammation; lack of progression** helps distinguish it from mucormycosis.

Treatment

- ▶ **Four pillars of management:** (1) **early initiation** of antifungal therapy; (2) **surgical debridement** of all necrotic tissue when feasible; (3) **rapid reversal of predisposing factors**; (4) **treat the underlying malignancy without waiting** to finish antifungals.
- ▶ **Surgery:** because thrombosis/necrosis impairs drug penetration, **debridement is an independent predictor of favourable outcome**; intra-operative frozen sections help delineate infected margins. Use a *moderated* approach — debride to the extent it is safe.
- ▶ **Reverse the host defect:** correct **hyperglycaemia and acidosis** (sodium bicarbonate improved survival in DKA mice), **taper corticosteroids**, and **avoid iron** — use a **conservative RBC-transfusion policy** (haemolysis liberates free iron).

Line	Drug	Dose	Notes
First-line	Liposomal AmB (LAmB)	5–10 mg/kg/day	Preferred for brain disease — best CNS penetration; consider 7.5–10 mg/kg/day for CNS, but no benefit above 10 mg/kg/day (autoinduction lowers levels)
First-line	AmB lipid complex (ABLC)	5 mg/kg/day	Less nephrotoxic than deoxycholate; possibly less effective than LAmB for CNS
First-line	AmB deoxycholate	1.0–1.5 mg/kg/day	Cheap, FDA-approved, but highly toxic and poor CNS penetration
Second-line / salvage	Isavuconazole	200 mg (372 mg isavuconazonium sulfate) load q8h ×6, then once daily	FDA-approved; rational empirical choice when septate-mould vs Mucorales is unresolved

Line	Drug	Dose	Notes
Second-line / salvage	Posaconazole	200 mg four times daily	Salvage only; lower blood levels than isavuconazole
Combination	Echinocandin + lipid polyene	Standard echinocandin doses	Synergy in murine disease; retrospective benefit in ROCM. Do NOT escalate echinocandin ≥ 3 mg/kg/day (paradoxical loss of benefit)

- ▶ **Primary therapy must be a polyene** except perhaps in mild, surgically excised, isolated suprafacial cutaneous disease in an immunocompetent host.
- ▶ **Deferasirox** is fungicidal *in vitro* and synergistic with LAmB in DKA mice; however human trial evidence is limited (see Coverage note).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Coronal section of face/skull showing ROCM spread** — Labels: *ethmoid/maxillary sinus (primary focus), nasal turbinate with black eschar, orbit with proptosis & chemosis, extraocular muscles, optic nerve, cavernous sinus (thrombosis), internal carotid artery, frontal lobe extension, hard-palate necrotic ulcer.*
- ▶ **Histopathology of Mucorales** — Labels: *broad ribbon-like aseptate hypha (6–30 μ m), right-angle (90°) branching, thrombosed blood vessel with intravascular hyphae (angioinvasion), surrounding tissue infarction.*

Clinical / Diagnostic significance

- ▶ In any **diabetic with sinusitis + facial/orbital pain, numbness, or proptosis**, suspect ROCM and act emergently — delay is lethal.
- ▶ **Hyperglycaemia with new sinusitis and possible orbital extension** warrants suspicion even with no known history of diabetes.
- ▶ **Bilateral proptosis/ophthalmoplegia** = **cavernous-sinus thrombosis**, a neurosurgical/ophthalmic emergency.
- ▶ Diagnostic workup: **urgent ENT endoscopy + biopsy/KOH + histopathology + fungal culture, MRI brain/orbit/sinuses**, glycaemic and acid-base assessment.
- ▶ **Never give voriconazole** if mucormycosis is in the differential — it worsens disease.
- ▶ Management is **multidisciplinary** (Internal medicine/Endocrine, ENT, Ophthalmology, Neurosurgery, Microbiology) with combined medical + surgical therapy.

High-yield exam pointers

- ▶ **ROCM** = most common form worldwide; diabetes/DKA is the classic host; India has disproportionately high incidence (further amplified by COVID-19 + steroids).
- ▶ ***Rhizopus oryzae/R. delemar** = *commonest agents; aseptate, broad, ribbon-like hyphae, right-angle branching*.*
- ▶ Central mechanism = **free iron + GRP78/CotH-mediated angioinvasion**; **deferoxamine** is a risk factor (xenosiderophore).
- ▶ Hallmark sign = **black necrotic eschar** (nasal/palatal); periorbital skin is **dusky**, not bright-red.
- ▶ **MRI > CT** for orbital/CNS extent; **culture positive in <50%** — alert lab, do not homogenise tissue; **PCR not FDA-approved**.
- ▶ **First-line** = **liposomal amphotericin B 5–10 mg/kg/day + early surgical debridement + control of diabetes/acidosis/iron**.
- ▶ **Isavuconazole and posaconazole** are second-line/salvage; **avoid voriconazole**.
- ▶ Disseminated disease mortality **>90%**; mucormycosis-related **necrotising fasciitis ~80%**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 224 “Mucormycosis”** (Spellberg & Ibrahim), incl. Tables 224-1 (taxonomy) and 224-2 (antifungal options) and Fig. 224-1 (histopathology).

Coverage note: The provided chapter text is **truncated at the start of the adjunctive-deferasirox phase-2 trial sentence**, so the final human trial outcome (the *DEFEAT-Mucor*-type result showing no benefit/possible harm of adjunctive deferasirox) and any concluding outcome/mortality figures for ROCM specifically were not in the supplied text and are therefore stated only as far as the text supports. **Hyperbaric oxygen** as adjunctive therapy is *not* mentioned in the provided text and has been deliberately omitted to avoid fabrication.



Strongyloides Hyperinfection Syndrome

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — *Strongyloides stercoralis* is a soil-transmitted intestinal nematode that is **unique among helminths** (along with *Capillaria*) in its ability to complete its entire life cycle and replicate within the human host through **autoinfection**, allowing infection to persist silently for decades. **Hyperinfection syndrome** is the dangerous acceleration of this autoinfection cycle, with massive multiplication of filariform larvae within the normal migratory route (gut → lungs), triggered by impaired cell-mediated immunity. When larvae spread beyond this route to organs such as the CNS, liver, kidney, skin and peritoneum, the condition is termed **disseminated strongyloidiasis**. It carries a

very high mortality (approaching 100% untreated, ~25% even when treated) and is most often unmasked by glucocorticoid therapy.

Life cycle & pathophysiology (basis of hyperinfection)

- **Acquisition:** filariform larvae in faecally-contaminated soil penetrate skin/mucosa → bloodstream → lungs → ascend bronchial tree → swallowed → mature into adult worms embedded in proximal small-bowel mucosa.
- The minute (1–2 mm) **parthenogenetic adult females** produce eggs that hatch in the mucosa into **rhabditiform larvae** (~250 µm, short buccal cavity).
- **Autoinfection:** some rhabditiform larvae transform *within the bowel* into invasive **filariform larvae** (~450 µm) that penetrate the colonic wall or perianal skin and re-enter the circulation — perpetuating internal reinfection without fresh exogenous exposure.
- This autoinfection cycle is normally **restrained by intact cell-mediated (Th2) immunity and eosinophils**. When this restraint fails, larval numbers amplify exponentially → **hyperinfection**, and disrupted gut mucosa allows **translocation of enteric gram-negative bacteria** → bacteraemia/sepsis.

Risk factors / Predisposing conditions

Category	Specific predisposing factors
Drugs (greatest risk)	High-dose / prolonged corticosteroids (the single most important trigger); other immunosuppressants — calcineurin inhibitors, chemotherapy, biologics
Viral / retroviral	HTLV-1 infection (classic, strong association — shifts immunity away from protective Th2); AIDS/HIV
Haematological / malignancy	Haematologic malignancies (lymphoma, leukaemia); cytotoxic chemotherapy
Transplantation	Solid-organ and haematopoietic stem-cell transplantation (donor-derived transmission described)
Host / nutritional	Malnutrition, alcohol use disorder, diabetes, chronic debilitating illness, hypogammaglobulinaemia
Epidemiological exposure	Residence in / travel to Southeast Asia, sub-Saharan Africa, Brazil , endemic SE United States; immigrants, refugees, military personnel — <i>even decades earlier</i> (latent autoinfection)

- ▶ **Exam pearl:** Strongyloides hyperinfection is the classic helminth disease **precipitated by steroids** — eosinophilia is *not* protective once steroids blunt the immune response, and (importantly) eosinophilia is often **suppressed by the very steroids** that precipitate the syndrome.

Clinical presentation

Uncomplicated (chronic) strongyloidiasis — often asymptomatic or:

- ▶ **Cutaneous:** recurrent **urticaria** (often buttocks); **larva currens** — a *pathognomonic*, pruritic, raised, serpiginous track that advances rapidly (up to **10 cm/h**).
- ▶ **GI:** mid-epigastric pain mimicking peptic ulcer (aggravated by food), nausea, watery diarrhoea, bloating, occult GI bleeding, weight loss.
- ▶ **Eosinophilia** that fluctuates over time; pulmonary symptoms rare.

Hyperinfection / disseminated disease — overwhelming, multi-system and often fulminant:

System	Manifestations
Gastrointestinal	Severe colitis/enteritis, malabsorption, paralytic ileus, intestinal obstruction , perforation, massive GI haemorrhage
Pulmonary	Pneumonitis, cough, wheeze, haemoptysis , diffuse infiltrates/ARDS, respiratory failure; larvae/eggs in sputum
Bloodstream	Recurrent gram-negative bacteraemia / polymicrobial sepsis from enteric flora translocation — a frequent presenting feature
CNS	Gram-negative (E. coli/enteric) meningitis , brain abscess; larvae may be seen in CSF
Skin	Widespread purpuric/petechial eruption, “thumbprint” periumbilical purpura from migrating larvae
Other	Hepatic, renal, peritoneal involvement; progression to shock and death

- ▶ **Red flag combination:** an immunosuppressed (especially steroid-treated) patient with **recurrent gram-negative sepsis or enteric meningitis + unexplained ileus/abdominal signs + pulmonary infiltrates**, particularly with a remote tropical exposure, is hyperinfection until proven otherwise.

Diagnosis / Investigations

- ▶ **Stool microscopy** — demonstrates motile **rhabditiform larvae** (not eggs); short buccal cavity distinguishes them from hookworm larvae. *Single stool sensitivity is low (~30%; detects only ~one-third of uncomplicated cases)* → request **serial (3–7) samples**.

- ▶ **Concentration / culture techniques** — agar-plate culture and Baermann concentration markedly raise sensitivity.
- ▶ **Duodenal sampling** — aspiration or biopsy of duodenojejunal contents (string test) when stools repeatedly negative.
- ▶ **Serology (ELISA)** — sensitive (~90% sensitivity/specificity, CDC assay) for *uncomplicated/chronic* infection; cross-reacts with other helminths. **Indicated to screen before immunosuppression / transplantation**, especially with eosinophilia or endemic exposure.
- ▶ **PCR / molecular assays** — increasing sensitivity and species specificity.
- ▶ **In hyperinfection:** larval burden is huge, so a **single stool exam is usually positive**; filariform larvae are readily found in **stool, sputum, BAL fluid, CSF and surgical drainage fluid** — i.e. sample the migration sites.
- ▶ **Supportive:** eosinophilia + mild anaemia in chronic disease; **eosinophilia is frequently ABSENT in hyperinfection (poor prognostic sign)**; hypoproteinaemia, deranged LFTs, and diffuse pulmonary infiltrates on imaging; blood cultures growing **enteric gram-negative organisms**.

Treatment

- ▶ **Drug of choice** — Ivermectin, more effective than albendazole:
 - *Uncomplicated:* ivermectin 200 µg/kg/day orally for 1–2 days.
 - *Alternative:* albendazole 400 mg orally twice daily for 3 days (less effective).
- ▶ **Hyperinfection / disseminated disease:**
 - Prolonged ivermectin continued daily until at least 14 days after stool/sputum become and remain larva-negative.
 - In immunocompromised hosts, **repeat the ivermectin course ~2 weeks after the initial treatment**; with ongoing immunosuppression, **regular suppressive dosing (e.g. monthly ivermectin)** may be needed.
 - When oral route impossible (ileus): ivermectin has been given **per rectum** or **parenterally** (veterinary preparation under single-patient expanded-access protocols).
- ▶ **Adjuncts:** broad-spectrum antibiotics for concurrent gram-negative sepsis/meningitis; supportive care for ARDS, ileus, fluid/electrolyte derangement; **taper/withdraw glucocorticoids and other immunosuppression** wherever feasible.
- ▶ **Even asymptomatic infection must be treated** because of the lifelong risk of fatal hyperinfection — eradication is the goal (monitor falling eosinophil count and antibody titre as response markers).

Prevention / screening (high-yield):

- ▶ Screen all at-risk patients (serology ± stool) **BEFORE** starting corticosteroids, chemotherapy, biologics, or transplantation, especially with any history — even remote — of residence in an endemic area.
- ▶ **Presumptive ivermectin treatment** is warranted in seropositive (or strongly exposed) patients even when stool examination is negative.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Life cycle of Strongyloides stercoralis** (labels):* filariform larva penetrates skin → bloodstream → lungs / alveoli → ascends trachea, swallowed → adult female in small-bowel mucosa (parthenogenesis) → eggs hatch → rhabditiform larva (~250 µm); *branch the three fates — (a) Direct/Indirect free-living cycle in soil, (b) Autoinfection (rhabditiform → filariform → perianal skin/colonic wall → recirculate), and (c) Hyperinfection/Dissemination (with immunosuppression → massive filariform larvae → lungs, CNS, liver, kidney, skin + gram-negative sepsis*).*
- ▶ **Diagram 2 — “Autoinfection → Hyperinfection → Dissemination” arrow ladder,** annotated with the immune trigger (**steroids / HTLV-1 / impaired CMI**) at the step where control is lost.

Clinical / Diagnostic significance

- ▶ Classic “**steroid-unmasked**” parasitosis — always exclude/treat Strongyloides before immunosuppressing a patient from an endemic area.
- ▶ **Recurrent enteric gram-negative bacteraemia or E. coli meningitis** in an immunosuppressed host should prompt a search for Strongyloides as the conduit.
- ▶ **Eosinophilia is paradoxically a good sign** (intact immunity); its absence in a deteriorating immunosuppressed patient is ominous.
- ▶ Untreated dissemination is **near-uniformly fatal** — early empirical ivermectin saves lives when suspicion is high.

High-yield exam pointers

- ▶ **Autoinfection** makes Strongyloides the helminth that can persist **for decades** and the only common one to cause **fatal hyperinfection**.
- ▶ **Greatest single risk factor = corticosteroids**; strongest infective co-factor = HTLV-1.
- ▶ **Larva currens** (10 cm/h serpiginous track) is *pathognomonic*; **periumbilical “thumbprint” purpura** suggests dissemination.
- ▶ Stool ova-and-parasite finds **larvae, not eggs**; **single stool ~30% sensitive** → do serial stools + agar-plate culture; serology (ELISA ~90%) for screening.
- ▶ **Hyperinfection:** larvae in sputum/BAL/CSF; **single stool usually positive**; eosinophilia often absent.

- ▶ Ivermectin 200 µg/kg/day is drug of choice; in dissemination continue ≥ 2 weeks after larvae clear and repeat course in the immunosuppressed.
- ▶ Screen + treat before immunosuppression / transplant; treat even asymptomatic carriers.
- ▶ Mortality: ~100% untreated, ~25% treated — outcome hinges on early recognition.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Intestinal Nematode Infections” (Strongyloidiasis section: life cycle, autoinfection/hyperinfection/dissemination, larva currens, HTLV-1 and glucocorticoid risk, diagnosis, ivermectin treatment).
- ▶ **CMDT 2026** — “Protozoal & Helminthic Infections” (Strongyloidiasis: risk factors, mortality figures ~100%/25%, ELISA sensitivity, screening before immunosuppression, ivermectin regimens for hyperinfection).

Coverage note: The corpus has no dedicated infectious-disease subspecialty textbook in the spec (specialty_books empty); depth is therefore drawn from Harrison 22e + CMDT 2026, which together cover the topic comprehensively. The “thumbprint periumbilical purpura” sign is universally-accepted standard ID teaching included for completeness though not verbatim in the two cited chapters.



Role of CD4 Count in the Management of HIV Infection

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — The CD4+ T lymphocyte is the principal target cell of HIV and the central pivot of immune competence; the **absolute CD4 count** (cells/µL) is therefore the single most widely used marker for *staging, prognosis* and *guiding opportunistic-infection (OI) prophylaxis* in HIV. HIV preferentially infects and depletes CD4+ helper T cells (gp120 binds the 55-kDa CD4 molecule plus a co-receptor, CCR5 or CXCR4), so the count is a direct readout of the degree of immunodeficiency. It is complementary to, not a substitute for, the **plasma HIV RNA (viral load)** — the count measures *immune damage already done*, the viral load measures *active replication and treatment response*.

CD4 cell biology — what the count actually measures

- ▶ CD4 is a glycoprotein on **helper (Th) T lymphocytes**, also on monocytes/macrophages and dendritic cells; it is the primary HIV receptor.
- ▶ In an untreated patient the count falls at an **average of ~50 cells/µL per year**; when it crosses **<200/µL** the immunodeficiency is severe enough to expose the patient to OIs and AIDS-defining neoplasms.

- ▶ The count thus serves four management roles: (1) **stage** the disease, (2) **risk-stratify** for specific OIs, (3) decide **start/stop of OI prophylaxis**, and (4) **monitor immune reconstitution** on antiretroviral therapy (ART).

CD4-based CDC staging and the AIDS-defining threshold

The CDC (MMWR 2014) classifies HIV by CD4 count (count takes precedence; percentage used only if count missing) for persons aged ≥ 6 years:

Stage	CD4 count (cells/ μ L)	CD4 percentage
Stage 1	≥ 500	$\geq 26\%$
Stage 2	200–499	14–25%
Stage 3 (AIDS)	< 200	$< 14\%$

- ▶ A diagnosis of AIDS is made in any person ≥ 6 years with HIV and a CD4 $< 200/\mu$ L (Stage 3) or a CD4 percentage $< 14\%$, or who develops an AIDS-defining (stage-3) opportunistic illness regardless of count.
- ▶ The 200/ μ L cut-off is evidence-based: cohort studies show AIDS develops within ~ 3 years in $> 80\%$ of untreated persons whose counts fall below this level.

CD4 count and the spectrum of opportunistic disease

The CD4 count predicts *which* complications are likely, allowing a focused differential at any given count:

Approx. CD4 (cells/ μ L)	Characteristic complications
> 500	Acute retroviral syndrome, persistent generalised lymphadenopathy; later — herpes zoster, vaginal candidiasis, oral hairy leukoplakia, Kaposi sarcoma
200–500	Bacterial pneumonia, pulmonary TB, mucocutaneous candidiasis, ITP
< 200	** <i>Pneumocystis jirovecii</i> pneumonia (PCP), toxoplasmosis, cryptococcosis, coccidioidomycosis, cryptosporidiosis**
< 50	* <i>Disseminated Mycobacterium avium complex (MAC), CMV retinitis, CNS lymphoma, disseminated histoplasmosis*</i>

- ▶ This graded relationship (Harrison Fig. 208-32; CMDT Fig. 36-1) is the basis for using the count to anticipate, prevent and empirically treat OIs.

CD4 thresholds for opportunistic-infection prophylaxis (start / stop)

Decisions on prophylaxis are based on CD4 count, recent viral load and prior OI history (NIH/CDC/IDSA guidelines):

Pathogen	Start primary prophylaxis	First-choice agent	Stop (immune reconstitution)
P. jirovecii (PCP)	CD4 <200/ μ L, CD4 <14%, oropharyngeal candidiasis, or prior PCP	TMP-SMX 1 DS tab daily	CD4 >200/ μ L for $\geq$ 3 months on ART
Toxoplasma gondii	Toxoplasma IgG-positive and CD4 <100/ μ L	TMP-SMX 1 DS tab daily	CD4 >200/ μ L + HIV RNA suppressed $\geq$ 3 months
M. avium complex	CD4 <50/ μ L <i>only if ART not initiated</i> (rarely needed now)	Azithromycin 1200 mg weekly	Once on fully suppressive ART
<i>Cryptococcus</i> / <i>CMV</i>	Secondary (post-disease) prophylaxis only	Fluconazole / valganciclovir	CD4 >100/ μ L for $\geq$ 6 months + suppression
<i>Histoplasma</i> (endemic)	Prior disease or CD4 <150/ μ L with high risk	Itraconazole 200 mg	CD4 >150/ μ L $\geq$ 6 months on ART

- ▶ **Key teaching point:** a single TMP-SMX DS tablet covers **both PCP and toxoplasmosis**, so the practical rule is — start co-trimoxazole when CD4 <200/ μ L and continue until immune reconstitution.
- ▶ Prophylaxis is *safely discontinued* once ART raises the CD4 above the starting threshold (and viral load is suppressed) — prophylaxis decisions are dynamic, driven by the **trend** of the CD4.

Role of CD4 in initiating and monitoring ART

- ▶ **When to start ART:** Current DHHS guidance recommends **ART for everyone with HIV, as soon as possible after diagnosis, regardless of CD4 count or viral load — the count no longer gates whether to treat, but still informs timing and urgency**.
- ▶ **Urgency by CD4:** With **advanced disease** (CD4 <50/ μ L) ART should be started as soon as possible. When an OI is diagnosed concurrently and CD4 $\geq$ 50/ μ L, a 2–4 week delay may be considered (treating the OI first) to reduce the severity of immune reconstitution inflammatory syndrome (IRIS) — relevant especially to TB and cryptococcal meningitis.
- ▶ **Expected response to ART:** a rapid $\geq$ 1-log (10-fold) fall in HIV RNA within 1–2 months, suppression to <50 copies/mL by ~6 months, and a CD4 rise of ~100–150 cells/ μ L over the same period.
- ▶ **Monitoring frequency** (CMDT Table 36-5): CD4 every 3–6 months; this can be reduced to **every 12 months** once viral load is suppressed on ART for 2 years with CD4 >300/ μ L, and routine CD4 monitoring becomes **optional/unnecessary** once CD4 is consistently >350–500/ μ L with sustained virologic suppression. Thereafter **viral load** is the chief monitoring tool.

- ▶ **IRIS** (Table 208-12): paradoxical worsening or unmasking of an OI weeks–months after starting ART; most common when ART is begun at $\text{CD4} < 50/\mu\text{L}$ with a precipitous drop in viral load, classically with TB.

Limitations and pitfalls of CD4 interpretation

- ▶ Subject to **diurnal variation**, transient depression with intercurrent illness or recent vaccination, and **inter-/intra-laboratory variability** — therefore the **trend matters more than a single value**.
- ▶ The **CD4 percentage** is more stable; $<14\% \approx \text{CD4} < 200/\mu\text{L}$, and a percentage of $\sim 15\% \approx 200$ cells/ μL .
- ▶ After **splenectomy** the absolute count is unreliable (artefactual lymphocytosis) — use the **CD4 percentage**.
- ▶ The CD4 count says nothing about viral replication; **viral load is the more accurate marker of activity and ART response**, providing prognostic information independent of the count.
- ▶ Patients immunised when CD4 was $<100/\mu\text{L}$ should be **re-immunised** once the count recovers to $>200/\mu\text{L}$ for an adequate response; live vaccines are avoided at $\text{CD4} < 200/\mu\text{L}$.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ “**CD4 staircase**” — **CD4 count vs opportunistic disease**: Draw a vertical CD4 axis (cells/ μL) marked at 500, 200, 50. Place labelled boxes at each level — >500 : herpes zoster, oral hairy leukoplakia, vaginal candidiasis, Kaposi sarcoma; <200 : PCP, toxoplasmosis, cryptococcosis, coccidioidomycosis, cryptosporidiosis; <50 : disseminated MAC, CMV retinitis, CNS lymphoma, histoplasmosis. Add a dashed line at 200 = “**AIDS / start PCP prophylaxis**.”
- ▶ **Natural-history curve**: time on X-axis; plot **falling CD4** against **rising/plateauing HIV RNA**, labels — *acute retroviral syndrome*, *clinical latency* (~ 10 yrs, *decline* $\sim 50/\mu\text{L}/\text{yr}$), *symptomatic/AIDS* ($<200/\mu\text{L}$).

Clinical / Diagnostic significance

- ▶ Establishes **stage and prognosis**, and identifies the patient who has progressed to **AIDS** even when asymptomatic.
- ▶ Directs **OI prophylaxis** (start and stop) and shapes the **empirical differential** when a person with HIV presents acutely (e.g., headache + $\text{CD4} < 100 \rightarrow$ think cryptococcal meningitis/CNS toxoplasmosis).
- ▶ Confirms **immune reconstitution** on ART (rising CD4) and flags risk of **IRIS** when baseline CD4 is very low.
- ▶ A baseline CD4 is part of the initial work-up alongside HIV RNA, genotypic resistance testing, CBC/chemistry, hepatitis and toxoplasma serology, and TB screening.

High-yield exam pointers

- ▶ AIDS = CD4 <200/ μ L (or <14%) OR an AIDS-defining illness in a person with HIV.
- ▶ CDC stages: 1 $\geq$ 500, 2 = 200–499, 3 <200 cells/ μ L.
- ▶ Untreated CD4 declines ~50 cells/ μ L per year; median time to AIDS ~10 years.
- ▶ PCP prophylaxis at <200, toxoplasmosis (IgG+) at <100, MAC at <50 (only if ART deferred) — TMP-SMX covers PCP *and* toxoplasma.
- ▶ Stop PCP prophylaxis when CD4 >200/ μ L for $\geq$ 3 months on ART.
- ▶ ART is for everyone regardless of CD4 — CD4 now guides *timing/urgency*, not eligibility; start ASAP if CD4 <50.
- ▶ Expect a CD4 rise of ~100–150/ μ L in the first months of effective ART.
- ▶ IRIS is most frequent when ART starts at CD4 <50/ μ L, classically with TB/cryptococcus.
- ▶ Use CD4 **percentage** ($\approx$ 15% = 200/ μ L) when the absolute count is unreliable (post-splenectomy, acute illness).
- ▶ **Trend > single value**; viral load, not CD4, is the marker of treatment response.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Human Immunodeficiency Virus Disease: AIDS and Related Disorders” (CDC CD4 staging Table 208-2; CD4–opportunistic-disease relationship; NIH/CDC/IDSA 2024 OI prophylaxis thresholds Table 208-11; DHHS principles of ART/when-to-start; IRIS characteristics Table 208-12).
- ▶ **CMDT 2026** — “HIV Infection & AIDS” (CD4 as prognostic/prophylaxis marker and its limitations; CD4–OI Figure 36-1; prophylaxis thresholds; health-care maintenance and CD4 monitoring frequency Table 36-5).



Scrub typhus

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Scrub typhus is an acute, mite-borne, febrile zoonosis caused by *Orientia tsutsugamushi*, an obligately intracellular gram-negative bacterium of the family **Rickettsiaceae**. It is transmitted to humans by the bite of larval **trombiculid mites (chiggers)** and is characterised pathologically by **endothelial-cell infection with increased vascular permeability (vasculitis)**. The classic clinical triad is an **eschar** at the chigger-bite site, **regional/generalised lymphadenopathy**, and a transient **maculopapular rash**, on a background of high fever. It is endemic across the “**tsutsugamushi triangle**” of Asia-Pacific (including India), is a leading cause of **acute undifferentiated febrile illness and fever of unknown origin**, and is highly responsive to **doxycycline**.

Etiology, vector and epidemiology

- **Organism:** *Orientia tsutsugamushi* (genus *Orientia*, family Rickettsiaceae). It differs substantially from *Rickettsia* species both **genetically** and in **cell-wall composition** — notably it **lacks lipopolysaccharide (LPS)** and has no peptidoglycan, hence its separation into a distinct genus. Related species *O. chuto* (south-western Asia) and *Candidatus O. chiloensis* (Chile) are emerging.
- **Vector & reservoir:** larval **trombiculid mites = chiggers** (*Leptotrombidium deliense* and others). The chigger is the **only stage that feeds on a host**; the mite is both vector and reservoir, the organism being maintained by **transovarial transmission**. Infected chiggers cluster in areas of **heavy scrub vegetation during the wet season**.
- **Antigenic diversity:** *O. tsutsugamushi* shows **remarkable antigenic diversity** (classically the *Karp*, *Gilliam* and *Kato* serotypes). Immunity to the **homologous strain wanes over 1–3 years**, and cross-protective immunity against heterologous strains may be lost in as little as **1 month** — hence reinfection is common (in some areas >3% of the population is infected/reinfected each month).
- **Geography:** endemic and **re-emerging** in eastern and southern Asia, northern Australia and islands of the western Pacific and Indian Oceans — the “**tsutsugamushi triangle**”. A major cause of acute febrile illness in **India and China**; more common in rural areas but increasingly urban, and now recognised in travellers.
- **Other transmission:** vertical (transplacental), **transfusion**, and **occupational/laboratory** exposures are documented.

Feature	Scrub typhus
Organism	<i>Orientia tsutsugamushi</i> (lacks LPS)
Vector	Larval trombiculid mite (chigger), e.g. <i>Leptotrombidium deliense</i>
Incubation period	6–21 days (≈1–3 weeks)
Pathognomonic sign	Eschar (tache noire) ± regional lymphadenopathy
Rash	Macular/maculopapular, trunk, day 4–8, fleeting
Drug of choice	Doxycycline (alt: azithromycin, chloramphenicol)
Untreated mortality	~6% (classic) up to 10–30% in severe series

Pathogenesis

- Chigger bite **inoculates organisms into the dermis**; *O. tsutsugamushi* spreads **lymphohaematogenously** and infects **vascular endothelial cells** (and macrophages).
- The central lesion is a **disseminated vasculitis / vasculitic perivasculitis** with **increased vascular permeability**, producing oedema, hypovolaemia, microvascular leak and multi-organ ischaemia — the same final common pathway shared by all rickettsioses.

- ▶ At the bite site, local vasculitis and necrosis produce the **eschar** (a black, crusted, painless ulcer with an erythematous halo); the draining nodes enlarge first (**regional lymphadenopathy**), reflecting initial lymphogenous spread.
- ▶ Severe disease reflects widespread endothelial injury → **interstitial pneumonitis/ARDS**, **myocarditis**, **meningoencephalitis**, **hepatitis**, **AKI** and, late, **haemophagocytosis**.

Clinical features

- ▶ **Onset**: after a 6–21-day (1–3 week) incubation, abrupt **high fever**, **severe headache**, **myalgia**, **malaise**, **chills**, **backache**, **cough** and **gastrointestinal symptoms** (nausea, vomiting, diarrhoea in nearly two-thirds — corresponding to mucosal erosions/haemorrhage).
- ▶ **Eschar (most useful sign)**: a papule at the bite site that ulcerates into a **black, painless, crusted eschar (tache noire)**, typically in moist/covered intertriginous skin. It is **highly suggestive but not always present** — recognised in only ~19% in a South Korean series, and in <50% of **returning travellers**; absence does not exclude the diagnosis.
- ▶ **Lymphadenopathy**: tender **regional** node enlargement near the eschar, sometimes becoming **generalised** — a helpful clue.
- ▶ **Rash**: **macular** → **maculopapular**, mainly on the **trunk**, appearing around **day 4–8**; it may be fleeting or absent (rash in <40%), peaking ~day 8 and occasionally lasting up to 21 days.
- ▶ **Relative bradycardia** (pulse–temperature dissociation) is characteristic.
- ▶ **Complications**: **pneumonitis/ARDS**, **myocarditis**, **meningoencephalitis** or **aseptic meningitis**, **acute kidney injury**, **hepatitis** and **haemophagocytic lymphohistiocytosis (HLH)**; ARDS or haemophagocytosis tends to develop in the **second–third week**. Infection confers **prolonged immunity against homologous strains** but only transient immunity against heterologous strains.

Investigations / Diagnosis

- ▶ **Supportive laboratory findings** (shared rickettsial signature): **thrombocytopenia**, **normal or low WBC count**, **elevated hepatic aminotransferases**, **hyperbilirubinaemia**, **raised creatinine**, **hyponatraemia**, **raised CRP**, and **hypoalbuminaemia**.
- ▶ **Serology (reference standard)**: **indirect immunofluorescence assay (IFA)** and **indirect immunoperoxidase assay** are the **gold standard** but are expensive and of limited availability; a fourfold rise in paired acute/convalescent titres is confirmatory. **ELISA** detecting *Orientia*-specific antibodies and **rapid lateral-flow chromatographic tests** are widely used point-of-care options.
- ▶ **PCR (most sensitive)**: amplification of *Orientia* genes is **most sensitive from the eschar** (eschar crust/swab), and can also be done on blood/buffy coat; best performed **before doxycycline** is started.
- ▶ **Culture**: possible from early blood but requires a **BSL-3 laboratory**; rarely used. **Combined ELISA + PCR** is recommended where available.

- ▶ ***Weil-Felix test** (*Proteus OX-K agglutination*) is the classic cheap field test for scrub typhus but is insensitive and non-specific*, and is now largely superseded by IFA/ELISA/PCR.

Differential diagnosis

- ▶ The major mimics of acute undifferentiated tropical fever: **dengue, malaria, leptospirosis, enteric (typhoid) fever, Q fever, viral haemorrhagic fevers, other rickettsioses, and meningitis**. Co-infection (e.g. with malaria) can occur.
- ▶ Discriminators favouring scrub typhus: **an eschar, lymphadenopathy, relative bradycardia, lymphocytosis and elevated CRP** (the last three help distinguish it from dengue). In endemic regions it is a recognised cause of **obscure fever / FUO, especially in children**.

Treatment

- ▶ **Drug of choice: doxycycline 100 mg orally twice daily** — produces rapid defervescence (often within 48 h, a near-diagnostic therapeutic response). **Minocycline 100 mg BID** is an equivalent tetracycline.
- ▶ **Duration:** continue for at least **3 days after the patient is afebrile** (regimens of **7–15 days**); **short courses risk relapse**.
- ▶ **Severe disease:** the INTREST trial (Varghese et al., *NEJM* 2023) found **no difference** between IV doxycycline and IV azithromycin monotherapy, but **combination doxycycline + azithromycin** lowered 28-day mortality, day-7 complications and day-5 persistent fever — combination is preferred in severe/complicated cases.
- ▶ **Alternatives / special groups:** **azithromycin 500 mg/day for 3 days** (similar efficacy, fewer adverse effects) and **chloramphenicol 500 mg QID** — both are the agents of choice in **pregnancy** and in **doxycycline allergy/intolerance**. Some Thai strains are relatively doxycycline/chloramphenicol-resistant and respond to **azithromycin + rifampicin**.
- ▶ **Supportive care:** ICU support for ARDS (ventilation), myocarditis, AKI (renal replacement) and shock as needed.

Setting	Regimen
Uncomplicated (DOC)	Doxycycline 100 mg PO BID (or minocycline 100 mg BID); ≥3 days after afebrile (7–15 days)
Severe / complicated	IV doxycycline + IV azithromycin combination (INTREST trial)
Pregnancy / doxy allergy	Azithromycin 500 mg/day ×3 or chloramphenicol 500 mg QID
Doxy/chloramphenicol-poor response (Thailand)	Azithromycin + rifampicin

Prevention: there is **no effective vaccine** (antigenic diversity limits vaccine development). Personal protection — **insect repellents on skin and clothing, protective clothing, avoidance of scrub**

vegetation — is key; routine antibiotic chemoprophylaxis is NOT recommended for asymptomatic travellers (CDC).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — The eschar with regional lymphadenopathy:** draw a limb/trunk with a central **black crusted eschar** surrounded by an **erythematous halo**, an arrow to the draining **enlarged regional lymph node**, and a faint **macular rash over the trunk**. Labels: *Eschar (tache noire)*, *Erythematous halo*, *Regional lymphadenopathy*, *Truncal maculopapular rash*, *Chigger bite site*.
- ▶ **Diagram 2 — Transmission cycle:** *Trombiculid mite (Leptotrombidium)* → **larval chigger bites human** → *Orientia tsutsugamushi* inoculated into skin → **endothelial infection** → **vasculitis** → systemic disease; with a side loop showing **transovarial transmission** keeping the mite as both vector and reservoir. Labels: *Chigger (larva)*, *Orientia tsutsugamushi*, *Transovarial transmission*, *Human (incidental host)*, *Endothelial vasculitis*.

Clinical / Diagnostic significance

- ▶ A leading, **treatable** cause of **acute undifferentiated febrile illness**, **FUO** and **sepsis** in the Asia-Pacific — empirical **doxycycline** should be started promptly on clinical/epidemiological suspicion without waiting for serology.
- ▶ **Always search for the eschar** in skin folds (axilla, groin, neck, genitalia, under breasts) — it is the single most useful diagnostic clue and is easily missed.
- ▶ **Eschar + thrombocytopenia + transaminitis + relative bradycardia** in a patient from an endemic area is a near-classic combination.
- ▶ **Untreated mortality** is significant (~6% classic; **10–30%** in severe hospitalised series). **Poor prognostic markers:** hypotension/vasopressor need, ICU admission, **age >60 years**, **absence of an eschar** (delays diagnosis), pregnancy, **leukocytosis** and **hypoalbuminaemia**.
- ▶ A **rapid response to doxycycline** (**defervescence in ~48 h**) is itself a useful diagnostic/therapeutic confirmation.

High-yield exam pointers

- ▶ Causative organism: ***Orientia tsutsugamushi** — *a Rickettsiaceae that lacks LPS, separating it from genus Rickettsia**.
- ▶ Vector = **larval trombiculid mite (chigger)**, *Leptotrombidium deliense*; reservoir maintained by **transovarial transmission**.
- ▶ Endemic area = “**tsutsugamushi triangle**”; incubation **6–21 days**.
- ▶ **Classic triad:** **eschar (tache noire) + regional lymphadenopathy + truncal maculopapular rash**, with **relative bradycardia**.

- ▶ Eschar present in only ~19–50% of cases — its absence does not exclude the disease.
- ▶ PCR of the eschar = most sensitive; IFA / indirect immunoperoxidase = gold-standard serology; Weil-Felix OX-K is the classic but insensitive test.
- ▶ Labs: thrombocytopenia, transaminitis, hyponatraemia, normal/low WBC.
- ▶ Doxycycline 100 mg BID is the drug of choice; doxycycline + azithromycin combination for severe disease (INTREST trial); azithromycin/chloramphenicol in pregnancy.
- ▶ Serious complications: ARDS/pneumonitis, myocarditis, meningoencephalitis, AKI, HLH.
- ▶ No vaccine; prevention is by mite-bite avoidance.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Rickettsial Diseases" (general rickettsial pathophysiology; *Scrub Typhus* section — *Orientia tsutsugamushi*, chigger/trombiculid biology, epidemiology, clinical features, eschar, diagnosis and treatment regimens including doxycycline + azithromycin combination).
- ▶ CDMT 2026 — "Viral & Rickettsial Infections" (Scrub Typhus: essentials of diagnosis, tsutsugamushi triangle, relative bradycardia, eschar frequency [~19%], laboratory findings, IFA/ELISA/PCR, differential diagnosis, prognosis/poor-prognostic factors, treatment including the INTREST trial, doxycycline/minocycline/azithromycin/chloramphenicol).
- ▶ Coverage note: The corpus emphasises IFA/indirect immunoperoxidase and PCR; it does not explicitly detail the Weil-Felix (*Proteus* OX-K) test or name the Karp/Gilliam/Kato serotypes — these are included here as universally accepted standard internal-medicine teaching and flagged accordingly. Numeric epidemiological values in Harrison's Table 192-1 were partly garbled in the text extract; figures quoted here are taken from the verified narrative text (incubation 6–21 days, untreated case-fatality ~6%).



Seroconversion Illness in HIV (Acute Retroviral Syndrome)

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — *Seroconversion illness* (the **acute retroviral syndrome** / **acute HIV syndrome** / **primary HIV infection**) is the symptomatic, self-limiting acute viral illness that appears in the interval between acquisition of HIV and the appearance of detectable anti-HIV antibody. It develops ~3–6 weeks after primary infection in an estimated 50–70% of newly infected individuals, coincides with the burst of high-level plasma viremia and wide dissemination/seeding of lymphoid tissue, and clinically resembles **acute infectious mononucleosis**. Recognising it is a high-stakes opportunity: the patient is intensely infectious, standard antibody tests may still be negative, and early diagnosis permits immediate antiretroviral therapy (ART).

Pathogenesis & timing (why the illness occurs)

- ▶ After mucosal/parenteral entry there is a brief “eclipse” phase (virus replicating locally, not yet detectable in plasma); virus is then carried to draining lymph nodes and other lymphoid compartments rich in CD4+ T-cell targets, producing a **burst of high-level plasma viremia**.
- ▶ The symptomatic illness coincides with this **peak viremia** and the seeding of lymphoid organs; symptoms subside as the **HIV-specific immune response** (CD8+ CTL, then antibody/ADCC) develops and viremia is curtailed toward the viral “set-point.”
- ▶ **Immunologic perturbations:** initial fall in total lymphocytes and both CD4+ and CD8+ subsets; later a **transient selective expansion of CD8+ T cells** producing **inversion of the CD4:CD8 ratio**. CD4+ counts usually remain mildly depressed afterward.
- ▶ The magnitude of the initial viremic burst does **not** reliably correlate with subsequent rate of disease progression; however, ~10% of patients manifest a **fulminant** immunologic/clinical course after primary infection.
- ▶ **Opportunistic infections can occur even during this acute phase**, reflecting the transient profound immunodeficiency at peak viremia.
- ▶ Symptomatic seroconversion severe enough to seek medical attention has been **suggested to indicate increased risk of an accelerated course**, though this remains debated; primary infection (with or without an acute syndrome) is typically followed by **clinical latency / smouldering low-level disease activity**.

Clinical features

The picture is that of a non-specific acute viral syndrome (“mononucleosis-like”), typically lasting **one to several weeks** and resolving spontaneously. *Clinical findings in the acute HIV syndrome (Harrison Table 208-10):*

System	Manifestations
General	Fever, pharyngitis, lymphadenopathy (~70%), headache/retro-orbital pain, arthralgia/myalgia, lethargy/malaise, anorexia, weight loss
Dermatologic	Erythematous maculopapular rash (face/trunk), mucocutaneous ulceration (oral, anal, genital)
Gastrointestinal	Nausea, vomiting, diarrhoea
Neurologic	Aseptic meningitis , encephalitis , peripheral neuropathy, myelopathy, Guillain-Barré-like illness

- ▶ The combination of **fever + pharyngitis + generalised lymphadenopathy + maculopapular rash + painful mucocutaneous (oral/genital) ulcers** is the most suggestive cluster and distinguishes it from EBV/CMV mononucleosis (in which ulcers and rash without ampicillin are uncommon).

- ▶ Fever, rash, pharyngitis and myalgia are reported **less frequently in those infected by injection drug use** than by sexual contact.
- ▶ Most recover spontaneously, often left with only a mildly depressed CD4+ count; the illness is then followed by a prolonged **clinical latency** (median time to AIDS ~10 years untreated; average CD4 decline ~50/ μ L per year).

Laboratory diagnosis — the window period & marker kinetics

The central diagnostic problem is that **antibodies appear only ~3–12 weeks after infection**, so antibody-only tests may be falsely negative during seroconversion. Markers become detectable in a characteristic order:

Marker	Approx. time to detectability	Diagnostic role
HIV-1 RNA (NAT / viral load)	Earliest ($\approx$ 10 days; after the eclipse phase)	Confirms acute infection when antibody is negative
p24 antigen	Days–~2 weeks (before antibody)	Component of the 4th-generation combo assay
Anti-HIV antibody	~3–12 weeks (4th-gen detects in 99% by ~6 weeks; median ~2 weeks)	Basis of screening/confirmatory assays

- ▶ **Fiebig staging** describes the evolution of acute infection from **stage I (HIV RNA positive alone)** through to **stage VI (HIV RNA + full Western blot positive)**, charting the sequential appearance of RNA $\rightarrow$ p24 $\rightarrow$ antibody bands.
- ▶ **Recommended initial test:** a **fourth-generation HIV-1/2 antigen/antibody combination immunoassay** (detects HIV-1 & HIV-2 antibody **plus p24 antigen**) — narrows the window versus older antibody-only EIA.
- ▶ **CDC testing algorithm:** reactive 4th-gen combo $\rightarrow$ **HIV-1/HIV-2 antibody differentiation immunoassay** (e.g., *Bio-Rad Geenius*). If the differentiation assay is **negative or indeterminate but a NAT (HIV-1 RNA) is positive** $\rightarrow$ **diagnosis of acute HIV-1 infection**. A combo-reactive specimen with repeatedly negative differentiation and **undetectable NAT** is presumed **false-positive** (e.g., recent influenza vaccination, autoantibodies, pregnancy-related alloantibodies).
- ▶ **Caveat:** low-level viremia **<1000 copies/mL** on NAT may be a false positive — interpret cautiously.
- ▶ The screening EIA is highly sensitive (**>99.5%**) but imperfectly specific in low-risk populations, so a reactive screen **always** needs a more specific confirmatory step before a diagnosis is given. The older stand-alone **Western blot** has been superseded in the algorithm by the antibody **differentiation assay plus NAT**.

- ▶ **Supportive non-specific findings:** lymphopenia (and other cytopenias), transient atypical lymphocytosis, raised transaminases/ESR — reinforcing the mononucleosis-like character.

Differential diagnosis

- ▶ Epstein–Barr virus and CMV infectious mononucleosis; **acute toxoplasmosis**; **acute viral hepatitis**; **secondary syphilis**; **rubella/measles/parvovirus/enteroviral exanthems**; **streptococcal pharyngitis**; **acute aseptic meningitis** of other viral cause; and drug reactions.
- ▶ A high index of suspicion plus a careful sexual/exposure history is essential, because the antibody screen may still be negative — *a negative antibody test does not exclude acute HIV*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Natural history curve (Pantaleo–Fauci graph):** X-axis = time (weeks → years); left Y-axis = CD4+ T-cell count (cells/ μ L), right Y-axis = HIV RNA copies/mL. Label: *Primary infection* → *Acute HIV syndrome (wide dissemination of virus; seeding of lymphoid organs)* with **peak plasma viremia** and **CD4 nadir**, then **partial CD4 rebound + fall of viremia to set-point**, *Clinical latency*, *Constitutional symptoms*, *Opportunistic diseases*, *Death*.
- ▶ **Diagnostic window / marker-kinetics timeline:** X-axis = days–weeks from infection; plot sequential appearance of HIV RNA → **p24 antigen** → **anti-HIV antibody**, mark the **eclipse phase** and **window period**, and annotate **Fiebig stages I–VI**.

Clinical / Diagnostic significance

- ▶ **Extreme transmissibility:** peak plasma (and genital) viral load during seroconversion makes onward transmission highly efficient — a key driver of epidemic spread; diagnosis enables counselling, partner notification and **treatment-as-prevention (U=U)**.
- ▶ **Treat immediately:** current guidance is to **start ART as soon as possible in everyone, including acute HIV infection, regardless of CD4 count** — rationale includes earlier viral suppression, blunting immune damage from the outset, limiting seeding of the latent reservoir, and reducing transmission.
- ▶ Obtain baseline **CD4 count**, **plasma HIV RNA (viral load)**, **genotypic resistance testing**, and screen for co-infections (**RPR/VDRL**, **hepatitis B and C**, **other STIs**) before/at ART initiation.
- ▶ Distinguish from **post-exposure prophylaxis (PEP)** scenarios: a person presenting with acute retroviral syndrome already has established infection (treat as such), not a candidate for PEP.
- ▶ Pitfall to avoid in exams and wards: **do not rely on a single antibody EIA** in a recently exposed symptomatic patient — add **p24/NAT**.

High-yield exam pointers

- ▶ Synonyms: **acute retroviral syndrome** = **acute HIV syndrome** = **primary HIV infection** = **seroconversion illness**.

- ▶ Occurs in ~50–70% of infections, ~3–6 weeks post-exposure; lasts 1 to several weeks; mononucleosis-like.
- ▶ Classic cluster: fever + pharyngitis + lymphadenopathy (~70%) + maculopapular rash + painful muco-cutaneous (oral/genital) ulcers; may include aseptic meningitis.
- ▶ Window period: antibodies appear ~3–12 weeks; HIV RNA is the earliest marker, then p24 antigen, then antibody.
- ▶ First-line test = 4th-generation Ag/Ab combo immunoassay (Ab + p24); confirm with HIV-1/2 differentiation assay; antibody-negative + NAT-positive = acute HIV.
- ▶ Fiebig stages I–VI track RNA → p24 → Western-blot positivity.
- ▶ Immunology: transient CD4 fall, CD8 expansion, CD4:CD8 inversion; ~10% have a fulminant course.
- ▶ Management = start ART immediately regardless of CD4; baseline CD4, viral load, resistance genotype, STI/hepatitis screen.
- ▶ A negative HIV antibody test does NOT exclude acute infection — pursue p24/NAT if clinically suspected.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Human Immunodeficiency Virus Disease: AIDS and Related Disorders" (Acute HIV Infection; Clinical Manifestations; Table 208-10 *Clinical Findings in the Acute HIV Syndrome*; Fig. 208-33 *The Acute HIV Syndrome*; Laboratory Diagnosis — 4th-generation EIA, p24 antigen, NAT, CDC algorithm Fig. 208-31).
- ▶ CDMT 2026 — "HIV Infection & AIDS" (laboratory testing algorithm and window-period kinetics, Table 36-2; recommendation to start ART in all, including acute infection).



Systemic Protozoal Infections

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Protozoa are microscopic single-celled eukaryotic parasites. *Systemic* (blood-and-tissue) protozoa are those that invade the bloodstream and deep organs rather than remaining confined to the gut lumen, producing disseminated, often life-threatening disease. Their defining feature is the capacity (like bacteria) to **multiply within the human host** and to evade immunity either by **antigenic variation** (*Trypanosoma brucei*) or by **intracellular survival** (*Plasmodium*, *Babesia*, *Leishmania*, *Toxoplasma*, *Trypanosoma cruzi*). A naïve patient suffering a first infection is usually the most severely affected, because partial immunity later limits parasite numbers; immunocompromised hosts (especially PLWH) are prone to dissemination, and several of these infections are **AIDS-defining**.

Classification of systemic (blood & tissue) protozoa

Organism	Disease	Vector / mode	Key target / hallmark
<i>Plasmodium</i> (6 species; esp. <i>P. falciparum</i>)	Malaria	Female <i>Anopheles</i> mosquito	Erythrocytes; cyclical fever, cerebral malaria
<i>Babesia</i>	Babesiosis	<i>Ixodid</i> (hard) ticks	Erythrocytes; severe in asplenia
<i>Trypanosoma cruzi</i>	Chagas disease	Reduviid (triatomine) bug faeces	Cardiomyopathy, megaesophagus/megacolon
<i>T. brucei gambiense</i> / <i>rhodesiense</i>	African trypanosomiasis (sleeping sickness)	Tsetse fly (<i>Glossina</i>)	Chancre, CNS invasion
<i>Leishmania</i> (>20 species)	Visceral / cutaneous / mucocutaneous leishmaniasis	Sandfly (<i>Phlebotomus</i>)	Intracellular amastigotes in macrophages
<i>Toxoplasma gondii</i>	Toxoplasmosis	Cat-faeces oocysts, tissue cysts, transplacental	Brain (ring-enhancing lesions), eye, fetus
<i>Naegleria</i> , <i>Acanthamoeba</i> , <i>Balamuthia</i>	Amebic meningoencephalitis	Free-living, fresh/brackish water, soil	CNS — almost universally fatal

- ▶ Three immune-evasion mechanisms underpin systemic spread: **antigenic variation**, **intracellular sequestration**, and **endothelial cytoadherence** (*P. falciparum*).
- ▶ Immunocompromise predisposes to disseminated infection with *Leishmania*, *Toxoplasma*, *Cryptosporidium* and *T. cruzi*.

Malaria (*Plasmodium*)

- ▶ Six *Plasmodium* species infect humans; the classically described are ***P. falciparum***, ***P. vivax***, ***P. ovale***, ***P. malariae*** and the zoonotic ***P. knowlesi***. *P. falciparum* dominates sub-Saharan Africa, causing >80% of infections and ~90% of malarial deaths.
- ▶ *P. falciparum* is uniquely dangerous because it **invades erythrocytes of all ages** (very high parasitaemia), **cytoadheres to vascular endothelium** (sequestration → organ damage), and is most prone to **drug resistance**. *P. vivax/ovale* invade only reticulocytes (lower parasitaemia) and form dormant liver **hypnozoites** causing relapse.

Feature	<i>P. falciparum</i>	<i>P. vivax</i> / <i>ovale</i>
RBC preference	All ages	Reticulocytes (<i>vivax</i> needs Duffy antigen)
Parasitaemia	Very high	Low (seldom >2%)

Feature	<i>P. falciparum</i>	<i>P. vivax</i> / <i>ovale</i>
Relapse (hypnozoite)	No	Yes — needs primaquine
Severe disease	Common	Uncommon

- ▶ **Severe falciparum malaria** (Table 231-2): cerebral malaria (unarousable coma >30 min post-convulsion, GCS <11), severe anaemia (Hb <5 g/dL), acidosis (lactate ≥5 mmol/L, “respiratory distress”), acute kidney injury (creatinine >265 μmol/L), noncardiogenic pulmonary oedema/ARDS, hypoglycaemia (<2.2 mmol/L; aggravated by quinine), shock, DIC/bleeding, **blackwater fever** (massive haemoglobinuria), and **hyperparasitaemia** (>5% in nonimmune, >10% in any patient).
- ▶ **Diagnosis:** Giemsa-stained **thick and thin blood films** remain the gold standard — thick film is sensitive (detects ~0.001% parasitaemia) and quantifies the parasite count, thin film allows species identification. **Rapid antigen tests** (PfHRP2-based dipsticks) are simple and sensitive but do not quantify parasitaemia and can be missed by *pfhrp2* deletions.
- ▶ **Treatment:** Uncomplicated falciparum malaria → an oral **artemisinin-based combination therapy (ACT)** (artemisinin derivative + a longer-acting partner drug). *P. vivax/ovale/malariae* and *P. knowlesi* → chloroquine (or ACT) plus, for vivax/ovale, **primaquine** for radical cure of liver hypnozoites (screen for G6PD deficiency first).
- ▶ **Severe malaria** → immediate parenteral **artesunate 2.4 mg/kg IV stat, repeated at 12 h and 24 h, then daily**; IV artesunate reduced mortality by ~22.5% versus quinine in African children. *Pfkelch13* mutations confer artemisinin resistance (SE Asia, now East Africa).

Leishmaniasis

- ▶ Caused by >20 species of **obligate intracellular** *Leishmania*, transmitted by sandflies; the parasite lives as non-flagellate **amastigotes** inside macrophages and as flagellate promastigotes in the vector. Three clinical syndromes: **visceral (VL)**, **cutaneous (CL)** and **mucocutaneous/mucosal (ML)**.
- ▶ **Visceral leishmaniasis (kala-azar, “black fever”)**: an AIDS-defining illness; presents with prolonged fever, **massive splenomegaly** (the cardinal feature), hepatomegaly, lymphadenopathy, weight loss, darkening of skin and hypergammaglobulinaemia/pancytopenia. >90% of global VL occurs in **India, Bangladesh, Sudan, Ethiopia and Brazil**.
- ▶ **Diagnosis:** demonstration of amastigotes in **splenic, bone-marrow or lymph-node aspirate smears**; serology with the **rK39** antigen (rapid point-of-care test, though it stays positive for years after cure).
- ▶ **Treatment:** **Pentavalent antimony** (sodium stibogluconate / meglumine antimoniate) remains the drug of choice in most regions, **but antimony resistance is widespread in Bihar (India)**, where **liposomal/deoxycholate amphotericin B** or oral **miltefosine** (the first effective oral

antileishmanial; teratogenic) is preferred. Combination regimens (e.g., single-dose liposomal amphotericin B followed by miltefosine or paromomycin) are used.

- ▶ **Post-kala-azar dermal leishmaniasis (PKDL)** follows VL on the Indian subcontinent as nodular/macular skin infiltration and is a parasite reservoir. **Mucocutaneous (espundia)** disease (New World *L. (Viannia) braziliensis*) destroys the nasal septum and palate and does not heal spontaneously.

Toxoplasmosis

- ▶ *Toxoplasma gondii* is an **obligate intracellular** parasite acquired by ingesting **oocysts** (cat faeces-contaminated food/water), **tissue cysts** (undercooked meat) or **transplacentally**. **Tachyzoites** cause acute, invasive disease; latent **bradyzoite tissue cysts** persist lifelong, predominantly in the CNS.
- ▶ **Immunocompetent host:** usually asymptomatic, or a self-limited infectious-mononucleosis-like illness; ocular disease (chorioretinitis) may occur.
- ▶ **Immunocompromised host (AIDS, transplant):** reactivation of latent cysts produces **toxoplasmic encephalitis** — multiple **ring-enhancing lesions** on contrast CT/MRI (the leading cause of focal brain lesions in advanced HIV); fatal unless treated.
- ▶ **Congenital toxoplasmosis:** from primary maternal infection; severity is greatest with early-gestation infection (visual, hearing and cognitive impairment), while late-infected infants may appear normal but develop **chorioretinitis** decades later.
- ▶ **Treatment:** **pyrimethamine + sulfadiazine + leucovorin (folinic acid)** is first-line for toxoplasmic encephalitis (typically ≥ 6 weeks); **clindamycin** substitutes for sulfadiazine (or TMP-SMX when pyrimethamine is unavailable). In pregnancy, **spiramycin** is used to prevent transmission before 18 weeks; pyrimethamine/sulfadiazine/folinic acid is used after seroconversion later in pregnancy.

Other systemic protozoa — trypanosomiasis, babesiosis, free-living amebae

- ▶ **Chagas disease (T. cruzi): transmitted in reduviid-bug faeces in Latin America; also via transfusion, transplantation and mother-to-child. After acute parasitaemia, the parasite multiplies intracellularly (amastigotes) in muscle and ganglion cells; a minority later develop chronic cardiomyopathy and megaoesophagus/megacolon*.*
- ▶ **African trypanosomiasis (sleeping sickness):** tsetse-fly-borne; a painful **chancre** at the bite is a clue. **T. b. gambiense** (West/Central Africa) causes chronic low-grade parasitaemia with late CNS invasion over months–years; **T. b. rhodesiense** (East Africa) causes high parasitaemia with early CNS invasion and death within weeks. Antigenic variation drives recurrent waves of parasitaemia.

- ▶ **Babesiosis:** *Babesia* infects erythrocytes (ixodid-tick borne, NE/Midwest USA); ranges from a nonspecific febrile illness to severe haemolytic disease in **asplenic** patients. Standard therapy is **atovaquone plus azithromycin**.
- ▶ **Free-living amebic CNS infection:** *Naegleria fowleri* (warm fresh water/hot springs) causes fulminant, usually fatal **primary amebic meningoencephalitis (PAM)** — pyogenic-looking CSF with motile trophozoites; *Acanthamoeba* and *Balamuthia mandrillaris* cause indolent **granulomatous amebic encephalitis (GAE)** with a space-occupying lesion, chiefly in the immunocompromised; *Acanthamoeba* also causes **keratitis** (corneal trauma, contact-lens wearers). **Miltefosine**-containing combinations are recommended despite a poor prognosis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Plasmodium life cycle (mosquito–human):** label *sporozoites*, *hepatocyte (exo-erythrocytic schizont / hypnozoite)*, *merozoites*, *ring trophozoite*, *schizont*, *gametocytes*, *female Anopheles mosquito*.
- ▶ **Classification flow-box “Systemic protozoa”:** two columns — *Blood protozoa* (*Plasmodium*, *Babesia*, *Trypanosoma*) and *Tissue protozoa* (*Leishmania*, *Toxoplasma*, free-living amebae) — each labelled with vector and target organ.

Clinical / Diagnostic significance

- ▶ **Travel/exposure history is pivotal:** malaria must be the first consideration in any febrile returned traveller or immigrant from an endemic area; locally acquired malaria has re-emerged in parts of the USA.
- ▶ **Microscopy of stained blood/aspirate smears** is the unifying diagnostic tool (malaria — thick/thin films; VL — splenic/marrow amastigotes; African trypanosomiasis — bloodstream trypomastigotes).
- ▶ **Imaging:** contrast CT/MRI for toxoplasmic encephalitis (multiple ring-enhancing lesions) and amebic GAE (space-occupying lesion).
- ▶ **Asplenia and HIV/immunosuppression** convert several of these from mild to fulminant or AIDS-defining infections — a key management pearl.
- ▶ Severe falciparum malaria is a **medical emergency** requiring parenteral artesunate, glucose monitoring (hypoglycaemia), and watch for concomitant bacteraemia at high parasitaemia.

High-yield exam pointers

- ▶ Systemic protozoa **multiply within the host** and evade immunity by **antigenic variation** (*T. brucei*) or **intracellular survival** (*Plasmodium*, *Leishmania*, *Toxoplasma*).
- ▶ *P. falciparum* = highest mortality; invades all RBCs, cytoadherence/sequestration → **cerebral malaria**, **blackwater fever**, **ARDS**, **AKI**, **hypoglycaemia**.

- ▶ Severe malaria → IV artesunate 2.4 mg/kg at 0, 12, 24 h then daily; vivax/ovale relapse → primaquine (check G6PD).
- ▶ VL = kala-azar; cardinal sign massive splenomegaly; dx by rK39 + splenic/marrow amastigotes; antimony resistant in Bihar → amphotericin B / miltefosine.
- ▶ Toxoplasmic encephalitis = commonest cause of ring-enhancing brain lesions in AIDS; Rx pyrimethamine + sulfadiazine + folinic acid; spiramycin in early pregnancy.
- ▶ Chagas (reduviid bug) → cardiomyopathy + megaesophagus; African sleeping sickness (tsetse fly) → chancre + CNS disease.
- ▶ Naegleria → fatal PAM (warm freshwater); Acanthamoeba/Balamuthia → GAE + keratitis.
- ▶ AIDS-defining systemic protozoa: *visceral leishmaniasis, toxoplasmosis, cryptosporidiosis, disseminated T. cruzi***.

SOURCE & COVERAGE

Harrison 22e — Ch 228 “Introduction to Parasitic Infections” (primary); supplemented by Ch 230 “Amebiasis and Infection with Free-Living Amebae”, Ch 231 “Malaria”, Ch 233 “Leishmaniasis”, and Ch 235 “Toxoplasma Infections”. **Coverage note:** Ch 234 (Trypanosomiasis) text was not provided; the Chagas and African-trypanosomiasis content above is grounded in the Ch 228 overview only — specific antitrypanosomal drug regimens (e.g., benznidazole/nifurtimox, suramin/pentamidine/melarsoprol/eflornithine/fexinidazole) are standard textbook therapy but were not verifiable against the supplied chapters and are therefore omitted from the drug tables. The “six *Plasmodium* species” figure is from Ch 228; Ch 231 tabulates the five classical species (with *P. ovale* now split into two subspecies).



Tabulate the pathogens involved in viral encephalitis in India, the characteristic presentation of each infection and the management for each

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Encephalitis is inflammation of the brain *parenchyma* caused most often by a virus (occasionally by a primary autoimmune process), and is distinguished from meningitis by the presence of altered consciousness, behavioural change, focal neurological deficits and/or seizures. When the meninges are co-involved the term *meningoencephalitis* is used. In India the aetiologic spectrum is distinctive: **herpes simplex virus** dominates sporadic adult cases, while **Japanese encephalitis virus** is the single largest cause of epidemic encephalitis, and several India-relevant emerging agents (**Nipah**, **Chandipura**, **dengue**, **chikungunya**, **West Nile**, **Kyasanur Forest disease**) round out the picture. The

clinical importance lies in separating the *one treatable cause* (HSV) from the many supportively-managed arboviruses, since empirical acyclovir saves lives.

Aetiologic framework relevant to India

- ▶ **Sporadic, year-round, all ages:** herpesviruses — HSV-1 (commonest sporadic cause), VZV, EBV, CMV (immunocompromised).
- ▶ **Epidemic / seasonal arboviral (monsoon & post-monsoon):** Japanese encephalitis virus (JEV), West Nile virus (WNV), dengue (DENV 1–4), chikungunya virus (CHIKV) — all mosquito-borne.
- ▶ **Emerging zoonotic / regional outbreaks:** Nipah virus (Kerala, West Bengal), Chandipura virus (central/western India, paediatric), Kyasanur Forest disease virus (Karnataka, tick-borne).
- ▶ **Post-infectious / chronic:** measles → subacute sclerosing panencephalitis (SSPE); rubella → progressive rubella panencephalitis.
- ▶ **Other neurotropic:** rabies virus (encephalitic/paralytic), enteroviruses (EV-A71, EV-D68 → acute flaccid myelitis).

Tabulation — pathogen, vector/reservoir, characteristic presentation and management

Pathogen (family)	Vector / reservoir / epidemiology in India	Characteristic clinical presentation	Diagnosis	Management
Herpes simplex virus-1 (Herpesviridae)	None — sporadic, all seasons; commonest cause of sporadic fatal encephalitis	Acute febrile illness with <i>inferomedial frontotemporal</i> signs — olfactory/gustatory hallucinations, anosmia, bizarre behaviour, memory loss, aphasia, focal seizures	CSF lymphocytic pleocytosis ± RBCs; CSF HSV PCR (sens ~96%, spec ~99%); MRI T2/FLAIR temporal-lobe signal; EEG periodic temporal sharp-slow complexes (2–3 s)	IV acyclovir 10 mg/kg q8h × 21 days (neonates 20 mg/kg q8h); start empirically in all suspected viral encephalitis
Japanese encephalitis virus (Flaviviridae)	<i>Culex tritaeniorhynchus</i> mosquito; amplifiers = pigs + ardeid wading birds (herons); rice-field belt; monsoon/post-monsoon; children mainly	Largely subclinical; ~1% develop encephalitis — high fever, reduced sensorium, <i>parkinsonian/dystonic movement disorder</i> , seizures, acute flaccid paralysis; CFR ~20–30%	CSF lymphocytic pleocytosis; anti-JEV IgM (MAC-ELISA) in CSF/serum; MRI <i>thalamic</i> , substantia nigra & basal-ganglia lesions	Supportive (ICP, seizures, ventilation); no specific antiviral ; vaccine-preventable (SA14-14-2 live-attenuated;

Pathogen (family)	Vector / reservoir / epidemiology in India	Characteristic clinical presentation	Diagnosis	Management
				inactivated Vero/IXIARO)
Nipah virus (Paramyxoviridae, <i>Henipavirus</i>)	<i>Pteropus</i> fruit bats; date-palm sap, pig intermediate host; person-to-person & nosocomial spread; Kerala/W. Bengal outbreaks	Influenza-like prodrome → rapidly progressive encephalitis with reduced consciousness, brainstem signs, segmental myoclonus, dystonia; respiratory illness; CFR 67–92%; late relapse (3.4–7.5%)	ELISA (serum & CSF) and RT-PCR of urine/respiratory secretions (not blood)	Supportive; ribavirin used (unproven); strict barrier/contact-droplet isolation; outbreak containment
Chandipura virus (Rhabdoviridae)	Sandflies & mosquitoes; reservoir hedgehogs; central/western India; children; recurrent outbreaks	Rapid influenza-like onset (fever, vomiting, abdominal pain) → altered sensorium & seizures within hours; CFR ~45–80%; <i>virus/cells often NOT detectable in CSF</i>	RT-PCR/serology; CSF typically bland	Supportive intensive care only; high early mortality
Dengue virus 1–4 (Flaviviridae)	<i>Aedes aegypti</i> ; hyperendemic across India	Usually “break-bone fever”; neurological forms = dengue encephalopathy/encephalitis, reduced sensorium, seizures (often with thrombocytopenia, plasma leak)	NS1 antigen / RT-PCR (acute); IgM ELISA (convalescent); leukopenia, thrombocytopenia, raised AST	Supportive fluid management; avoid aspirin/NSAIDs (bleeding); no specific antiviral
Chikungunya virus (Togaviridae, <i>Alphavirus</i>)	<i>Aedes aegypti</i> / <i>Ae. albopictus</i>	Fever with severe migratory small-joint polyarthritides & rash; uncommon neuroinvasive disease (meningoencephalitis), esp. neonates/elderly	RT-PCR (acute) / IgM serology	Paracetamol + NSAIDs for arthralgia; supportive; FDA-approved live-attenuated vaccine exists
West Nile virus (Flaviviridae)	<i>Culex</i> mosquitoes; birds reservoir	Mostly subclinical; <1% neuroinvasive — encephalitis, meningitis, <i>poliomyelitis-like acute flaccid paralysis</i> , movement disorders	CSF WNV IgM (best test; reaches 70–80% by day 7); MRI thalamus/basal ganglia/brainstem	Supportive only; no proven antiviral

Pathogen (family)	Vector / reservoir / epidemiology in India	Characteristic clinical presentation	Diagnosis	Management
Varicella-zoster virus (Herpesviridae)	Reactivation; immunocompromised	Encephalitis via CNS <i>vasculopathy</i> — multifocal ischaemic/haemorrhagic infarcts; ± preceding zoster	CSF VZV PCR and CSF IgM (complementary)	IV acyclovir; consider adjunctive glucocorticoid (unproven)
Measles virus → SSPE (Paramyxoviridae)	Past measles in early childhood; latency 6–8 yr	Progressive cognitive decline, myoclonus, seizures, spasticity in 5–15 yr olds	EEG periodic high-voltage complexes (3–8 s); markedly raised CSF anti-measles antibody/oligoclonal bands	No definitive cure; isoprinosine ± intrathecal IFN-α; prevent via measles vaccination
Kyasanur Forest disease virus (Flaviviridae)	<i>Haemaphysalis</i> ticks; monkeys; Karnataka (Western Ghats)	Biphasic — haemorrhagic febrile illness then, in a minority, a second phase of <i>meningoencephalitis</i>	RT-PCR / IgM serology	Supportive; inactivated KFD vaccine used in India for prevention
Rabies virus (Rhabdoviridae)	Dog bite (commonest in India); bats	<i>Furious</i> rabies — hydrophobia, aerophobia, autonomic storm; <i>paralytic (dumb)</i> — ascending paralysis; near-100% fatal	Antigen in brain/nuchal skin biopsy; PCR of saliva/CSF	No effective therapy once symptomatic; prevention = post-exposure prophylaxis (wound care, vaccine, RIG)

Key India-specific entities — expanded points

- ▶ **HSV-1 encephalitis** is the *only* common viral encephalitis with effective specific therapy. NMDA-receptor antibodies appear in up to 25% of recovered patients and may cause relapse/worsening weeks later — this requires immunotherapy, not antiviral escalation.
- ▶ **Japanese encephalitis** is the most significant viral encephalitis of Asia (~68,000 cases and ~13,600–20,400 deaths/year). India runs a JE vaccination programme in endemic districts; pig/bird amplification and irrigated rice ecology drive transmission. A *parkinsonian movement disorder with bilateral thalamic MRI lesions* is the exam hallmark.
- ▶ **Nipah** is the highest-lethality entity (CFR up to ~92%) — recognise the date-palm-sap and fruit-bat exposure history, brainstem/myoclonic signs, and the public-health imperative of isolation and contact tracing.

- ▶ **Chandipura** is a peculiarly *Indian paediatric* rhabdoviral encephalitis with explosive course and high mortality, in which CSF is characteristically unremarkable for virus.

General diagnostic approach

- ▶ **CSF (mandatory unless raised ICP):** lymphocytic pleocytosis (>5 cells/ μL in $>95\%$), mildly raised protein, *normal glucose*; collect ≥ 20 mL, freeze 5–10 mL for PCR/metagenomics.
- ▶ **CSF PCR** is the primary test for HSV, VZV, CMV, EBV, HHV-6, enteroviruses; **arboviral diagnosis rests on virus-specific IgM** (CSF/serum, MAC-ELISA) since viraemia is transient.
- ▶ **Neuroimaging:** MRI temporal lobes $\rightarrow$ HSV; bilateral thalami/basal ganglia $\rightarrow$ flaviviruses (JE, WNV); deep-grey/brainstem $\rightarrow$ arboviral.
- ▶ **EEG:** periodic lateralised temporal complexes $\rightarrow$ HSV; SSPE periodic bursts.
- ▶ **Metagenomic next-generation sequencing (mNGS)** of CSF for obscure/immunocompromised cases.

Principles of management

- ▶ **Empirical IV acyclovir** in every patient with suspected viral encephalitis (especially with focal features) *while awaiting PCR* — discontinue if HSV excluded.
- ▶ **Supportive ICU care:** ICP monitoring, fluid restriction (avoid hypotonic fluids, watch SIADH), fever suppression, standard anticonvulsants, airway/ventilatory support, prophylaxis against aspiration, DVT and pressure ulcers.
- ▶ **Pathogen-specific:** CMV — ganciclovir + foscarnet; arboviruses (JE, WNV, dengue, chikungunya, Chandipura, Nipah) — supportive only.
- ▶ **Prevention is decisive:** JE vaccine (endemic districts), KFD vaccine (Karnataka), measles vaccine (prevents SSPE), rabies PEP, and vector control (mosquito-source reduction, repellents/DEET, bed-nets, full-sleeve clothing).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled axial MRI brain panels:** (1) *HSV* — asymmetric T2/FLAIR hyperintensity of right temporal lobe (label: temporal lobe, insula, cingulate gyrus); (2) *Japanese encephalitis* — bilateral thalamic T2/FLAIR lesions (label: thalamus, substantia nigra, basal ganglia).
- ▶ **Transmission-cycle schematic for JE:** label *Culex tritaeniorhynchus* mosquito $\rightarrow$ *amplifying hosts* (pig, ardeid wading bird/heron) $\rightarrow$ *dead-end host* (human), with rice-field habitat.

Clinical / Diagnostic significance

- ▶ The clinical priority is *not to miss treatable HSV*; a negative early (≤ 72 h) HSV CSF PCR does not exclude it — repeat in 1–3 days if suspicion is high.

- ▶ *Movement disorder + bilateral thalamic lesions* in an endemic child = JE until proven otherwise; *bat/date-palm-sap exposure with brainstem signs and respiratory failure* = Nipah (isolate immediately).
- ▶ Hypoglycorrhachia or persisting CSF neutrophilia should redirect toward bacterial, tuberculous, fungal or amoebic causes (*Naegleria*, *Balamuthia*).
- ▶ Autoimmune encephalitis (anti-NMDA-R, LGI1, CASPR2) is the key non-infective mimic and may follow HSV encephalitis.

High-yield exam pointers

- ▶ HSV-1 = **commonest sporadic**; JEV = **commonest epidemic** viral encephalitis in India.
- ▶ Acyclovir 10 mg/kg IV q8h × 21 days — memorise dose; start empirically, do not wait for PCR.
- ▶ JE: *Culex tritaeniorhynchus*; pig + ardeid-bird amplifiers; parkinsonism; bilateral thalamic MRI; anti-JEV IgM diagnostic; SA14-14-2 / IXIARO vaccines.
- ▶ Nipah: Henipavirus, *Pteropus* bats, date-palm sap, CFR 67–92%, PCR of urine/respiratory secretions (not blood), barrier nursing.
- ▶ Chandipura: Indian rhabdovirus, children, sandfly-borne, CFR 45–80%, CSF often bland.
- ▶ WNV diagnosis = CSF IgM (not PCR); KFD = Karnataka, *Haemaphysalis* tick, vaccine available.
- ▶ Arboviral encephalitides (JE, WNV, dengue, chikungunya, Chandipura, Nipah) → **supportive treatment only**; prevention via vaccine + vector control.
- ▶ SSPE = **late measles complication**, periodic EEG, raised CSF anti-measles antibody, preventable by vaccination.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Encephalitis" (HSV dosing, CSF/PCR/MRI/EEG, SSPE, differential diagnosis) and "Arthropod-Borne and Rodent-Borne Virus Infections" (Japanese encephalitis, West Nile, dengue, chikungunya, Chandipura, Kyasanur Forest disease epidemiology and presentation); "Common Viral Respiratory Infections"/Hendra–Nipah section (Henipavirus biology).
- ▶ CMDT 2026 — "Viral & Rickettsial Infections" (Japanese encephalitis essentials, diagnosis, vaccines and prognosis; Nipah virus clinical features, CFR, diagnostic ELISA/PCR; supportive management).

Coverage note: The spec flags India-specific epidemiology as thin, and this is accurate — Harrison/CMDT confirm the pathogens, vectors, presentations and management used above, but do **not** give India-state-wise incidence figures or the Indian national JE/AES surveillance data; those administrative specifics are outside the corpus and have not been fabricated. Chandipura,

Nipah-India and KFD are corpus-supported as Indian entities. Rabies is included as a universally-accepted neurotropic viral encephalitis though it is conventionally discussed separately.



Toxoplasmosis

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — Toxoplasmosis is a zoonosis caused by the obligate intracellular coccidian protozoan *Toxoplasma gondii*. The **cat (Felidae)** is the *definitive host* in which the sexual cycle and oocyst formation occur, while humans and other warm-blooded animals are *intermediate hosts*. Up to a third of the world's population is latently infected. Acute acquired infection is asymptomatic in 80–90% of immunocompetent persons, but the parasite persists lifelong as tissue cysts; the major clinical burden falls on three groups — the **immunocompromised** (reactivation encephalitis), the **fetus/newborn** (congenital toxoplasmosis), and persons with **ocular disease** (chorioretinitis).

Etiology, Life Cycle & Transmission

- ▶ **Organism & forms:** *T. gondii* exists in three forms — the rapidly dividing invasive **tachyzoite** (infects all nucleated cells except RBCs; causes tissue damage), the slow-replicating **bradyzoite** within **tissue cysts** (persist in CNS, skeletal/cardiac muscle, retina — the chronic/latent stage), and the environmentally hardy **oocyst** (sexual-stage product shed only in cat faeces, sporulating to 8 sporozoites after 2–3 days in air).
- ▶ **Life cycle:** The **enteroepithelial (sexual) cycle** occurs only in the cat intestine, producing unsporulated oocysts in faeces; an acutely infected cat may excrete up to **100 million oocysts/day**. In intermediate hosts the **asexual cycle** proceeds — ingested cysts/oocysts release organisms that transform into tachyzoites, disseminate, and ultimately encyst as bradyzoites (tissue cysts appear 7–10 days after infection).
- ▶ **Routes of transmission:**
 - **Oral (commonest):** ingestion of **tissue cysts** in raw/undercooked meat (lamb, pork, beef, venison) or **sporulated oocysts** from soil/water/food contaminated by cat faeces; also unpasteurised goat milk, untreated water, raw shellfish (filter-feeders concentrate oocysts).
 - **Transplacental** (tachyzoites) → congenital toxoplasmosis.
 - **Blood transfusion / solid-organ or haematopoietic stem-cell transplantation** (donor → seronegative recipient).
 - Rarely **laboratory accident** (needlestick, infected tissue).
- ▶ **Genotypes:** Northern-hemisphere strains are predominantly 3 clonal genotypes; **South/Central American strains are more virulent**, atypical, and cause severe ocular and even sepsis-like disease in immunocompetent hosts — a travel history is diagnostically important.

Pathogenesis, Pathology & Immune Response

- ▶ Released bradyzoites/sporozoites invade gut epithelium → transform into **tachyzoites** → disseminate as free organisms or inside phagocytes (“Trojan horse”) to lymph node, muscle, myocardium, retina, placenta and CNS. Hallmark lesion: **cell death and focal necrosis with surrounding mononuclear inflammation**.
- ▶ **Control is mainly cell-mediated**: a strong TH1 response with IL-12 and IFN- γ (plus CD4⁺ and cytolytic CD8⁺ T cells, activated macrophages) contains the parasite; humoral antibody is parasitocidal with complement (basis of the *Sabin-Feldman dye test*).
- ▶ In the **immunocompromised or fetal host**, failure of T-cell immunity (notably CD8⁺ loss) permits unchecked tachyzoite spread → **necrotizing encephalitis, pneumonitis, myocarditis**. Reactivation in AIDS is almost always from **spontaneous rupture of latent cysts** in the brain when CD4⁺ count <100/ μ L.
- ▶ **Pathology by site**: lymph node — *follicular hyperplasia with clusters of epithelioid histiocytes encroaching on germinal centres* (Piringer-Kuchinka pattern); CNS — necrotizing encephalitis with microglial nodules and cyst-bearing necrotic borders; eye — necrotizing retinochoroiditis; *T. gondii* is the commonest cause of posterior uveitis in immunocompetent persons.

Clinical Manifestations (Four Syndromes)

Syndrome	Host	Key features
1. Acute acquired	Immunocompetent	80–90% asymptomatic. Commonest sign = bilateral, non-tender cervical lymphadenopathy (also suboccipital, supraclavicular); mononucleosis-like illness — fever (<40°C), malaise, headache, sore throat, myalgia, atypical lymphocytosis. Self-limited over weeks–months; rarely pneumonitis, myocarditis, polymyositis, encephalitis (virulent strains)
2. Congenital	Fetus / newborn	Follows primary maternal infection in pregnancy . Transmission rises with gestational age (~15% 1st trimester → ~65% 3rd) but severity falls — early infection → abortion, stillbirth, severe disease; late → usually asymptomatic at birth. Classic <i>Sabin tetrad</i> : hydrocephalus, intracranial (diffuse) calcifications,

Syndrome	Host	Key features
		chorioretinitis, and convulsions; also microcephaly, intellectual disability, strabismus
3. Ocular	Any (congenital or acquired)	Retinochoroiditis — blurred vision, scotoma, photophobia, eye pain; fundus shows yellow-white cotton-like patches with overlying vitritis (<i>“headlight in the fog”</i>), healing to pigmented scars. Causes ~35% of chorioretinitis in US/Europe; recurrent flares, esp. South-American strains
4. Reactivation in immunocompromised	AIDS, transplant, immunosuppressed	Toxoplasmic encephalitis (TE) is the principal CNS opportunistic infection in AIDS — subacute fever, headache, altered mental status (75%), focal deficits/hemiparesis, seizures (33%); sites = basal ganglia, corticomedullary junction, brainstem . Also pneumonitis (mimics PJP), myocarditis, chorioretinitis. >95% of TE in AIDS is reactivation, typically at CD4 ⁺ <100/μL

Diagnosis

- **Serology (mainstay in immunocompetent):** Acute infection suggested by **simultaneous IgM + IgG**, seroconversion, or a 4-fold (≥ 16 -fold) titre rise. IgG (Sabin-Feldman dye test, IFA, ELISA) appears at 2–3 weeks, peaks 6–8 weeks, persists for life. IgM (double-sandwich IgM-ELISA, IgM-ISAGA) rises early but may **persist >1 year** — a positive IgM alone does not prove recent infection. **IgG avidity testing** (high avidity = infection >3–4 months ago) helps date infection in pregnancy. Circulating **IgA** favours acute/congenital infection.
- **Molecular:** PCR is the mainstay for detecting organism in **amniotic fluid** (congenital — replaced fetal blood sampling), CSF, blood, aqueous/vitreous humour, BAL. Highly specific but variably sensitive — a **negative PCR does not exclude** toxoplasmosis.
- **Histology / isolation:** demonstration of **tachyzoites** in tissue/fluid = acute infection; isolated cysts indicate only past/latent infection. Lymph-node biopsy shows the characteristic reactive pattern.
- **Immunocompromised (TE):** based on **clinical picture + positive IgG (IgM usually negative) + neuroimaging**. CT/MRI show **multiple ring-enhancing lesions** at the basal ganglia and

corticomedullary junction; MRI is most sensitive. Predictive value of a typical picture in a seropositive AIDS patient is ~80%. A favourable **empirical therapeutic trial** (>50% improve by day 3, >90% by day 7) is diagnostic; non-response or a **solitary lesion** suggests **primary CNS lymphoma** (EBV-positive CSF PCR) and warrants **stereotactic brain biopsy**.

- **Congenital/newborn:** persistence of IgG beyond 12 months, or positive IgM/IgA after the first week of life, is diagnostic; assess eyes, brain (imaging) and CSF as up to 25% are seronegative at birth.
- **Ocular:** typical retinal lesion + positive serum IgG; intra-ocular antibody production (Goldmann-Witmer coefficient) or ocular-fluid PCR/Western blot in atypical cases.

Treatment & Prophylaxis

- **Mechanism note:** anti-*Toxoplasma* drugs act only on **tachyzoites** — they control disease but **do not eradicate tissue cysts**. Folinic acid (**leucovorin**) is added to counter pyrimethamine marrow toxicity (NOT folic acid).

Setting	Regimen (from source)
Immunocompromised / TE (acute)	Pyrimethamine (200 mg load, then 50 mg/d if <60 kg, 75 mg/d if >60 kg) + sulfadiazine (1000 mg qid <60 kg; 1500 mg qid >60 kg) + leucovorin 10–25 mg/d, minimum 6 weeks. Sulfa intolerance → clindamycin 600 mg qid. Resource-poor / pyrimethamine unavailable → TMP-SMX (5 mg/kg TMP + 25 mg/kg SMX bid)
Ocular (immunocompetent)	Pyrimethamine + sulfadiazine or clindamycin × 6 weeks, ± prednisone; treat sight-threatening lesions (macula/optic disc)
Acute lymphadenopathy (immunocompetent)	Usually no therapy ; treat only if severe/persistent or visceral (2–4 weeks)
Pregnancy	Spiramycin 1 g tid until delivery for early acute infection (does not cross placenta; cuts transmission ~60%). After 18 weeks or documented fetal infection → pyrimethamine + sulfadiazine + folinic acid (pyrimethamine avoided in 1st trimester — teratogenic)
Congenital (neonate)	Pyrimethamine 1 mg/kg + sulfadiazine 100 mg/kg + folinic acid for 1 year; prednisone 1 mg/kg/d if indicated
Primary prophylaxis (AIDS)	If seropositive and CD4 ⁺ <100/μL → TMP-SMX 1 double-strength tab daily (also prevents PJP). Alternatives: dapsone-pyrimethamine, atovaquone ± pyrimethamine. Stop when CD4 ⁺ >200/μL for ≥3 months

Setting	Regimen (from source)
Secondary prophylaxis (maintenance)	Pyrimethamine + sulfadiazine (or clindamycin/TMP-SMX) + leucovorin until immune reconstitution; stop when CD4 ⁺ >200/ μ L for ≥ 6 months on ART (with repeat MRI)

Prevention

- ▶ **Cook meat** to a safe internal temperature (≈ 63 – 66°C ; ground meat/poultry higher) and rest; **freezing to -20°C** kills tissue cysts.
- ▶ Wash hands, fruits and vegetables; avoid raw shellfish and unpasteurised milk.
- ▶ **Cat-litter precautions:** change the litter box **daily** (fresh oocysts are non-infective for ~ 48 h before sporulation), preferably by a non-pregnant, HIV-negative person; wear gloves for gardening; keep cats indoors and feed only cooked/commercial food.
- ▶ Screen **donor and recipient** serology before transplantation; counsel seronegative pregnant and immunocompromised persons. Some countries screen pregnant women (France, Austria) and/or newborns (Denmark, Massachusetts).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Life cycle of Toxoplasma gondii* (circular):* label Definitive host (cat) $\rightarrow$ enteroepithelial/sexual cycle $\rightarrow$ unsporulated oocyst in faeces $\rightarrow$ sporulated oocyst (8 sporozoites) **in soil/water**; Intermediate hosts (**human, sheep, pig, rodent, birds**) $\rightarrow$ tachyzoites (**acute, infect all nucleated cells**) $\rightarrow$ tissue cysts with bradyzoites **in CNS/muscle/retina**; **arrows for undercooked meat and transplacental** routes to humans.**
- ▶ **MRI brain in toxoplasmic encephalitis:** label **multiple ring-enhancing lesions, basal ganglia, corticomedullary junction, surrounding vasogenic oedema.**

Clinical / Diagnostic significance

- ▶ *T. gondii* is the **commonest cause of focal brain lesions / mass lesions in AIDS** — empirical anti-toxoplasma therapy with imaging follow-up is standard; failure to improve points to CNS lymphoma.
- ▶ A **solitary ring-enhancing lesion** or **negative Toxoplasma IgG** in an AIDS patient argues against TE and toward lymphoma/other diagnoses $\rightarrow$ consider early biopsy.
- ▶ In **pregnancy**, the IgM/IgG plus **avidity** panel and **amniotic-fluid PCR** guide the choice between spiramycin and pyrimethamine-based therapy and decisions on continuation of pregnancy.
- ▶ **Ocular toxoplasmosis** is the leading infectious cause of posterior uveitis; recurrence and macular involvement threaten vision.
- ▶ **Antiretroviral therapy** (immune reconstitution to CD4⁺ >200/ μ L) is the key to discontinuing both primary and secondary prophylaxis.

High-yield exam pointers

- ▶ Cat = definitive host; oocysts shed **only** in cat faeces; humans = intermediate host.
- ▶ Three forms: **tachyzoite** (acute, all nucleated cells, spares RBCs), **bradyzoite/tissue cyst** (latent), **oocyst** (sexual stage, environmental).
- ▶ Sabin-Feldman dye test = reference IgG serology; IgM-ISAGA and avidity date infection; PCR of amniotic fluid for congenital diagnosis.
- ▶ Sabin classic tetrad of congenital disease: **hydrocephalus, intracranial calcification, chorioretinitis, convulsions**; transmission ↑ but severity ↓ with later gestation.
- ▶ TE in AIDS at CD4⁺ <100/μL: **multiple ring-enhancing** basal-ganglia/corticomedullary lesions; >90% respond to empirical therapy by day 7.
- ▶ Pyrimethamine + sulfadiazine + leucovorin = standard; clindamycin if sulfa-intolerant; TMP-SMX alternative and the prophylactic agent of choice (covers PJP too).
- ▶ Spiramycin = drug of choice in early pregnancy (doesn't cross placenta); **avoid pyrimethamine in the 1st trimester**.
- ▶ Primary prophylaxis: TMP-SMX at CD4⁺ <100/μL; stop at CD4⁺ >200/μL ×3 months (primary) or ×6 months (secondary).
- ▶ Drugs kill tachyzoites **only** — never eradicate cysts; add **folinic acid (leucovorin)**, not folic acid.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Toxoplasma Infections” (etiology, life cycle, transmission, pathogenesis, immune response, clinical syndromes, serologic/PCR/imaging diagnosis, treatment doses, AIDS prophylaxis thresholds, prevention).
- ▶ **CMDT 2026** — “Protozoal & Helminthic Infections: Toxoplasmosis” (four clinical syndromes, current serologic/PCR algorithm, drug regimens, spiramycin in pregnancy, chemoprophylaxis) and HIV chapter for TE prophylaxis.
- ▶ *Coverage note:* The **Sabin classic tetrad** (hydrocephalus, intracranial calcification, chorioretinitis, convulsions) is universally accepted standard internal medicine; Harrison lists the component features (hydrocephalus, microcephaly, intellectual disability, chorioretinitis, epilepsy) without naming the eponymous tetrad. The *Goldmann-Witmer coefficient* and *Piringer-Kuchinka* lymph-node pattern are named per standard usage; Harrison/CMDT describe the underlying tests/histology.



Treatment and Prevention of Cholera

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Cholera is an acute, toxin-mediated diarrhoeal disease caused by *Vibrio cholerae* serogroup O1 or O139 (the serogroups with epidemic potential) that can, within hours, produce profound, rapidly progressive dehydration and death. The severe form is termed **cholera gravis**. Death results almost entirely from **hypovolaemic shock** and metabolic acidosis driven by massive secretory (rice-water) stool loss; consequently, prompt, aggressive fluid and electrolyte repletion converts a historically lethal illness into a self-limited one. Management therefore rests on two pillars — *rehydration* (the cornerstone) and *adjunctive antibiotics/zinc* — while prevention combines water-sanitation-hygiene (WASH) measures with oral cholera vaccination.

Principles of treatment — rehydration is paramount

- ▶ **Goal:** rapidly restore euvolaemia, then maintain hydration by replacing ongoing losses until diarrhoea stops. Treatment intensity is guided by the **degree of dehydration** (Table below) and the patient's age/weight.
- ▶ **Oral rehydration solution (ORS)** is the mainstay for mild–moderate dehydration. It exploits the **hexose–Na⁺ co-transport mechanism**: glucose (or galactose) is actively transported across the gut mucosa, dragging Na⁺ with it; Cl[−] and water follow passively. *This transport pathway remains intact even when cholera toxin is active*, which is why ORS works despite ongoing toxin-driven secretion.
- ▶ **WHO reduced (“low”)-osmolarity ORS** is now recommended for dehydrating diarrhoea of any cause. Composition (mmol/L): Na⁺ 75, K⁺ 20, Cl[−] 65, citrate 10, glucose 75 — **total osmolarity 245 mOsm/L**. Each sachet (added to 1 L safe water) contains NaCl 2.6 g, trisodium citrate dihydrate 2.9 g, KCl 1.5 g and anhydrous glucose 13.5 g.
- ▶ **Homemade ORS** (when sachets unavailable): 0.5 teaspoon (½ small spoonful) table salt + 6 level teaspoons table sugar in 1 L of safe water; supplement potassium via **bananas or green coconut water**.
- ▶ **Rice-based ORS** is considered superior to standard ORS specifically in cholera. ORS may be given by **nasogastric tube** if the patient cannot drink.
- ▶ **Continue feeding/breast-feeding** during treatment; encourage potassium-rich intake.

Dehydration assessment and fluid prescription

Degree	Key clinical findings	Fluid loss	Treatment
None/mild	Thirst only	<5% body wt	ORS to replace losses (e.g. ≥10 y: ½–1 cup, max 1 L/d)
Moderate	Thirst, postural hypotension, weakness, tachycardia, ↓skin turgor, dry mouth, no tears	5–10% body wt	ORS <i>ad libitum</i> , up to max 2 L/d (give within first 4 h; weight-based volumes)

Degree	Key clinical findings	Fluid loss	Treatment
Severe	Lethargy/unconsciousness (“floppiness”), weak/absent pulse, inability to drink, sunken eyes/fontanelles	>10% body wt	IV fluids (see below)

- ▶ **Severe dehydration** → IV resuscitation. Use **Ringer’s lactate** (best commercial choice because profound acidosis, pH <7.2, is common; if unavailable, normal saline). It *must* be supplemented with **potassium**, preferably given orally.
- ▶ **Volume schedule (WHO)**: give **100 mL/kg in the first 3 h** (first 6 h in children <12 months) — start rapidly then slow down — for a **total of 200 mL/kg in the first 24 h**. Continue until the patient is awake, can ingest ORS, and no longer has a weak pulse.
- ▶ Alternatively framed: in severely dehydrated patients (>10% body wt) the **total deficit can be replaced within the first 3–4 h**, with half in the first hour. **Transient muscle cramps and tetany are common** during rapid repletion.
- ▶ Thereafter switch to **oral therapy**, matching intake to output. Patients with continued large-volume diarrhoea may need prolonged IV fluids.
- ▶ **Hypokalaemia** can be severe but responds to K⁺ (IV or oral). *Where monitoring staff are inadequate, the oral route for both rehydration and potassium is safer than IV.*

Composition of cholera stool vs. replacement fluid

Fluid (mmol/L)	Na ⁺	K ⁺	Cl ⁻	Base
Adult cholera stool	135	15	100	45
Child cholera stool	100	25	90	30
Ringer’s lactate	130	4*	109	28

Ringer’s lactate is relatively K⁺- and base-poor versus stool, which is why additional potassium (oral preferred) is mandatory to replace stool losses.*

Adjunctive antibiotics and zinc

- ▶ Antibiotics are **not necessary for cure**, but an agent to which the organism is susceptible **shortens the duration and volume of fluid loss and hastens clearance of the organism from stool**. Hence give to patients with **moderate or severe dehydration**.

Class / drug	Adult dose	Paediatric dose
Azithromycin (macrolide; agent of choice)	Single 1-g oral dose	Single 20 mg/kg dose
Erythromycin (macrolide)	250 mg PO QID × 3 days	12.5 mg/kg/dose QID × 3 days
Doxycycline (tetracycline)	Single 300-mg dose (non-pregnant)	>8 y: single 4–6 mg/kg dose
Tetracycline	500 mg PO QID × 3 days (non-pregnant)	>8 y: 12.5 mg/kg/dose QID × 3 days
Ciprofloxacin (fluoroquinolone)	500 mg PO BID × 3 days	15 mg/kg BID × 3 days

- ▶ **Resistance caveats:** macrolides (azithromycin/erythromycin) are the **agents of choice**; resistance to **tetracyclines** is **widespread**, and **fluoroquinolone resistance is increasing** — use these only where susceptibility is confirmed.
- ▶ **Zinc** reduces the volume and severity of diarrhoea in young children, including cholera: <6 months → 10 mg/day for 10 days; 6 to <60 months → 20 mg oral zinc/day for 10 days.

Prevention — sanitation, surveillance and vaccines

- ▶ **General/public-health measures:** provision of safe water and sanitary disposal of faeces, **improved nutrition**, and care with **food preparation and storage** in the household significantly reduce incidence. Prevent spread by **infected or asymptomatic carriers** moving from endemic to non-endemic regions (the probable route of the 2010 Haiti outbreak).
- ▶ **Oral cholera vaccines (OCV)** — two types developed to maximise mucosal immunity: **oral killed vaccines** and **live attenuated vaccines**.
- ▶ **Three oral KILLED vaccines are WHO-prequalified:**
 - **BivWC (Shanchol; Shantha Biotechnics, Hyderabad, India)** — both biotypes/serotypes of *V. cholerae* O1 and O139, *without* supplemental cholera toxin B (CTB) subunit; manufacture being terminated.
 - **Euvichol / Euvichol-Plus (Eubiologics, Seoul, South Korea)** — currently supplies the vast majority of global control-programme vaccine.
 - **WC-rBS (Dukoral; Valneva, Sweden)** — both biotypes/serotypes of *V. cholerae* O1 supplemented with 1 mg recombinant CTB subunit per dose.
- ▶ **Killed-vaccine schedule/efficacy:** given as a 2- or 3-dose regimen, doses ~14 days apart, providing ~60–85% **protection** for the first few months. **Boosters:** WC-rBS after 2 years (≥6 y) or 6 months (children 2–5 y); BivWC gave ~60% **protection over 5 years** in a Kolkata study (~40% in children ≤5 y). Even a **single dose** confers some outbreak protection (40% all / 63% severe cholera over 6 months) but **no protection in children <5 y** with one dose. **Herd immunity** is predicted once coverage >50%; killed vaccines are **safe in high-HIV-prevalence populations**.

- ▶ **Live attenuated vaccine:** CVD 103-HgR (Vaxchora; Emergent BioSolutions) — derived from a classic strain that **lacks the cholera-toxin genes**; FDA-approved for travellers (ages 2–64 y) but **not WHO-prequalified**. Single oral dose; **90% and 80% efficacious** against severe cholera at 10 and 90 days post-vaccination in volunteer challenge.
- ▶ **Global strategy:** the Global Task Force on Cholera Control (GTFCC) strategy (launched 2017, WHO secretariat) aims to **cut cholera deaths by 90% and eliminate cholera in up to 20 countries by 2030**, integrating **WASH programmes + vaccination** and a **Global Vaccine Stockpile** (used mainly for *reactive*, often single-dose, campaigns owing to shortages).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Hexose- Na^+ co-transport / basis of ORS.** Label: intestinal villus enterocyte; SGLT1 glucose- Na^+ co-transporter on apical membrane; **glucose; Na^+ ; Cl^- and H_2O following passively;** Na^+/K^+ -ATPase on basolateral membrane; note “*pathway intact despite cholera toxin.*” Contrast with adjacent crypt cell showing cholera-toxin $\rightarrow \uparrow \text{cAMP} \rightarrow \text{Cl}^-/\text{water}$ secretion (the diarrhoea).
- ▶ **Diagram 2 — Fluid-management flowchart by dehydration severity.** Boxes labelled: Assess dehydration $\rightarrow$ None-mild (ORS) / Moderate (ORS up to 2 L) / Severe (IV Ringer’s lactate 100 mL/kg in 3 h, total 200 mL/kg/24 h + oral K^+) $\rightarrow$ transition to maintenance ORS, with the endpoint “awake, drinking, normal pulse.”

Clinical / Diagnostic significance

- ▶ **Diagnosis:** suspect in any patient ≥ 5 y with acute watery diarrhoea in/near an endemic area, or with severe dehydration. Confirm by stool **dark-field microscopy** (darting motility, immobilised by specific antiserum), culture on TCBS or TTG agar, **Cary-Blair transport / alkaline-peptone water** enrichment, or **point-of-care antigen dipstick** in the field.
- ▶ **Labs reflect volume/electrolyte loss:** raised haematocrit (haemoconcentration), prerenal azotaemia, **bicarbonate < 15 mmol/L** with a high **anion gap** acidosis, arterial pH ~ 7.2 , and usually normal $\text{Na}^+/\text{K}^+/\text{Cl}^-$ — guiding the Ringer’s lactate + potassium choice.
- ▶ **Management pearl:** complications (acute tubular necrosis, shock) are *purely* a consequence of dehydration and are **averted by adequate fluid/electrolyte therapy** — the disease is then self-limited over a few days.

High-yield exam pointers

- ▶ **Rehydration is the single most important intervention; death is from hypovolaemic shock.**
- ▶ WHO low-osmolality ORS = 245 mOsm/L (Na 75, K 20, Cl 65, citrate 10, glucose 75).
- ▶ Severe case = **Ringer’s lactate**, 100 mL/kg in 3 h (6 h if < 12 mo), 200 mL/kg in 24 h, plus oral potassium.

- ▶ Rice-based ORS > standard ORS in cholera; ORS works via **glucose–Na⁺ co-transport** (intact despite toxin).
- ▶ Antibiotics are **adjunctive** (reduce stool volume/duration, hasten clearance) for **moderate/severe** dehydration — **azithromycin 1 g single dose** is first choice; tetracycline/FQ resistance rising.
- ▶ **Zinc**: 10 mg/day (<6 mo) or 20 mg/day (6–<60 mo) for **10 days** in children.
- ▶ **Three WHO-prequalified killed OCVs**: Shanchol (BivWC), Euvichol/Euvichol-Plus, Dukoral (WC-rBS, +CTB); live attenuated = **Vaxchora (CVD 103-HgR)**.
- ▶ **GTFCC 2017 goal**: 90% fewer deaths and elimination in up to 20 countries by **2030** via WASH + vaccine.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 173 “Cholera and Other Vibrioses”** (Waldor & Ryan); Tables 173-1 to 173-4 (dehydration assessment, treatment by severity, ORS and stool/IV electrolyte composition). All drug doses, ORS/Ringer's compositions, vaccine names and efficacy figures are taken directly from this chapter. *Coverage note*: the chapter fully covers this topic; SGLT1 is named in the diagram per universally accepted physiology (Harrison cites the “hexose–Na⁺ co-transport” mechanism without naming the transporter).



Tropical Pulmonary Eosinophilia

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Tropical pulmonary eosinophilia (TPE) is a distinct *hyper-responsive* syndrome that develops in a minority of individuals infected with the lymphatic-dwelling filarial nematodes **Wuchereria bancrofti** and **Brugia malayi**. It is characterised by paroxysmal nocturnal cough and wheeze, diffuse pulmonary infiltrates, intense peripheral blood eosinophilia (>3000/μL), markedly elevated serum IgE and antifilarial antibody, and a dramatic response to diethylcarbamazine (DEC). It is best understood as an *occult (amicrofilaraemic) filariasis* in which microfilariae are cleared from blood and trapped in the lungs, where they provoke an exuberant allergic-inflammatory reaction.

Etiology & Epidemiology

- ▶ **Causative parasites**: the lymphatic-dwelling filariae **W. bancrofti** and **B. malayi** — the same species that cause lymphatic filariasis. TPE is therefore one end of the clinical spectrum of bancroftian/brugian filariasis.
- ▶ **Vectors**: *Culex* mosquitoes (urban) and *Anopheles/Aedes* (rural) transmit *W. bancrofti*; *Mansonia* and *Anopheles* transmit *B. malayi*. Infective L3 larvae are deposited on skin during the mosquito bite.

- ▶ **Microfilarial periodicity:** both species are predominantly **nocturnally periodic** — microfilariae are scarce in peripheral blood by day and surge at night, which correlates with the characteristic *nocturnal* respiratory symptoms of TPE.
- ▶ **Adult worms** reside in afferent lymphatics or lymph nodes and may remain viable for **more than two decades**, providing a chronic antigenic stimulus.
- ▶ **Geography:** most cases reported from **India, Pakistan, Sri Lanka, Brazil, Guyana and Southeast Asia**. A history of residence in a filaria-endemic region is near-universal.
- ▶ **Trend:** the incidence of TPE has *declined over the past decade*, probably reflecting global mass drug administration (MDA) for elimination of lymphatic filariasis.

Pathogenesis & Pathology

- ▶ TPE represents a state of **immunological hyper-responsiveness** to the filarial parasite rather than uncontrolled infection.
- ▶ **Microfilariae and parasite antigens are rapidly cleared from the bloodstream by the lungs** — this *pulmonary sequestration* explains the cardinal paradox of TPE: blood is characteristically **amicrofilaraemic** despite active filarial infection.
- ▶ Clinical symptoms result from **allergic and inflammatory (hypersensitivity) reactions** elicited by the trapped/cleared parasites within the lung.
- ▶ A **prominent, eosinophil-enriched intra-alveolar infiltrate** develops; degranulating eosinophils release **cytotoxic, proinflammatory eosinophil granule proteins** that mediate much of the tissue damage (eosinophilic alveolitis).
- ▶ In some patients, trapping of microfilariae in other reticuloendothelial organs causes **hepatomegaly, splenomegaly or lymphadenopathy**.
- ▶ **If untreated**, the chronic eosinophilic inflammation progresses to **interstitial fibrosis** and irreversible, progressive pulmonary damage.

Clinical Features

- ▶ **History:** residence in / travel to a filaria-endemic area.
- ▶ **Respiratory:** **paroxysmal cough and wheezing**, classically **nocturnal** (paralleling the nocturnal periodicity of microfilariae); dyspnoea; may mimic bronchial asthma.
- ▶ **Constitutional:** weight loss, low-grade fever, malaise.
- ▶ **Lymphoreticular:** **lymphadenopathy**; sometimes hepatosplenomegaly.
- ▶ **Hallmark laboratory clue:** **pronounced blood eosinophilia** (>3000 eosinophils/ μL).
- ▶ Symptoms are subacute–chronic and, untreated, can persist for months with progressive pulmonary impairment.

Investigations & Diagnostic Criteria

- ▶ **Peripheral blood eosinophilia** $>3000/\mu\text{L}$ (often very high).
- ▶ **Serum IgE**: total IgE markedly elevated (Harrison quotes 4–40 KIU/mL); **antifilarial antibody titres markedly raised** — both are characteristic.
- ▶ **Absence of microfilariae in peripheral blood** (occult filariasis) — a key feature distinguishing TPE from classical microfilaraemic filariasis.
- ▶ **Chest imaging (X-ray / CT)**: may be normal, but generally shows **increased bronchovascular markings**; **diffuse miliary lesions or mottled opacities** may be seen in the **middle and lower lung fields**.
- ▶ **Pulmonary function tests**: **restrictive** abnormalities in most cases, with **obstructive** defects in about half; reduced diffusion capacity reflects interstitial involvement.
- ▶ **BAL**: eosinophilic alveolitis (intra-alveolar eosinophil-rich infiltrate).
- ▶ **Therapeutic trial**: prompt clinical and haematological response to DEC strongly supports the diagnosis.

The composite diagnostic picture: endemic-area residence + nocturnal cough/wheeze + extreme eosinophilia ($>3000/\mu\text{L}$) + very high IgE & antifilarial antibody + characteristic radiology + restrictive PFT + rapid response to DEC.

Differential Diagnosis

TPE is one of the **pulmonary infiltrates with eosinophilia (PIE)** syndromes and must be distinguished from the conditions Harrison lists below.

Condition	Distinguishing pointers
Bronchial asthma	Allergic; lower-grade eosinophilia; no antifilarial antibody; no endemic exposure
Löffler's syndrome	Transient, migratory infiltrates from larval transit (e.g. <i>Ascaris</i>); self-limited
Allergic bronchopulmonary aspergillosis (ABPA)	Central bronchiectasis, <i>Aspergillus</i> -specific IgE/precipitins, mucoid impaction
EGPA / Churg-Strauss (allergic granulomatosis with polyangiitis)	Asthma + eosinophilia + vasculitis; ANCA in a proportion; multi-organ involvement
Other systemic vasculitides	Notably polyarteritis (periarteritis) nodosa
Chronic eosinophilic pneumonia	"Photographic-negative" peripheral infiltrates; idiopathic; steroid-responsive
Hypereosinophilic syndromes (HESs)	Persistent eosinophilia $>1500/\mu\text{L}$ with multi-organ damage; no filarial serology

PIE classification (Harrison Ch 299) for framing the answer:

Group	Examples
Primary pulmonary eosinophilic disorders	Acute eosinophilic pneumonia; Chronic eosinophilic pneumonia; EGPA (Churg-Strauss); Hypereosinophilic syndrome
Known-cause / secondary (TPE belongs here)	Asthma & eosinophilic bronchitis; ABPA; drug/toxin reaction; Infection — parasitic/helminthic disease (includes TPE); non-parasitic infection

Treatment

- ▶ **Diethylcarbamazine (DEC)** is the drug of choice: **4–6 mg/kg daily for 14 days** (note this is a longer course than the standard active-filariasis regimen).
- ▶ **Symptoms usually resolve within 3–7 days** of starting therapy — the rapid response is both confirmatory and therapeutic.
- ▶ **Relapse occurs in ~12–25% of cases** (sometimes after an interval of several years) and **requires re-treatment**.
- ▶ **Goal:** early, complete treatment prevents progression to **interstitial fibrosis** and chronic restrictive lung disease.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Filarial life cycle highlighting pulmonary trapping in TPE** — labels: *Mosquito vector (Culex / Anopheles) → Infective L3 larvae deposited on skin → Adult worms in lymphatics / lymph nodes → Microfilariae released into blood (nocturnal periodicity) → Microfilariae & antigens cleared and TRAPPED in the lung → Eosinophil-enriched intra-alveolar infiltrate (eosinophilic alveolitis) → Hypersensitivity reaction / high IgE & antifilarial antibody → Untreated → interstitial fibrosis.*
- ▶ **Schematic chest X-ray of TPE** — labels: *Increased bronchovascular markings, diffuse miliary / mottled opacities in mid & lower zones, bilateral involvement, (may be normal in some cases).*

Clinical / Diagnostic significance

- ▶ TPE is an important, **eminently treatable** cause of chronic cough, wheeze and pulmonary infiltrates in patients from the Indian subcontinent — readily mistaken for refractory asthma or miliary tuberculosis.
- ▶ The **triad of extreme eosinophilia (>3000/ μ L), very high IgE/antifilarial antibody, and amicrofilaraemia** in an endemic-area resident is highly suggestive and should prompt a DEC trial.

- ▶ Early diagnosis prevents irreversible interstitial fibrosis; relapse mandates follow-up and re-treatment.
- ▶ Conceptually links to public-health filariasis control: falling TPE incidence mirrors the success of WHO MDA programmes.

High-yield exam pointers

- ▶ TPE = occult/amicrofilaraemic filariasis caused by *W. bancrofti* & *B. malayi*; microfilariae are cleared and trapped in the lungs (absent in peripheral blood).
- ▶ Classic clue triad: nocturnal paroxysmal cough/wheeze + eosinophilia $>3000/\mu\text{L}$ + markedly raised IgE & antifilarial antibody.
- ▶ Symptoms are nocturnal because of the nocturnal periodicity of microfilariae.
- ▶ CXR: increased bronchovascular markings; mid/lower-zone miliary or mottled opacities; may be normal. PFT: restrictive in most, obstructive in half.
- ▶ Endemic in India, Pakistan, Sri Lanka, Brazil, Guyana, SE Asia; incidence falling with MDA.
- ▶ DEC 4–6 mg/kg/day $\times$ 14 days; response in 3–7 days; relapse 12–25% needs re-treatment.
- ▶ Untreated $\rightarrow$ interstitial fibrosis and progressive restrictive lung disease.
- ▶ It is a secondary (known-cause) PIE — i.e. pulmonary infiltrates with eosinophilia due to a parasitic/helminthic infection.
- ▶ Pathology = eosinophilic alveolitis: cytotoxic eosinophil granule proteins drive the lung injury.
- ▶ Differentiate from asthma, Löffler's syndrome, ABPA, EGPA (Churg-Strauss), chronic eosinophilic pneumonia, HES.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 240 "Filarial and Related Infections" (TPE epidemiology, pathology, clinical features, differential and DEC treatment; lymphatic filariasis etiology/vectors/periodicity) and Ch 299 "Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia" (PIE classification framing). *Coverage note:* Ch 299 does not name TPE explicitly but lists "Infection — parasitic/helminthic disease" among secondary PIE syndromes; the male predominance and young-adult (2nd–4th decade) preponderance often cited for TPE are not stated in the provided chapters and are given as standard textbook context only.



Tropical Splenomegaly

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — *Tropical splenomegaly* in internal-medicine usage refers to **Hyperreactive Malarial Splenomegaly (HMS)**, formerly called *Tropical Splenomegaly Syndrome (TSS)*. It is a **chronic complication of malaria** seen in long-term residents of malaria-endemic tropical regions, in whom an **aberrant, exaggerated immunologic response to repeated malarial infection** produces *massive splenomegaly*, hepatomegaly, marked **serum IgM** elevation and high malarial-antibody titres, with **anemia and hypersplenism**. It is a clinically important and *reversible* cause of massive splenomegaly that must be separated from haematologic malignancy.

Etiology & epidemiology

- ▶ **Cause:** chronic or repeated malarial infection in a genetically/immunologically predisposed host. Chronic malaria characteristically produces **hypergammaglobulinaemia, a normochromic normocytic anaemia, and (in some) splenomegaly**.
- ▶ **Host:** *residents of malaria-endemic areas in tropical countries* who mount an **abnormal immunologic response** to repeated infection — not a feature of acute single-episode malaria.
- ▶ **Geography:** holoendemic malarious belts of sub-Saharan Africa, Papua New Guinea, South-East Asia, the Indian subcontinent and Amazonia. Harrison notes that *in some tropical countries (e.g., New Guinea) the incidence of palpable splenomegaly may reach 60%* — emphasising that, in the tropics, a palpable spleen does not automatically equate with disease.
- ▶ **Implicated species:** *Plasmodium falciparum* and *P. malariae* are classically responsible (the (in Africa) peripheral B-cell lymphocytosis and chronic antigenic drive).

Pathogenesis (an immunologic, not a parasitic, disease)

The driving event is **uncontrolled, polyclonal B-cell over-production of IgM** in response to recurrent malarial antigen, with loss of normal T-cell suppressor control:

- ▶ Chronic infection → **marked elevation of serum IgM and malarial antibody titres**.
- ▶ Production of **cytotoxic IgM antibodies against CD8+ (suppressor) T lymphocytes** and antibodies to **CD5+ T lymphocytes**, with a resultant **increase in the CD4+ : CD8+ ratio**.
- ▶ Loss of suppressor-T-cell restraint → **uninhibited B-cell production of IgM** → formation of **cryoglobulins** (IgM aggregates and immune complexes).
- ▶ These immune complexes are cleared by the reticulo-endothelial (RE) system, stimulating **lymphoid hyperplasia and clearance (“work”) hypertrophy** of the spleen → progressive **massive splenomegaly**. **Hepatic sinusoidal lymphocytosis** is characteristic, and (in Africa) a **peripheral B-cell lymphocytosis** occurs.
- ▶ The same RE/lymphoid hyperplasia mechanism that enlarges the spleen drives **hypersplenism** (pooling and destruction of blood cells in congested, enlarged cords) → **anaemia and pancytopenia**.

This places HMS within the “**increased demand for splenic function / immune-and-RE hyperplasia**” mechanistic group of splenomegaly (Harrison Table 70-2), alongside other parasitic causes (leishmaniasis, trypanosomiasis).

Clinical features

- ▶ **Massive splenomegaly** — the dominant sign; the patient presents with an **abdominal mass** or a “**dragging**” sensation in the abdomen.
- ▶ **Occasional sharp abdominal pain** suggesting **perisplenitis** (capsular inflammation); massive enlargement may also cause early satiety and LUQ heaviness.
- ▶ **Hepatomegaly** is usually present alongside the splenomegaly.
- ▶ **Anaemia and some degree of pancytopenia (hypersplenism)** — fatigue, pallor, bleeding tendency.
- ▶ **Recurrent respiratory and skin infections** are common, and **many patients die of overwhelming sepsis** — the leading cause of death.
- ▶ Constitutional features (insidious onset over months–years); unlike acute malaria there is usually **no high parasitaemia** — in many cases **malaria parasites cannot be found on peripheral-blood smears by microscopy**.

Diagnosis: criteria & investigations

- ▶ **Peripheral smear:** often **negative for parasites** (low-grade/absent parasitaemia) — a negative film does NOT exclude HMS.
- ▶ **Serum immunoglobulins:** markedly raised **polyclonal IgM**; **high malarial antibody titres**.
- ▶ **Full blood count:** features of **hypersplenism** — splenomegaly with cytopenia(s), a **normal or hyperplastic bone marrow**, and response to splenectomy; anaemia ± leuko-/thrombocytopenia.
- ▶ **Liver/spleen histology:** **hepatic sinusoidal lymphocytosis** (a hallmark on liver biopsy); reactive lymphoid hyperplasia in the spleen.
- ▶ **Imaging — confirm and size the spleen:** **ultrasonography is the procedure of choice** (normal max cephalo-caudad diameter ≤13 cm; normal spleen <250 g and impalpable). The spleen is “**massively enlarged**” when palpable >8 cm below the left costal margin or weighs ≥1000 g. Bedside assessment uses **palpation** (bimanual / ballottement / *Middleton manoeuvre*) and **percussion** (*Nixon, Castell, Traube’s space*).
- ▶ **Therapeutic test: clinical and immunologic response (spleen regression, fall in IgM) to sustained antimalarial therapy** is itself a key diagnostic criterion and helps separate HMS from lymphoma.
- ▶ ****Fakunle diagnostic criteria** (standard tropical-medicine criteria — see Coverage note):* Major — (1) *gross splenomegaly (≥10 cm below costal margin) with no other local cause*; (2) *serum IgM ≥2 SD above the local mean*; (3) *high malarial antibody titres*; (4) *clinical and immunologic*

response to antimalarial therapy. Minor* — hepatic sinusoidal lymphocytosis, hypersplenism, normal-to-exaggerated lymphocyte responses, and familial clustering.

Differential diagnosis (causes of massive / tropical splenomegaly)

HMS must be distinguished from other causes of a *massive* spleen, especially haematologic malignancy (some HMS cases have been *mistaken for haematologic malignancy*):

Category	Conditions to exclude
Tropical infective	Visceral leishmaniasis (<i>kala-azar</i>), hepatic schistosomiasis, chronic malaria itself, trypanosomiasis
Haematologic malignancy	Chronic myeloid leukaemia, myelofibrosis with myeloid metaplasia, hairy-cell leukaemia, chronic lymphocytic leukaemia / lymphomas, polycythaemia vera
Infiltrative / storage	Gaucher's disease, amyloidosis, sarcoidosis, diffuse splenic haemangiomatosis
Congestive (portal HTN)	Cirrhosis, portal/splenic vein obstruction, " <i>Banti's disease</i> ", schistosomal periportal fibrosis
Immune	Autoimmune haemolytic anaemia, Felty's syndrome, SLE

Key separators: in HMS the smear is usually parasite-negative, IgM is very high, hepatic sinusoidal lymphocytosis is present, and the spleen **regresses on antimalarials** — features that argue against leishmaniasis (bone-marrow/splenic LD bodies), CML (Philadelphia chromosome, granulocytosis), and lymphoma (lymph-node/tissue biopsy).

Management & prognosis

- ▶ **Endemic-area residents: antimalarial chemoprophylaxis** (sustained/prolonged) — *results are usually good*, with gradual spleen regression and fall in IgM. Compliance over months is essential; relapse follows withdrawal.
- ▶ **Non-endemic settings (travellers/migrants): antimalarial treatment** is advised.
- ▶ **Standard regimens** (textbook practice — see Coverage note): long-term **proguanil** or **chloroquine** prophylaxis are the conventional agents; therapy is continued for a prolonged period with serial spleen-size and IgM monitoring.
- ▶ **Supportive:** treat anaemia/cytopenias of hypersplenism; aggressively investigate and treat intercurrent infection — **overwhelming sepsis is the chief killer**.
- ▶ **Splenectomy** is generally avoided (it does not treat the underlying immune disorder and adds lifelong infection risk); it is reserved for refractory hypersplenism/symptomatic massive splenomegaly, with appropriate pre-operative vaccination.

- **Prognosis / caveat:** in cases refractory to therapy, clonal lymphoproliferation may develop and can evolve into a malignant lymphoproliferative disorder — long-term follow-up is mandatory.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Spleen microanatomy (basis of culling/pitting & work hypertrophy).**
Labels: *splenic artery* → *central arteriole*, **white pulp** (B-cell follicle with germinal centre, marginal zone, peri-arteriolar T-cell sheath), **red pulp** (*pulp cords*, *pulp sinuses*), *sinusoidal slits/pores*, *reticulo-endothelial (macrophage) cells*, *splenic venous system*.
- **Diagram 2 — Pathogenesis flow of HMS.** Labels: *Repeated malarial infection* → *polyclonal B-cell activation* (↑IgM, cryoglobulins, immune complexes) → *anti-CD8 cytotoxic IgM* → *loss of suppressor T cells* → ↑CD4:CD8 ratio → *RE / lymphoid hyperplasia & clearance activity* → **massive splenomegaly + hepatomegaly + hypersplenism (anaemia, pancytopenia).**

Clinical / Diagnostic significance

- A reversible, treatable cause of massive splenomegaly in the tropics — early recognition averts unnecessary splenectomy or chemotherapy for a misdiagnosed “lymphoma.”
- The parasite-negative smear with very high IgM and antimalarial-responsive splenomegaly is the diagnostic signature.
- Demonstrates the spleen’s immune/RE “work hypertrophy” physiology and the concept of hypersplenism (splenomegaly + cytopenia + hyperplastic marrow + response to splenectomy).
- Carries a real risk of progression to clonal lymphoproliferative disease, mandating surveillance.

High-yield exam pointers

- *Tropical splenomegaly = Hyperreactive Malarial Splenomegaly (HMS) = old Tropical Splenomegaly Syndrome*; it is a **chronic complication of malaria** (*P. falciparum* / *P. malariae*).
- It is an **immunologic disorder**, NOT high parasitaemia — **smear is often parasite-negative**.
- Hallmarks: **massive splenomegaly + hepatomegaly + very high serum IgM + high malarial antibody titres + hepatic sinusoidal lymphocytosis** (+ peripheral B-cell lymphocytosis in Africa).
- Immunology: cytotoxic IgM vs CD8+ T cells, anti-CD5+ T-cell antibodies, ↑CD4:CD8 ratio, cryoglobulins.
- Presents as an abdominal “dragging” mass ± perisplenic pain, with **anaemia + pancytopenia** (hypersplenism); death is usually from overwhelming sepsis.
- **Massive spleen** = palpable >8 cm below the costal margin or ≥1000 g; **ultrasound** is the imaging of choice; normal spleen <250 g, ≤13 cm.
- Treatment = **prolonged antimalarial chemoprophylaxis/treatment** (good response in endemic areas); **avoid splenectomy**.

- ▶ Refractory cases may undergo **clonal lymphoproliferation** → **malignant lymphoproliferative disorder**.
- ▶ Remember the tropical massive-splenomegaly DDx: **kala-azar, schistosomiasis, CML, myelofibrosis, lymphoma/CLL, Gaucher's**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 231 “Malaria” (Chronic Complications of Malaria → *Hyperreactive Malarial Splenomegaly*: aetiology, immunopathogenesis, clinical features, treatment, lymphoma risk) and Ch 70 “Enlargement of Lymph Nodes and Spleen” (spleen structure/function, mechanisms of splenomegaly Table 70-2, massive-splenomegaly criteria and differential Table 70-3, hypersplenism, examination and imaging). **Coverage note (spec gap = true):** Harrison covers HMS only briefly within the Malaria chapter. Points **not explicitly in the provided Harrison text** but added as standard, universally-accepted tropical-medicine teaching, and flagged here: the **named* Fakunle diagnostic criteria*, the specific prophylactic drugs (proguanil / chloroquine) and the ≥ 10 cm spleen / IgM ≥ 2 SD thresholds, the role/avoidance of splenectomy**, and the detailed geographic distribution. All disease mechanisms, the IgM/CD8/CD5/CD4:CD8 immunology, clinical features, lymphoma risk, the “massively enlarged” definition (> 8 cm / ≥ 1000 g) and the splenomegaly differential are directly grounded in the two cited chapters.



Viral meningitis

Asked in: Paper III Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — **Viral meningitis** is an acute inflammation of the leptomeninges and subarachnoid space (SAS) caused by viral infection, producing headache, fever and meningeal irritation **without** the profound alteration of consciousness, seizures, or focal deficits that characterise encephalitis. It is the commonest cause of the “**aseptic meningitis syndrome**” — a clinical-laboratory picture of meningeal inflammation (CSF lymphocytic pleocytosis, normal glucose, negative routine bacterial Gram's stain and culture) — and is, in the immunocompetent adult, a generally **benign, self-limiting** illness. *Enteroviruses* account for the great majority of identified cases.

Etiology

- ▶ A specific viral cause is now identifiable in **60–90%** of cases using CSF PCR, culture and serology; CSF *cultures* alone are positive in only 30–70%, and about two-thirds of culture-negative “aseptic” cases yield a virus on **CSF PCR**.

- ▶ **Most important / common agents:** *Enteroviruses* (coxsackieviruses, echoviruses, numbered enteroviruses), *varicella-zoster virus* (VZV), *herpes simplex virus* (HSV-2 > HSV-1), *HIV*, and *arboviruses* (notably West Nile virus, WNV).
- ▶ **Less common:** HSV-1, human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), *lymphocytic choriomeningitis virus* (LCMV), mumps, Epstein-Barr virus (EBV), Zika and other non-WNV arboviruses.
- ▶ **Enteroviruses cause >85% of cases in which an agent is identified** — the single dominant cause.

Clinical manifestations

- ▶ **Cardinal features:** headache (almost invariable — frontal/retro-orbital, with **photophobia** and pain on eye movement), fever, and **nuchal rigidity** (often mild, only at the limit of neck anteflexion).
- ▶ **Constitutional:** malaise, myalgia, anorexia, nausea/vomiting, abdominal pain, diarrhoea; mild lethargy or drowsiness is common.
- ▶ **Red flags pointing AWAY from simple viral meningitis (suggest encephalitis or alternative diagnosis):** *stupor, coma, marked confusion, seizures, focal neurological signs*, or neuroimaging evidence of parenchymal involvement. These are NOT features of pure viral meningitis.
- ▶ **Etiological clues on examination** — search for exanthems, *hand-foot-mouth disease, herpangina*, pleurodynia, myopericarditis and haemorrhagic conjunctivitis (enterovirus); genital vesicles (HSV-2); chickenpox/shingles rash (VZV); parotitis/orchitis (mumps); cranial nerve palsies, especially V, VII, VIII (HIV).

Epidemiology

- ▶ Estimated incidence $\geq 75,000$ cases/year in the United States (not a nationally reportable disease).
- ▶ In temperate climates there is a marked **summer–autumn (non-winter) predominance**, reflecting the seasonality of *enterovirus* and *arbovirus* infection; peak monthly incidence ~ 1 case/100,000.
- ▶ **Seasonal/host clues:** enteroviruses — summer/fall, children <15 yr; arboviruses — summer/early fall, geographic clusters; **mumps** — late winter/early spring, males (M:F 3:1); LCMV — late fall/winter, exposure to house mice (*Mus musculus*), pet/laboratory rodents or their excreta.

CSF and laboratory diagnosis

- ▶ CSF examination is the single most important test. Typical viral profile:

Parameter	Viral (aseptic) meningitis	Contrast: pyogenic bacterial
Opening pressure	Normal/mildly raised (100–350 mmH ₂ O)	>180 mmH ₂ O (often markedly)

Parameter	Viral (aseptic) meningitis	Contrast: pyogenic bacterial
Cell type	Lymphocytic pleocytosis	Polymorphonuclear (PMN)
Cell count	Typically 25–500/ μ L (occasionally thousands with LCMV/mumps)	100–10,000/ μ L
Glucose	Normal	Low (<2.2 mmol/L; CSF/serum <0.4)
Protein	Normal/mildly raised (0.2–0.8 g/L)	High (>0.45 g/L)
Gram's stain	Negative	Positive in >60%

- **Exceptions to remember:** PMNs may *predominate in the first 48 h*, especially **echovirus 9, WNV, eastern equine encephalitis virus, and mumps** — a PMN pleocytosis occurs in ~45% of WNV meningitis and may persist a week before shifting to lymphocytes. PMN pleocytosis with low glucose also occurs with CMV in the immunocompromised.
- **Hypoglycorrhachia (low CSF glucose)** is atypical but occurs in 10–30% of mumps and LCMV cases (rarely echovirus/enterovirus, HSV-2, VZV). A lymphocytic pleocytosis *with low glucose* should still raise TB, fungal, *Listeria*, or neoplastic meningitis.
- **CSF PCR** — **diagnostic procedure of choice** for enteroviral and HSV CNS infection; far more sensitive than culture. Enteroviral RT-PCR sensitivity >95%, highest within 48 h, falling rapidly after day 5. The **FilmArray Meningitis/Encephalitis multiplex panel** detects HSV-1, HSV-2, enteroviruses, VZV, HHV-6 and human Parechovirus — but **NOT** CMV, WNV, LCMV or EBV.
- **Serology:** mainstay for **arboviruses (WNV)** — demonstration of **virus-specific IgM in CSF** or seroconversion (CSF WNV IgM more sensitive [>80% in neuroinvasive disease] than CSF RT-PCR ~70%); serology less useful for high-seroprevalence herpesviruses.
- **Viral culture** of CSF is generally poor-yield; ancillary isolation — enterovirus/adenovirus in stool; arbovirus/enterovirus/LCMV in blood; mumps/CMV in urine; enterovirus/mumps/adenovirus in throat washings. Stool enterovirus shedding persists weeks and is *not by itself diagnostic*.
- **Other tests:** full blood count, liver/renal function, ESR, C-reactive protein, electrolytes, glucose, amylase/lipase (mumps). **Neuroimaging (MRI > CT)** is not mandatory in uncomplicated cases but is indicated for altered consciousness, seizures, focal signs, atypical CSF, or immunocompromise. CSF **oligoclonal bands** can occur.

Specific viral etiologies — exam pearls

- ▶ **Enteroviruses** — >85% of identified cases; benign outside the neonatal period; supportive treatment, recovery without sequelae. Chronic/severe infection in neonates and the **hypo-/agammaglobulinaemic**.
- ▶ **HSV** — second to enteroviruses overall (~5% of cases, higher in adults / non-summer). In adults uncomplicated meningitis is mostly **HSV-2**, whereas **HSV-1 causes ~90% of HSV encephalitis**. Meningitis occurs in ~25–35% of **women** and ~10–15% of **men** at primary genital herpes; ~20% develop recurrent attacks. Most **recurrent (“benign lymphocytic”) aseptic meningitis — including cases formerly called Mollaret’s meningitis — is due to HSV** (diagnosed by CSF PCR; cultures often negative).
- ▶ **VZV** — suspect with concurrent chickenpox/shingles, but increasingly recognised **without rash**; frequency 3–20% across series.
- ▶ **Arboviruses (WNV, St. Louis, California group)** — geographic/seasonal clusters; avian deaths can be sentinel for WNV; diagnosis by CSF IgM.
- ▶ **Mumps** — parotitis/orchitis/oophoritis/raised lipase-amylase; clinical meningitis in 10–30% of parotitis; pleocytosis can exceed 1000/μL; incidence fell >95% after vaccination.
- ▶ **HIV** — aseptic meningitis in 5–10% at primary (seroconversion) infection; **cranial nerve V, VII, VIII palsies** are more frequent than with other viruses.
- ▶ **LCMV** — rodent exposure; leukopenia, thrombocytopenia, abnormal LFTs; may show marked pleocytosis and hypoglycorrhachia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Meningeal anatomy / lumbar puncture site (labelled):** scalp — skull — **dura mater** — **arachnoid mater** — **subarachnoid space (CSF, site of inflammation)** — **pia mater** — cerebral cortex; plus a spine schematic marking the **L3–L4 / L4–L5 interspace** for LP below the conus medullaris.
- ▶ **CSF interpretation flow-box (labelled):** “Meningeal signs → LP” → branch A *Lymphocytes + normal glucose + negative Gram’s stain* = **VIRAL/aseptic** → CSF PCR / WNV IgM; branch B *PMN + low glucose + positive Gram’s* = **bacterial**; branch C *Lymphocytes + low glucose* = **TB / fungal / Listeria / neoplastic**.

Clinical / Diagnostic significance

- ▶ **Differential diagnosis is the crux** — exclude mimics of aseptic meningitis: untreated/partially-treated bacterial meningitis; early TB, fungal or *T. pallidum* (neurosyphilis); *Mycoplasma*, *Listeria*, *Brucella*, *Coxiella*, *Leptospira*, *Rickettsia*; parameningeal foci; neoplastic meningitis; and non-infectious inflammatory disease (drug-induced hypersensitivity meningitis, SLE, sarcoidosis, Behçet’s, uveomeningitic syndromes).

- ▶ **Distinguishing bacterial from aseptic:** CSF protein >0.5 g/L and serum procalcitonin >0.5 ng/mL (sensitivity/specificity ~89%) favour bacterial; the validated **Bacterial Meningitis Score** predicts very low bacterial probability (NPV 99.7%) when *all* of — negative CSF Gram's stain, CSF neutrophils <1000/μL, CSF protein <80 mg/dL, peripheral ANC <10,000/μL, and no seizures — are met.
- ▶ **Treatment is principally supportive:** analgesics, antipyretics, antiemetics, fluid/electrolyte care. Empirical antibacterial (± aciclovir) cover is continued until bacterial meningitis is excluded.
- ▶ **Specific antiviral therapy** (benefit data limited): **IV aciclovir 15–30 mg/kg/day in 3 divided doses** for seriously ill HSV/VZV (and severe EBV) cases, stepping down to oral aciclovir 800 mg five times daily, famciclovir 500 mg tid, or valaciclovir 1000 mg tid for a total 7–14 days; mild cases — oral agents alone. *No proven specific therapy* for arboviral (e.g., WNV) disease. **HIV meningitis** → antiretroviral therapy. Per CMDT, antiviral therapy for aseptic meningitis in immunocompetent hosts is of *uncertain benefit* (self-limiting), and long-term oral valaciclovir prophylaxis does **NOT** prevent recurrent HSV-2 aseptic meningitis.
- ▶ **Special hosts:** patients with deficient humoral immunity (e.g., X-linked agammaglobulinaemia) should receive **immunoglobulin (IM γ-globulin or IVIg)**; intraventricular Ig (Ommaya reservoir) has been used for refractory chronic enteroviral meningitis.
- ▶ **Admission criteria:** immunocompetent patients with a classic CSF profile and no red flags may be managed at home with follow-up; **hospitalise** the immunocompromised and any with altered consciousness, seizures, focal signs, or atypical CSF.
- ▶ **Prevention:** vaccination prevents meningitis from **poliovirus, mumps, measles, rubella and varicella**; the recombinant zoster vaccine (Shingrix) is recommended for VZV prevention.

High-yield exam pointers

- ▶ **Aseptic meningitis** = lymphocytic pleocytosis + normal glucose + negative routine bacterial Gram's stain/culture; **viral causes are the commonest**.
- ▶ **Enteroviruses** cause >85% of identified viral meningitis; **summer–autumn** peak; children.
- ▶ **CSF PCR (RT-PCR) is the test of choice**; enteroviral RT-PCR best within **48 h**, declines after day 5.
- ▶ **HSV-2** = leading cause of recurrent / **Mollaret's** aseptic meningitis; **HSV-1** = **encephalitis**.
- ▶ **Early PMN predominance** can occur with **echovirus 9, WNV, EEE, mumps**; ~45% of WNV meningitis has CSF neutrophilia.
- ▶ **Low CSF glucose** in viral meningitis suggests **mumps or LCMV** (10–30%) — but always reconsider TB/fungal/Listeria.
- ▶ **Arbovirus (WNV) diagnosis** = **CSF virus-specific IgM** (more sensitive than CSF RT-PCR).
- ▶ **Profound coma, seizures or focal deficits** → think **encephalitis**, not pure meningitis.

- Treatment is **supportive**; aciclovir for HSV/VZV; **IVIg** for agammaglobulinaemia; antiretrovirals for HIV. **Prognosis in adults is excellent.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — “Acute Meningitis” (Viral Meningitis section: clinical manifestations, etiology, CSF/PCR/serology, specific viral etiologies, treatment, prognosis; comparison data from the Bacterial Meningitis section of the same chapter).
- **CMDT 2026** — “Viral & Rickettsial Infections” (enteroviral syndromes; antiviral/valaciclovir-prophylaxis caveat for HSV-2 aseptic meningitis) and “Nervous System Disorders” (current management framing).



What are the methods used to measure antimicrobial activity in the lab?

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Antimicrobial susceptibility testing (AST)* comprises the standardised in-vitro laboratory methods that quantify the activity of an antimicrobial agent against a bacterial isolate, expressed chiefly as the **minimal inhibitory concentration (MIC)** — the lowest drug concentration that inhibits visible growth of a microorganism under standardised laboratory conditions. AST converts a raw MIC into a clinically actionable category — *susceptible (S)*, *intermediate (I)*, or *resistant (R)* — by comparison with regulatory **breakpoints**, and thereby guides directed (pathogen-targeted) therapy, defines local resistance for the **antibiogram**, and underpins pharmacokinetic–pharmacodynamic (PK/PD) dosing. Methods are broadly **diffusion-based**, **dilution-based (quantitative)**, **automated/rapid phenotypic**, **specialised (bactericidal/synergy)**, and **molecular/genotypic**.

Core endpoints the laboratory measures

- **MIC** — lowest concentration inhibiting growth with a standardised inoculum and growth conditions; the central quantitative endpoint, reported in µg/mL (e.g., vancomycin MIC of 2 µg/mL flags reduced susceptibility in *S. aureus*).
- **Minimal bactericidal concentration (MBC)** — lowest concentration that **kills ≥99.9% (≥3 log₁₀)** of the original inoculum; distinguishes bactericidal from bacteriostatic action.
- **Breakpoint** — the MIC value(s) set by advisory bodies (**CLSI, EUCAST**) that partition isolates into S/I/R; derived from MIC distributions of clinical isolates, drug PK/delivery to the infection site, and clinical-trial outcome data. “Susceptible” predicts likely response to an appropriately dosed drug; “resistant” predicts poor/no response.

- ▶ **Bacteriostatic vs bactericidal** — inhibition of growth vs killing; bactericidal agents are preferred where host defences are impaired or limited (neutropenia, **meningitis**, **endocarditis**).
- ▶ **Tolerance** — organism inhibited but not killed (failure to activate autolysins); operationally an **MBC/MIC ratio ≥ 32** .
- ▶ **Postantibiotic effect (PAE)** — delayed regrowth of surviving bacteria after drug exposure (prominent with aminoglycosides), supporting extended-interval dosing.

Diffusion methods (qualitative / semi-quantitative)

- ▶ **Disk diffusion (Kirby–Bauer)** — standard inoculum (turbidity matched to the 0.5 McFarland standard) is lawn-spread on **Mueller–Hinton agar**; antibiotic-impregnated paper disks are applied; after **16–18 h** at **35 °C** the **zone of inhibition diameter (mm)** is measured and interpreted as S/I/R against CLSI/EUCAST tables. Cheap, flexible, the workhorse of most laboratories; gives a category, **not** a numeric MIC.
- ▶ **Gradient diffusion (E-test / epsilometer) — a plastic strip carrying a predefined exponential antibiotic gradient is laid on inoculated agar; an elliptical inhibition zone forms and the MIC is read where the ellipse intersects the strip**. Combines the simplicity of diffusion with a quantitative MIC; useful for fastidious organisms and for confirming key MICs (e.g., penicillin/pneumococcus, vancomycin/staphylococci).
- ▶ **D-test (double-disk approximation)** — erythromycin and clindamycin disks placed adjacently; flattening (“D” shape) of the clindamycin zone reveals **inducible clindamycin (MLS_B) resistance**.

Dilution (quantitative) methods — the reference for MIC and MBC

- ▶ **Broth dilution** — antibiotic prepared in **doubling (two-fold) serial dilutions** in Mueller–Hinton broth; each tube/well inoculated to a standard density ($\sim 5 \times 10^5$ CFU/mL); the **MIC is the lowest concentration with no visible turbidity** after overnight incubation.
 - *Macrodilution* uses tubes (labour-intensive); *microdilution* uses **96-well microtitre plates** and is the practical reference standard, allowing many drug/dilution combinations per plate.
- ▶ **Agar dilution** — antibiotic incorporated into agar plates at doubling dilutions; multiple isolates spot-inoculated onto each plate; MIC = lowest concentration inhibiting visible growth. Efficient when many isolates are tested against one drug (reference method for some organisms, e.g., *N. gonorrhoeae*).
- ▶ **MBC determination** — aliquots from the clear (no-growth) broth-dilution tubes are subcultured to drug-free agar; colony counts identify the lowest concentration giving **$\geq 99.9\%$ kill = MBC**; the **MBC/MIC ratio** defines tolerance.

Method	Output	Quantitative MIC?	Typical use
Disk diffusion (Kirby–Bauer)	Zone diameter → S/I/R	No	Routine first-line testing
E-test (gradient strip)	MIC (µg/mL)	Yes	Confirm key/borderline MICs, fastidious organisms
Broth microdilution	MIC (µg/mL)	Yes	Reference standard MIC
Agar dilution	MIC (µg/mL)	Yes	Reference for many isolates / one drug
Automated (VITEK 2, Phoenix, MicroScan)	MIC + S/I/R, hours	Yes	High-throughput routine labs

Automated, specialised and bactericidal methods

- ▶ **Automated systems** — VITEK 2, BD Phoenix, MicroScan use micro-volume broth-microdilution cards/panels with **turbidimetric/colorimetric growth monitoring** and software interpretation, delivering identification + MIC in hours; the basis of most clinical antibiograms.
- ▶ ***Serum bactericidal titre (Schlichter test)*** — highest dilution of the patient's serum (during therapy) that kills the infecting organism; historically used to gauge adequacy of therapy in endocarditis/osteomyelitis.
- ▶ **Synergy testing** —
 - *Checkerboard titration* → **fractional inhibitory concentration (FIC) index**: ≤ 0.5 = synergy, $> 0.5-4$ = indifference/additivity, > 4 = antagonism.
 - *Time-kill curves* → a $\geq 2 \log_{10}$ (≥ 100 -fold) greater kill by the combination vs the most active single agent defines synergy; also profiles bactericidal kinetics and PAE.
- ▶ **β -lactamase detection** — chromogenic **nitrocefin** test gives a rapid colour change with β -lactamase-producing organisms (e.g., *H. influenzae*, gonococci, staphylococci).
- ▶ **Screening / breakpoint agars** — e.g., oxacillin/cefoxitin screen for MRSA, vancomycin-screen agar; **population analysis profiling** detects **heteroresistant VISA (hVISA)**, which is *not detectable by routine susceptibility testing*.

Molecular / genotypic methods (detect resistance determinants)

- ▶ **Targeted nucleic-acid amplification (PCR/NAAT)** for resistance genes — *mecA* (methicillin resistance in *S. aureus*), *vanA/vanB* (VRE), *bla*_{KPC} / NDM / OXA-48 carbapenemases, *bla*_{CTX-M} (ESBL).
- ▶ **GeneXpert (Xpert MTB/RIF)** — simultaneous detection of *M. tuberculosis* and **rifampicin resistance** (*rpoB*); for mycobacteria, phenotypic AST uses **liquid culture** (BACTEC MGIT) and the **agar proportion method**.

- ▶ **MALDI-TOF mass spectrometry** — rapid species identification (and adjunctive resistance detection, e.g., carbapenemase hydrolysis assays).
- ▶ **Whole-genome sequencing (WGS)** — comprehensive resistome and epidemiological typing.
- ▶ Caveat: genotype predicts phenotype only for known mechanisms; **phenotypic AST remains the standard** because a gene may be present but unexpressed, or resistance may arise by uncharacterised routes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Disk-diffusion (Kirby–Bauer) plate** — Mueller–Hinton agar with confluent bacterial lawn; several antibiotic disks; clear circular *zone of inhibition* around a sensitive disk vs growth up to the edge of a resistant disk. Labels: *Mueller–Hinton agar, antibiotic disk, zone of inhibition (mm), confluent lawn (0.5 McFarland inoculum), susceptible, resistant*.
- ▶ **Broth microdilution row + MIC/MBC schematic** — a row of wells/tubes with doubling antibiotic concentrations: turbid (growth) wells then the first clear well = **MIC**; subculture of clear wells to agar with the first plate showing $\geq 99.9\%$ kill = **MBC**. Labels: *doubling dilutions ($\mu\text{g/mL}$), turbid = growth, first clear well = MIC, subculture $\rightarrow$ MBC, MBC/MIC ≥ 32 = tolerance*.

Clinical / Diagnostic significance

- ▶ Obtain specimens for culture **before** starting antibiotics so AST can convert empirical therapy into narrow-spectrum **directed therapy**, reducing toxicity, resistance selection, and *C. difficile* risk.
- ▶ MIC + breakpoint individualise drug choice — e.g., pneumococcal endocarditis treated by **penicillin MIC** (penicillin if MIC ≤ 2 $\mu\text{g/mL}$; ceftriaxone/vancomycin if higher); **meningitis breakpoints** are stricter (penicillin MIC 0.06 $\mu\text{g/mL}$) because of limited CSF penetration.
- ▶ The **MIC anchors PK/PD targets**: aminoglycosides $\rightarrow$ **C_{max}/MIC** (concentration-dependent); β -lactams $\rightarrow$ **T > MIC** (time-dependent); fluoroquinolones & vancomycin $\rightarrow$ **AUC/MIC** (e.g., AUC/MIC > 30 maximises fluoroquinolone kill of *S. pneumoniae*; > 125 for gram-negatives).
- ▶ The **cumulative antibiogram** (local S/I/R rates, usually annual) guides empirical regimens and stewardship; therapeutic drug monitoring (e.g., vancomycin) is interpreted against the MIC.
- ▶ Recognise the **MBC/MIC ratio** (tolerance) and **hVISA** as reasons for clinical failure despite a “susceptible” routine report.

High-yield exam pointers

- ▶ **MIC = lowest concentration inhibiting visible growth; MBC = lowest killing $\geq 99.9\%$ ($\geq 3 \log_{10}$).**
- ▶ **Kirby–Bauer disk diffusion**: Mueller–Hinton agar, **0.5 McFarland inoculum**, 16–18 h/35 °C, read **zone diameter** $\rightarrow$ S/I/R; gives a category, *not* an MIC.

- ▶ **Broth microdilution** = reference standard for numeric MIC; **agar dilution** for many isolates/one drug; E-test gives MIC by gradient diffusion.
- ▶ **Breakpoints** are set by CLSI / EUCAST; categories are S / I / R.
- ▶ **Tolerance** = MBC/MIC ≥ 32 ; **synergy** = FIC index ≤ 0.5 (checkerboard) or $\geq 2 \log_{10}$ extra kill (time-kill).
- ▶ **Automated systems**: VITEK 2, BD Phoenix, MicroScan (turbidimetric microdilution).
- ▶ **Molecular**: PCR for *mecA*, *vanA/B*, KPC/NDM/OXA; Xpert MTB/RIF for rifampicin resistance; MALDI-TOF for rapid ID; phenotypic AST still the gold standard.
- ▶ hVISA is missed by routine AST — needs **population analysis profiling**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Treatment and Prophylaxis of Bacterial Infections*” (MIC definition; bacteriostatic vs bactericidal; PK/PD indices C_{max}/MIC, T>MIC, AUC/MIC; postantibiotic effect; antibiogram); “*Bacterial Resistance to Antimicrobial Agents*” (MIC, breakpoints, S/I/R interpretation, resistance mechanisms); “*Infective Endocarditis*” (vancomycin/penicillin MICs, meningitis breakpoints, hVISA not detected by routine testing); diagnostic-microbiology content (*mecA*/NAAT detection).
- ▶ **CMDT 2026** — *Anti-infective Treatment* (mechanism/“tolerance”, MIC-targeted dosing) and *Common Problems in Infectious Diseases & Antimicrobial Therapy*.

Coverage note: The corpus (Harrison 22e, CMDT 2026) is pharmacology- and resistance-focused and covers the **endpoints** (MIC, breakpoints, S/I/R, bacteriostatic/bactericidal, tolerance, PK/PD, antibiogram, hVISA, *mecA*/NAAT) but is **thin on the step-by-step laboratory procedures**. The procedural detail of disk diffusion (Kirby–Bauer), broth macro-/micro-dilution, agar dilution, E-test, MBC determination, serum bactericidal titre, checkerboard/time-kill synergy, β -lactamase/nitrocefin and D-tests, automated systems and MALDI-TOF/WGS is supplied here from **universally accepted standard clinical microbiology (CLSI/EUCAST methodology)** and is faithful to that standard.



Respiratory system



Acute interstitial pneumonia

Asked in: Paper III May 2022 · Paper III Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — *Acute interstitial pneumonia (AIP)*, historically termed *Hamman-Rich syndrome*, is a rare and often fatal idiopathic interstitial pneumonia (IIP) characterised by the **acute**

onset of respiratory distress and hypoxemia in a previously healthy individual, with diffuse alveolar damage (DAD) as its histopathologic hallmark. It is essentially the idiopathic (cryptogenic) counterpart of ARDS: the clinical, radiologic, and pathologic picture is indistinguishable from ARDS but no precipitating cause is identified. AIP is grouped among the *acute/subacute* idiopathic interstitial pneumonias and carries a mortality of >50% within 6 months of presentation.

Where AIP sits — classification of interstitial lung disease

The interstitial lung diseases (ILDs / diffuse parenchymal lung diseases) are first divided into those of known and unknown cause; AIP belongs to the largest “unknown cause” group, the idiopathic interstitial pneumonias (IIPs).

ILD of known cause	ILD of unknown cause
Exposure — asbestosis, silicosis, radiation, drugs (methotrexate, amiodarone, nitrofurantoin, bleomycin, chemotherapeutics)	Idiopathic interstitial pneumonias (IIPs) — IPF, NSIP, RB-ILD, DIP, COP, AIP, lymphocytic interstitial pneumonia
Systemic / CTD — RA, scleroderma, polymyositis-dermatomyositis, SLE, Sjögren	Granulomatous — sarcoidosis
Granulomatous with vasculitis — GPA (Wegener’s), Churg-Strauss; HP	Other — LAM, pulmonary alveolar proteinosis, Langerhans cell histiocytosis, pleuroparenchymal fibroelastosis

- ▶ Among IIPs, AIP is one of only a few that **present acutely (days–weeks)**; most IIPs (e.g., IPF) are chronic and indolent.
- ▶ Other ILDs that can present *acutely* and enter the differential of AIP: **eosinophilic pneumonia**, **hypersensitivity pneumonitis (HP)**, **granulomatosis with polyangiitis (GPA)**, and an **acute exacerbation of IPF**.
- ▶ Because of overlapping clinical, imaging, and histopathologic features, a **multidisciplinary diagnosis** (pulmonologist + radiologist + pathologist ± rheumatologist) is the accepted standard for all IIPs, AIP included.

Clinical features & natural history

- ▶ **Demographics / onset:** AIP affects previously healthy adults with **no antecedent lung disease**; onset is abrupt.
- ▶ A **prodrome resembling an acute upper respiratory tract infection** (viral-like illness — fever, myalgia, cough) is common and precedes rapidly worsening dyspnea.
- ▶ **Acute respiratory distress and refractory hypoxemia** develop over days to a few weeks, frequently progressing to respiratory failure requiring mechanical ventilation.
- ▶ **Course / prognosis:** fulminant — **mortality >50% within 6 months**; **recurrences are common** in survivors. Importantly, those who do recover can show **substantial recovery of lung function**.

- ▶ **Physical signs (general to ILD):** end-inspiratory fine **bibasal crackles (rales)**; tachypnea, cyanosis and signs of advanced disease (digital clubbing, cor pulmonale) reflect severity.
- ▶ A central diagnostic difficulty is that AIP is **hard to distinguish from ARDS and from an acute exacerbation of an unsuspected underlying pulmonary fibrosis** — making AIP largely a diagnosis of exclusion.

Investigations

- ▶ **HRCT thorax (standard of care):** the most common findings are **patchy, bilateral ground-glass opacities**, with **dependent regions of air-space consolidation** — a picture that mirrors ARDS.
- ▶ **Pulmonary function tests:** like other ILDs, AIP produces a **restrictive defect** — reduced TLC, symmetrically reduced FEV1 and FVC (preserved/normal FEV1:FVC ratio), and a reduced DLCO; in the acute setting testing is often limited by the patient's critical status.
- ▶ **Arterial blood gases:** type I respiratory failure with widened A-a gradient.
- ▶ **Exclusion work-up (essential, as AIP is idiopathic):** rule out infection (including *Pneumocystis*, viral, atypical pneumonia), left heart failure, diffuse alveolar hemorrhage, drug toxicity and CTD — via cultures, BAL, echocardiography and **immune serologies** (e.g., anti-CCP, ANA).
- ▶ **Bronchoscopy + BAL:** chiefly used to **exclude infection and alveolar hemorrhage**; bronchoscopic samples are generally insufficient to *diagnose* an IIP.
- ▶ **Surgical (VATS) lung biopsy:** the only way to confirm DAD; however it carries a **short-term mortality of up to ~5%**, which is **higher in acutely presenting patients** — so the decision must weigh diagnostic yield against risk.

Histopathology — diffuse alveolar damage (DAD)

- ▶ The defining lesion of AIP on surgical lung biopsy is **diffuse alveolar damage (DAD)** — the same pattern seen in ARDS and in **acute exacerbations of underlying pulmonary fibrosis**.
- ▶ DAD classically evolves through two phases (*standard histology, see Coverage note*):
 - **Exudative (acute) phase** — interstitial/alveolar edema, capillary congestion, and **hyaline membranes** lining alveolar ducts.
 - **Organising (proliferative) phase** — **type II pneumocyte hyperplasia**, fibroblastic proliferation and loose interstitial fibrosis; this temporally *uniform* fibrosis helps separate AIP from the temporally heterogeneous UIP of IPF.

Differential diagnosis — AIP vs ARDS vs acute exacerbation of IPF

Feature	AIP (Hamman-Rich)	ARDS	Acute exacerbation of IIP/IPF
Precipitating cause	None identified (idiopathic)	Identifiable insult (sepsis, aspiration,	Occurs on known underlying pulmonary fibrosis

Feature	AIP (Hamman-Rich)	ARDS	Acute exacerbation of IIP/IPF
		trauma, pancreatitis, etc.)	
Prior lung disease	Absent	Usually absent	Present (e.g., IPF)
Onset	Acute, days–weeks	Acute (≤ 1 week of insult)	Acute (< 30 days)
HRCT	Bilateral ground-glass + dependent consolidation	Bilateral infiltrates / consolidation	New ground-glass + consolidation superimposed on fibrosis (honeycombing/reticulation)
Histology	DAD	DAD	DAD ($\pm$ organising pneumonia)
Mortality	$> 50\%$ at 6 months	Variable	Very high ($> 85\%$)

Treatment

- **Predominantly supportive** — AIP is managed like ARDS: **supplemental oxygen and mechanical ventilation** with lung-protective strategy, treatment of intercurrent infection, and supportive ICU care.
- **There is no proven drug therapy for AIP.**
- **Glucocorticoids** are *often given* (e.g., high-dose corticosteroids) but are **not clearly effective**, and the supporting evidence — extrapolated from other forms of DAD such as ARDS — is **controversial**.
- General supportive measures applicable to progressive ILD (oxygen, pulmonary rehabilitation) and, in highly selected survivors with progressive fibrosis, consideration of **lung transplantation**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **HRCT thorax (axial) in AIP** — labels: *bilateral ground-glass opacities; dependent (posterior/basal) air-space consolidation; relatively preserved non-dependent lung; absence of honeycombing.*
- **Histology of diffuse alveolar damage (DAD)** — labels: *alveolar space; hyaline membranes lining alveolar duct (exudative phase); type II pneumocyte hyperplasia; fibroblastic proliferation / interstitial thickening (organising phase); congested alveolar capillary.*

Clinical / Diagnostic significance

- AIP must be considered in any **previously healthy patient with rapidly progressive dyspnea, hypoxemia and bilateral infiltrates** once infection and cardiac failure are excluded — it is

frequently misdiagnosed as community-acquired pneumonia, COPD exacerbation or heart failure.

- ▶ It is a **diagnosis of exclusion**: clinically and radiologically identical to ARDS, so the absence of an ARDS trigger and the histologic demonstration of DAD (when biopsy is feasible) clinch the diagnosis.
- ▶ Recognising AIP carries **prognostic weight** (high early mortality, frequent recurrence) and shapes **goals-of-care discussions**, while reminding the clinician that no specific pharmacotherapy is established.
- ▶ Distinguishing AIP from an **acute exacerbation of IPF** matters because the latter implies pre-existing fibrosis and an even worse outlook; HRCT background fibrosis is the key discriminator.

High-yield exam pointers

- ▶ AIP = Hamman-Rich syndrome = **idiopathic ARDS**; histology = **diffuse alveolar damage (DAD)**.
- ▶ One of the **idiopathic interstitial pneumonias**; among the few IIPs with an **acute** presentation.
- ▶ **Prodrome** mimicking an upper respiratory tract viral illness is characteristic.
- ▶ **HRCT**: bilateral **ground-glass opacities + dependent consolidation**.
- ▶ **PFT**: restrictive pattern — ↓TLC, ↓FVC, ↓DLCO.
- ▶ **Mortality >50% within 6 months; recurrences common**; survivors may regain substantial lung function.
- ▶ **No proven drug therapy** — care is **supportive ± mechanical ventilation**; glucocorticoids used but unproven/controversial.
- ▶ Key differentials: **ARDS** (identifiable cause) and **acute exacerbation of IPF/IIP** (underlying fibrosis, mortality >85%).
- ▶ Confirmatory test = **surgical/VATS lung biopsy showing DAD**, but biopsy mortality is higher in acutely ill patients.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 304 "Interstitial Lung Disease" (AIP / Hamman-Rich subsection under *Acute or Subacute IIPs*; plus the chapter's general sections on ILD classification, history/examination, PFTs, HRCT, lung biopsy, and acute exacerbations of IIPs).

Coverage note (spec.gap = true): Harrison 22e covers AIP only briefly. The chapter explicitly supports: the Hamman-Rich eponym; classification among IIPs; acute respiratory-distress presentation with viral-like prodrome; >50% 6-month mortality with frequent recurrence and possible functional recovery; HRCT (ground-glass + dependent consolidation); DAD histology;

difficulty distinguishing from ARDS and acute exacerbation of fibrosis; and supportive treatment with no proven drug therapy and unproven glucocorticoids. Items added from universally accepted standard internal medicine but **not detailed in the provided chapter** (flagged here): the two-phase microscopic anatomy of DAD (exudative phase with hyaline membranes → organising/proliferative phase with type II pneumocyte hyperplasia and fibroblast proliferation), and the framing of AIP as a “diagnosis of exclusion.” These are accurate standard histopathology/diagnostic concepts; specific case definitions/criteria (e.g., Katzenstein/ATS-ERS formal diagnostic criteria) were not asserted as they are not given in the provided text.



Acute Pulmonary Embolism

Asked in: Paper III Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Pulmonary embolism (PE) is obstruction of the pulmonary arterial tree by thrombus that has usually embolised from a lower-limb deep-venous thrombosis (DVT); DVT and PE together constitute **venous thromboembolism (VTE)**. PE is “*the great masquerader*” — its symptoms and signs are non-specific, so a structured, probability-based pathway (clinical score → D-dimer → imaging → risk stratification → therapy) is essential. Acute PE spans a wide spectrum from clinically silent subsegmental clot to fulminant **massive** PE with cardiogenic shock and death from acute right-ventricular (RV) failure.

Aetiology and Pathophysiology

- ▶ **Virchow’s triad** — venous stasis, hypercoagulability and endothelial injury, usually with an inflammatory trigger, drive thrombus formation; activated platelets release microparticles that recruit neutrophils and form **neutrophil extracellular traps**, promoting thrombin generation.
- ▶ **Inherited thrombophilias** (autosomal dominant): *factor V Leiden* (activated protein C resistance) and the *prothrombin gene mutation* are commonest; antithrombin, protein C and protein S deficiencies are rarer but stronger.
- ▶ **Acquired**: antiphospholipid syndrome (APS — venous *and* arterial thrombosis, often needs lifetime anticoagulation), cancer, surgery/trauma, immobility, obesity, oestrogens, pregnancy and the first 6–12 weeks postpartum, long-haul travel, smoking, COPD, CKD, and inflammatory disease (IBD, RA).
- ▶ **Embolisation**: leg thrombi detach, traverse the vena cava and right heart, and lodge in the pulmonary arteries; *paradoxical* arterial embolism may occur through a patent foramen ovale.
- ▶ **Consequences**:

- *Gas exchange* — arterial hypoxaemia (present in ~85%) and a widened alveolar–arterial O₂ gradient from V/Q mismatch, increased alveolar dead space, right-to-left shunting and surfactant loss; reflex hyperventilation lowers PaCO₂.
- *Haemodynamics* — mechanical obstruction plus vasoconstrictors (serotonin, thromboxane A₂, endothelin) raise pulmonary vascular resistance → ↑RV wall tension → RV dilation, septal bowing into the LV, impaired LV filling, ↓cardiac output and hypotension. RV pressure overload also compresses the right coronary artery → **RV microinfarction** (troponin release) and BNP elevation from myocardial stretch.

Clinical Features and Classification

- ▶ **Symptoms** — unexplained **dyspnoea** is the most common (absent in ~25%); pleuritic chest pain (~⅓), cough, haemoptysis (modest), and syncope/pre-syncope with large emboli. Three PIOPED syndromes: *pleuritic pain/haemoptysis* (~60%), *isolated dyspnoea* (~25%), *circulatory collapse* (~10%).
- ▶ **Signs** — tachypnoea (commonest sign, RR >20), tachycardia, accentuated pulmonary component of S2, RV heave, crackles; with RV failure — raised JVP, fixed/narrow split S2, S3/S4, cyanosis and hypotension. Coexisting DVT (calf “charley-horse”, unilateral swelling/tenderness) is clinically apparent in only ~10%.
- ▶ **Severity classification (ESC / Harrison)** — guides every management decision:

Category	Frequency	Haemodynamics	RV / biomarkers	Prognosis
Massive (high-risk)	5–10%	SBP <90 mmHg / shock / arrest	Severe RV failure	High mortality
Submassive (intermediate-risk)	20–25%	Normotensive	RV dysfunction ± ↑troponin/BNP	May deteriorate abruptly
Low-risk	65–75%	Normotensive	Normal RV, normal biomarkers	Excellent

- ▶ *Special forms*: pulmonary infarction (peripheral, exquisitely pleuritic), and **non-thrombotic PE** — fat (long-bone/pelvic fracture), amniotic fluid, air, tumour, cement/bony fragment (after hip/knee replacement).

Diagnostic Approach

- ▶ **Step 1 — Pre-test probability**: *Wells score* (validated in ambulatory, not hospitalised, patients): clinical signs of DVT 3, alternative diagnosis less likely than PE 3, HR >100 = 1.5, immobilisation/surgery <4 wks = 1.5, prior PE/DVT 1.5, haemoptysis 1, cancer 1; **high likelihood if score >4**. Revised Geneva (objective only), PERC (8 items — excludes PE in low-risk ED patients) and the **YEARS** algorithm refine selection.

- ▶ **Step 2 — D-dimer:** quantitative ELISA, sensitivity >95%; a normal result *rules out* PE in low/intermediate probability. Not specific (raised in MI, sepsis, cancer, pregnancy, post-op) and unhelpful in inpatients. Use the **age-adjusted cut-off** ($\text{age} \times 10 \text{ ng/mL}$) in patients >50 yrs with low/intermediate probability. High-probability patients skip D-dimer and go straight to imaging.
- ▶ **Step 3 — Imaging:**
 - **CT pulmonary angiography (CTPA)** — principal test; demonstrates intraluminal filling defects to subsegmental level, gives a four-chamber view; an **RV:LV diameter ratio >1** predicts 30-day death and offers alternative diagnoses.
 - **V/Q lung scan** — second-line (contrast allergy, renal impairment, pregnancy); *high probability* = ≥ 2 segmental perfusion defects with normal ventilation; near-normal scan makes PE very unlikely.
 - **Venous compression ultrasonography** — first test for DVT; loss of vein compressibility (the “wink”) is the key sign; sensitivity/specificity >95% for symptomatic proximal DVT.
 - **Echocardiography** — not for diagnosis (most PE have normal echo) but invaluable for risk stratification and to exclude mimics (tamponade, MI, aortic dissection); *McConnell’s sign* = RV free-wall hypokinesis with preserved apex.
 - **Invasive pulmonary angiography / MR** — reserved for equivocal CT or when catheter intervention is planned.
- ▶ **Ancillary:**
 - **ECG** — sinus tachycardia (commonest); *S1Q3T3*; T-inversion V1–V4 (RV strain — most common abnormality); RBBB, AF.
 - **CXR signs (eponyms)** — *Westermarck’s sign* (focal oligemia), *Hampton’s hump* (peripheral pleural-based wedge of infarction), *Palla’s sign* (enlarged right descending pulmonary artery).
 - **Cardiac biomarkers** — troponin (RV microinfarction), BNP/NT-proBNP (RV stretch) — both prognostic.

Risk Stratification (prognosis-driven)

- ▶ **PESI** (11 variables) stratifies 30-day mortality into classes I–V (≈ 0 –1.6% in class I up to $\approx 25\%$ in class V). The **simplified PESI (sPESI)** uses 6 binary variables — **sPESI = 0 indicates low risk; ≥ 1 indicates high risk:**

sPESI variable (1 point each)
Age >80 years
History of cancer
Chronic cardiopulmonary disease

sPESI variable (1 point each)Pulse $\geq 110/\text{min}$ Systolic BP $< 100 \text{ mmHg}$ Arterial O₂ saturation $< 90\%$

- Combining a normotensive patient's sPESI/PESI with imaging RV strain and troponin/BNP separates *intermediate-low* from *intermediate-high* risk. PEITHO (n=1006, normotensive submassive PE) showed tenecteplase cut haemodynamic collapse (2.6% vs 5.6%) but trebled intracranial haemorrhage (2.0% vs 0.2%) — hence the standard for submassive PE is **anticoagulation with close monitoring**, reserving rescue thrombolysis for decompensation.

Management

- Anticoagulation** is the foundation; start empirically if suspicion is high and bleeding risk low.

Drug	Regimen (normal renal function)
UFH	80 U/kg bolus $\rightarrow$ 18 U/kg/h, target aPTT 60–80 s (anti-Xa 0.3–0.7 U/mL)
Enoxaparin (LMWH)	1 mg/kg SC twice daily
Fondaparinux	weight-based once daily SC (no HIT; reduce in renal failure)
Rivaroxaban	15 mg BD $\times$ 3 weeks $\rightarrow$ 20 mg OD
Apixaban	10 mg BD $\times$ 1 week $\rightarrow$ 5 mg BD
Dabigatran / Edoxaban	after ≥ 5 days parenteral heparin $\rightarrow$ dabigatran 150 mg BD / edoxaban 60 mg OD
Warfarin	bridge with parenteral agent ≥ 5 days until INR 2.0–3.0 $\times$ 2 readings

- DOACs are first-line for most patients (fixed dosing, no monitoring). **Warfarin (not DOAC)** for APS; LMWH/DOAC (avoid in GI cancer) for malignancy-associated VTE. For HIT, use argatroban or bivalirudin. Avoid DOACs in pregnancy/breastfeeding.
- Reversal:** protamine (heparin/LMWH), *idarucizumab* (dabigatran), *andexanet alfa*/PCC (anti-Xa DOACs).
- Duration:** ≥ 3 months; extended/indefinite therapy if no identifiable provoker, persistent risk factor, recurrent VTE, active cancer or APS (ESC 2019 abandons the “provoked vs unprovoked” dichotomy).
- Massive (high-risk) PE:**
 - Cautious fluid ($\approx 500 \text{ mL}$ normal saline — over-filling worsens RV strain); **noradrenaline** (vasopressor) + **dobutamine** (inotrope); **VA-ECMO** for refractory shock.

- **Systemic thrombolysis** — **alteplase (rt-PA) 100 mg IV over 2 h** (0.6 mg/kg, max 50 mg, over 15 min in cardiac arrest); major bleeding ~10%, intracranial haemorrhage 2–3%.
Contraindications: intracranial disease, recent surgery/trauma, active bleeding, recent stroke.
- **Catheter-directed therapy** (pharmacological / mechanical / pharmacomechanical, incl. ultrasound-assisted low-dose thrombolysis) and **surgical pulmonary embolectomy** when thrombolysis fails or is contraindicated.
- ▶ **IVC filter** — only for (1) active bleeding precluding anticoagulation or (2) recurrent VTE despite adequate anticoagulation; prefer a *retrievable* filter.
- ▶ **Prophylaxis** — low-dose UFH (5000 U BD/TDS), LMWH (enoxaparin 40 mg OD), fondaparinux, or mechanical (IPC/graduated stockings) when anticoagulation is contraindicated.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic-and-management algorithm flowchart** — boxes: *Suspected PE* → *assess clinical probability (Wells)* → *low/intermediate: D-dimer (normal → PE excluded; raised → CTPA)* / *high: straight to CTPA* → *PE confirmed* → *risk stratify (BP, RV function, troponin, sPESI)* → *Low-risk: anticoagulate ± early discharge* | *Submassive: anticoagulate + monitor* | *Massive (hypotension): thrombolysis / embolectomy + haemodynamic support*.
- ▶ **Pathophysiology of RV failure in PE** — labels: *PE* → *↑pulmonary vascular resistance* → *↑RV wall tension* → *RV dilation & dysfunction* → *interventricular septal shift* → *↓LV preload* → *↓cardiac output & systemic BP* → *↓coronary perfusion* → *RV ischaemia/microinfarction (troponin↑)* → *circulatory collapse*.

Clinical / Diagnostic significance

- ▶ A *normal D-dimer* with low pre-test probability safely avoids imaging and radiation; conversely, never delay imaging in a high-probability patient.
- ▶ **RV:LV ratio >1 on CTPA**, a positive troponin and RV dysfunction on echo identify the patient who looks stable but may collapse — admit and monitor.
- ▶ *Saddle embolus* on CT is usually haemodynamically stable and treated with anticoagulation alone — **haemodynamics, not clot bulk, predict mortality**.
- ▶ **CTEPH** complicates ~2% of acute PE; follow patients with persistent dyspnoea/PH at ~6 weeks and 6 months with echocardiography — pulmonary thromboendarterectomy can be curative.
- ▶ *Post-PE syndrome* (persistent dyspnoea, fatigue, reduced exercise capacity, residual RV dysfunction) affects up to half of survivors.

High-yield exam pointers

- ▶ PE = “great masquerader”; commonest symptom **dyspnoea**, commonest sign **tachypnoea**, commonest ECG finding **sinus tachycardia** (then T-inversion V1–V4, then S1Q3T3).

- ▶ Eponyms: **Westermarck** (oligaemia), **Hampton's hump** (infarct), **Palla** (enlarged RDPA), **McConnell** (RV free-wall hypokinesis, apical sparing).
- ▶ Wells: high probability if >4; age-adjusted D-dimer = $\text{age} \times 10 \text{ ng/mL}$ (>50 yrs).
- ▶ CTPA is the principal diagnostic test; V/Q second-line; **compression USG** for DVT.
- ▶ Classification: **massive** 5–10%, **submassive** 20–25%, **low-risk** 65–75%; **sPESI ≥ 1 = high risk**.
- ▶ Massive PE: **alteplase 100 mg over 2 h** + noradrenaline + dobutamine $\pm$ VA-ECMO.
- ▶ **DOAC first-line**; warfarin for APS; LMWH/DOAC for cancer; argatroban/bivalirudin for HIT.
- ▶ IVC filter only for anticoagulation contraindication or recurrent VTE despite anticoagulation.
- ▶ **PEITHO** — thrombolysis in submassive PE prevents collapse but causes intracranial bleeding $\rightarrow$ monitor, don't lyse routinely.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "*Deep-Venous Thrombosis and Pulmonary Thromboembolism*" (classification, Wells criteria, D-dimer, CTPA/V/Q/echo, anticoagulation regimens, thrombolysis, IVC filter, CTEPH, prophylaxis).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — "*Pulmonary Thromboembolism: Presentation and Diagnosis*" and "*Pulmonary Thromboembolism: Prophylaxis and Treatment*" (pathophysiology, PIOPED syndromes, clinical prediction rules incl. Geneva/PERC/YEARS, PESI/sPESI, PEITHO, systemic/low-dose/catheter thrombolysis, surgical embolectomy).
- ▶ **CMDT 2026** — "*Pulmonary Disorders*" (three-tier risk stratification, current anticoagulation/thrombolysis/embolectomy management, admission criteria).



Acute respiratory distress syndrome

Asked in: Paper III Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Adult respiratory distress syndrome is now termed **acute respiratory distress syndrome (ARDS)** because the syndrome also occurs outside adulthood. It is an acute inflammatory lung-injury syndrome presenting as **noncardiogenic permeability pulmonary edema**, severe hypoxemia, bilateral pulmonary opacities, reduced lung compliance, and acute respiratory failure. It is a clinical syndrome, not a single disease; there is no diagnostic gold standard, so diagnosis requires a compatible insult, exclusion of hydrostatic edema as the primary cause, and assessment of oxygenation severity.

Etiology and risk factors

- ▶ **Common causes:** most cases are due to **pneumonia and sepsis** (about 40-60%), followed by aspiration of gastric contents, trauma, multiple transfusions, and drug overdose.
- ▶ **Risk increases** with multiple predisposing insults, older age, chronic alcohol abuse, pancreatitis, pneumonia/sepsis, and greater severity of critical illness.

Direct lung injury	Indirect lung injury
Pneumonia, including viral pneumonias	Sepsis
Aspiration of gastric contents	Severe trauma, multiple fractures, flail chest, head injury
Pulmonary contusion	Multiple transfusions
Near-drowning	Pancreatitis
Toxic inhalation, smoke, chlorine, ammonia	Burns, shock, DIC
Fat/air/amniotic embolism, miliary TB	Drug overdose, postcardiopulmonary bypass

Pathophysiology and phases

- ▶ Central lesion is **diffuse alveolar damage** with injury to **alveolar-capillary endothelium** and **type I pneumocytes**, causing leakage of protein-rich edema fluid into interstitium and alveoli.
- ▶ Cytokines and mediators (**IL-1, IL-6, IL-8, TNF-alpha, leukotriene B4**) recruit neutrophils; neutrophils release proteases, reactive oxygen species and NETs, worsening epithelial and endothelial injury.
- ▶ **Surfactant dysfunction** and alveolar flooding produce dependent atelectasis, low compliance, intrapulmonary shunt, refractory hypoxemia, increased work of breathing and eventual respiratory failure.
- ▶ Pulmonary vascular injury causes **microthrombi**, increased dead space, pulmonary hypertension and sometimes hypercapnia; hypoxemia and hypercapnia further impair alveolar sodium and water clearance.

Phase	Time course	Pathology / clinical implication
Exudative	First 0-7 days; symptoms often 12-36 h after insult, sometimes delayed 5-7 days	Neutrophil-rich edema, hyaline membranes, surfactant loss, severe dyspnea, tachypnea, refractory hypoxemia
Proliferative	About day 7-21	Organization of exudate, type II pneumocyte proliferation, repair; some develop early fibroproliferation
Fibrotic	Around >3 weeks or persistent ARDS	Interstitial/alveolar-duct fibrosis, bullae, low compliance, dead

Phase	Time course	Pathology / clinical implication
		space, pulmonary hypertension, pneumothorax risk

Diagnostic criteria and classification

- ▶ Use the **Berlin definition**: acute onset within 1 week of a known clinical insult or new/worsening respiratory symptoms; bilateral opacities on chest radiograph or CT not fully explained by effusion, lobar collapse or nodules; respiratory failure not fully explained by cardiac failure or fluid overload.
- ▶ If no clear ARDS risk factor is present, perform objective assessment such as **echocardiography** to exclude hydrostatic pulmonary edema.
- ▶ Oxygenation severity is assessed on PEEP or CPAP ≥ 5 cm H₂O:

Severity	PaO ₂ /FiO ₂ ratio
Mild ARDS	>200 to $\leq$ 300 mm Hg
Moderate ARDS	>100 to $\leq$ 200 mm Hg
Severe ARDS	$\leq$ 100 mm Hg

- ▶ Proposed newer updates permit ARDS assessment in selected nonintubated patients on high-flow nasal oxygen or noninvasive support using PaO₂/FiO₂ or SpO₂/FiO₂ ratios; arterial PaO₂ should still be checked when feasible.

Clinical features and investigations

- ▶ Presentation is **rapid-onset dyspnea**, tachypnea, labored breathing, intercostal retractions, crackles, high oxygen requirement and hypoxemia poorly corrected by supplemental oxygen.
- ▶ CXR shows diffuse or patchy **bilateral opacities** that may become confluent; heart size is usually normal and pleural effusions are small or absent, unlike typical cardiogenic pulmonary edema.
- ▶ CT shows bilateral infiltrates with marked heterogeneity and dependent edema/atelectasis; lung ultrasound may show nonhomogeneous B lines, irregular pleura, subpleural or translobar consolidation and reduced pleural sliding.
- ▶ ABG quantifies PaO₂/FiO₂, hypercapnia and pH; evaluate the precipitant with cultures, sepsis workup, aspiration history, trauma/transfusion/drug history and organ dysfunction assessment.
- ▶ Important differentials are **cardiogenic pulmonary edema**, bilateral pneumonia, diffuse alveolar hemorrhage, acute interstitial pneumonitis, hypersensitivity pneumonitis, radiation/toxin pneumonitis and neurogenic pulmonary edema.

Management

- ▶ **Treat the cause first:** early antibiotics and source control for sepsis/pneumonia, aspiration precautions, trauma/burn management, stop offending drugs, and manage shock without persistent fluid overload.
- ▶ Provide ICU bundled care: VTE prophylaxis, stress-ulcer/aspiration prevention when indicated, avoidance of excessive sedation, ventilator liberation protocols, nutrition preferably enteral, prevention of catheter infections and prompt recognition of VAP/nosocomial infection.
- ▶ **Lung-protective ventilation:** use tidal volume about **6 mL/kg predicted body weight** (not actual weight), target **plateau pressure** ≤ 30 cm H₂O, RR generally ≤ 35 /min, SpO₂ 88-95% or PaO₂ 55-80 mm Hg, and reduce FiO₂ as soon as possible, preferably ≤ 0.6 when feasible.
- ▶ **PEEP:** titrate PEEP to recruit alveoli, maintain oxygenation and reduce FiO₂, while avoiding overdistension, hypotension and reduced cardiac output; no single PEEP-setting method is universally superior.
- ▶ **Prone ventilation:** in severe ARDS, especially PaO₂/FiO₂ < 150 mm Hg, early prolonged proning (about ≥ 16 h/day) improves oxygenation and has shown mortality benefit in experienced centers; avoid or be cautious with unstable spine, raised ICP, massive hemoptysis, recent facial/tracheal surgery or severe hemodynamic instability.
- ▶ **Conservative fluids:** after shock is corrected, restrict fluids and use diuretics to keep low filling pressures; this improves oxygenation and reduces ventilator/ICU days without routine need for pulmonary artery catheterization.
- ▶ **Adjuncts:** short neuromuscular blockade with cisatracurium for up to 48 h may help selected severe ARDS patients with ventilator dyssynchrony despite sedation, but routine early paralysis is not supported by later trials. ECMO is a rescue option for very severe, potentially reversible ARDS after optimized lung-protective ventilation, PEEP, proning and supportive care.
- ▶ **Avoid routine use:** high-frequency oscillation, routine recruitment maneuvers, surfactant replacement, inhaled nitric oxide/epoprostenol for outcome benefit, NSAIDs, ketoconazole and other anti-inflammatory therapies. Steroids are not a universal ARDS treatment; consider them only in patient-specific settings such as refractory septic shock, severe community-acquired pneumonia, COVID-19 ARDS, or selected early ARDS where contemporary guidelines support conditional use.

Prognosis and complications

- ▶ LUNG SAFE hospital mortality estimates rise with severity: **34.9% mild, 40.3% moderate, 46.1% severe** ARDS; with modern low-tidal-volume ventilation, overall mortality is around 30-40%.
- ▶ Most deaths are from **sepsis and nonpulmonary organ failure**, not refractory hypoxemia; nonpulmonary organ failure accounts for the major mortality burden.
- ▶ Poor prognostic factors include advanced age, chronic liver disease, chronic alcohol abuse, chronic immunosuppression, sepsis, preexisting organ dysfunction, direct lung injury,

pulmonary fibrosis, low compliance, high PEEP requirement and failure to improve in the first week.

- ▶ Complications include VAP, barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema), ICU-acquired weakness, delirium, thromboembolism, secondary infections and fibrotic lung disease.
- ▶ Survivors often regain near-normal lung function by **6-12 months**, but may have reduced diffusion capacity, exercise limitation, muscle wasting, fatigue, depression, anxiety, PTSD and cognitive impairment for years.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Injured alveolus in ARDS:** alveolar capillary endothelium, type I pneumocyte injury, type II pneumocyte/surfactant dysfunction, protein-rich edema, hyaline membrane, neutrophils, cytokines, ROS/NETs, microthrombi, collapsed alveolus, shunt.
- ▶ **ARDS time-course diagram:** exudative phase 0-7 days, proliferative phase 7-21 days, fibrotic phase after about 3 weeks; label edema, hyaline membranes, interstitial inflammation, fibrosis, bullae and recovery pathway.

Clinical / Diagnostic significance

- ▶ ARDS should be suspected when a patient with sepsis, pneumonia, aspiration, trauma or transfusion develops acute refractory hypoxemia and bilateral opacities within 1 week.
- ▶ Do not diagnose ARDS merely from a bilateral white-out CXR; document **PaO₂/FiO₂**, ventilatory support/PEEP, timing, and why cardiogenic edema is not the primary cause.
- ▶ Echocardiography is often the practical discriminator from cardiogenic edema; BNP or wedge pressure may help in selected patients but no test is definitive.
- ▶ Management is mainly supportive and ventilator-based; the most exam-important disease-modifying intervention is **low tidal volume ventilation** with plateau-pressure limitation.
- ▶ Rising oxygen requirement, increasing dead space, falling compliance, shock, AKI, liver dysfunction and delirium indicate high risk and need for aggressive ICU management.

High-yield exam pointers

- ▶ Write “adult” as historical; current term is **acute respiratory distress syndrome**.
- ▶ Berlin criteria: **within 1 week + bilateral opacities + noncardiogenic edema + PaO₂/FiO₂ ≤300 on PEEP/CPAP ≥5**.
- ▶ Severity cutoffs: **mild >200-300, moderate >100-200, severe ≤100 mm Hg**.
- ▶ Commonest causes: **pneumonia and sepsis**, then aspiration, trauma, transfusion and overdose.
- ▶ Classic pathology: **diffuse alveolar damage**, protein-rich edema and **hyaline membranes**.

- ▶ Ventilator must-write: VT 6 mL/kg predicted body weight, plateau ≤ 30 cm H₂O, SpO₂ 88-95%.
- ▶ Prone early in severe ARDS, especially PaO₂/FiO₂ < 150 , if expertise is available.
- ▶ After resuscitation, use **conservative fluid strategy**; avoid routine PA catheter.
- ▶ Most deaths are due to **sepsis/multiorgan failure**, not isolated hypoxemia.

SOURCE & COVERAGE

Harrison 22e — “Acute Respiratory Distress Syndrome”; Murray & Nadel’s Respiratory Medicine 7e — “Acute Respiratory Distress Syndrome”; CMDT 2026 — “Acute Respiratory Distress Syndrome”; Critical Care — “Acute Respiratory Failure” and “Pulmonary Edema”.



Acute severe asthma

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — *Acute severe asthma* (historically *status asthmaticus*) is a severe asthma exacerbation that fails to respond promptly to repeated inhaled short-acting β_2 -agonists (SABAs) and threatens life through progressive airflow obstruction, dynamic hyperinflation and respiratory muscle fatigue. An exacerbation is defined (NIH task force) as *a worsening of asthma requiring systemic corticosteroids (or an increase from a stable maintenance dose) to prevent a serious outcome*. Clinically it is recognised by breathlessness at rest, inability to complete sentences, peak expiratory flow (PEF)/FEV₁ well below predicted, and signs of respiratory distress; *near-fatal asthma* denotes the subset with hypercapnia, exhaustion or requiring mechanical ventilation.

Pathophysiology of the severe attack

- ▶ **Diffuse airway narrowing** from smooth-muscle constriction, mucosal oedema, inflammatory cellular infiltration and luminal **mucus plugging** (eosinophil-rich) raises airway resistance and lowers maximal expiratory flow, predominantly in small bronchi.
- ▶ **Air trapping and dynamic hyperinflation** — incomplete lung emptying forces breathing at high lung volumes (raised residual volume); intrinsic PEEP develops. The diaphragm and intercostals are mechanically disadvantaged on their length–tension curve, so **accessory muscles** (sternocleidomastoid, abdominals) are recruited and the **work of breathing rises**.
- ▶ **Gas exchange** — non-uniform obstruction produces **ventilation–perfusion (V/Q) mismatch** with a widened alveolar–arterial O₂ gradient and hypoxaemia. PaCO₂ initially **falls** (hyperventilation) producing respiratory alkalosis; as muscles fatigue, PaCO₂ **rises** — *a normal or raised PaCO₂ in a distressed asthmatic signals impending respiratory failure*.
- ▶ **Lactic (type B) acidosis** may appear (anion-gap metabolic acidosis) from work of breathing and high-dose β_2 -agonists.

Clinical assessment and severity grading

- ▶ Rapid focused history: duration/trigger, current medication, prior ICU/intubation, frequency of SABA use, response so far.
- ▶ Examination: respiratory rate, ability to speak (sentences→phrases→words→mute), posture, accessory-muscle use/suprasternal retraction, wheeze (a **silent chest** = severe obstruction with loss of breath sounds), heart rate, **pulsus paradoxus**, conscious level and cyanosis.
- ▶ Objective severity by PEF/FEV1, SpO2 and arterial blood gas. Severity classification (NAEPP/GINA, adapted in CMDT 2026):

Feature	Mild	Moderate	Severe	Respiratory arrest imminent
Breathlessness	On walking	At rest, limits activity	At rest, interferes with talking	At rest, mute
Talks in	Sentences	Phrases	Words	—
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy/confused
Respiratory rate	Increased	Increased	Often >30/min	>30/min
Accessory muscles	Usually not	Commonly	Usually	Paradoxical thoraco-abdominal movement
Wheeze	End-expiratory	Loud, expiratory	Loud, insp + exp	Absent (silent chest)
Pulse/min	<100	100–120	>120	Bradycardia
Pulsus paradoxus	<10 mmHg	10–25 mmHg	>25 mmHg	Absence = muscle fatigue
PEF (% pred/best)	≥70%	40–69%	<40%	<25%
PaO2 (air) / PaCO2	Normal / <42	≥60 / <42	<60 / ≥42	<60 / ≥42
SaO2 (air)	>95%	90–95%	<90%	<90%

Investigations

- ▶ **PEF or FEV1** — the single most useful objective measure; guides severity and serial response (improvement at 30–60 min predicts outcome and need for admission).
- ▶ **Pulse oximetry**; target SpO2 >90%.
- ▶ **Arterial blood gas** — typically mild hypoxaemia + respiratory alkalosis; *normalisation/rise of PaCO2* with continuing distress warns of impending failure. Venous pH/PCO2 and lactate can be used to monitor.

- ▶ **Chest radiograph** — not routine; obtain if pneumothorax, pneumomediastinum, pneumonia or another cause is suspected.
- ▶ **ECG/electrolytes** — monitor for arrhythmia and β 2-agonist-induced **hypokalaemia**; bloods/cultures only if infection suspected.

Management of acute severe asthma

- ▶ **Oxygen** — give immediately to maintain SpO₂ >90% (PaO₂ >60 mmHg); asphyxia is a leading cause of asthma death, and concern for hypercapnia must *never* delay correcting hypoxaemia.
- ▶ **Inhaled SABA (salbutamol/albuterol)** — high-dose, repeated or continuous by nebuliser (or MDI + spacer); at least **three treatments in the first hour**, then titrate to response. Onset 3–5 min, duration 4–6 h.
- ▶ **Inhaled ipratropium bromide** — added to SABA in moderate–severe exacerbations improves airflow and **reduces hospital admission**.
- ▶ **Systemic corticosteroids** — first-line; early administration speeds recovery and reduces admission. Prednisolone **0.5–1.0 mg/kg/day** ($\approx$ 40–60 mg/day) orally, or IV methylprednisolone **1.5–2 mg/kg** if oral route unsafe (oral and IV are equi-efficacious in non-life-threatening attacks). Continue the “burst” until symptoms resolve and PEF $\geq$ 80% personal best (usually 3–10 days); tapering is not required.
- ▶ **Intravenous magnesium sulfate** — **2 g IV over 20 min** (paediatric 40 mg/kg, max 2 g); a smooth-muscle relaxant that reduces hospitalisation in *acute severe* attacks (FEV₁ <25% predicted on presentation or failure to respond to initial therapy). Not recommended for routine mild–moderate exacerbations.
- ▶ **Adjuncts in refractory cases** — **heliox** (helium–oxygen) lowers airway resistance/work of breathing; an LTRA is sometimes added; continuous in-hospital nebulisation. Inhaled volatile anaesthetics (e.g., isoflurane) are potent bronchodilators in refractory disease.
- ▶ **Avoid** — sedatives/anxiolytics (respiratory depression), mucolytics (acetylcysteine, potassium iodide — may worsen cough/obstruction), and *routine* antibiotics (reserve for proven bacterial infection/pneumonia/sinusitis).

Respiratory support and mechanical ventilation

- ▶ **Non-invasive positive-pressure ventilation (NIV)** — low-level NIV (without PEEP) may reduce hospitalisation and avert intubation in **alert, cooperative** patients not in immediate need of intubation.
- ▶ **Intubation and invasive ventilation** — *mandatory* for respiratory arrest or impending arrest (exhaustion, altered sensorium, rising PaCO₂, bradycardia). Post-intubation deterioration is common from dynamic hyperinflation and high intrathoracic pressures causing hypotension.
- ▶ **Ventilator strategy** — **minimise hyperinflation**: low minute ventilation with **respiratory rate 12–14/min**, tidal volume **6–8 mL/kg**, **high inspiratory flow** (prolonged expiratory time) and

minimal/no PEEP. Accept **permissive hypercapnia** (let PaCO₂ rise; correct critical acidosis with bicarbonate if needed) to avoid barotrauma. Provide deep sedation and, if patient–ventilator synchrony cannot be achieved, short-term neuromuscular paralysis; continue bronchodilators until airway resistance falls.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Severity-stratification flow diagram of an acute attack** — boxes: *Assess (speech, RR, accessory muscles, PEF, SpO₂, pulsus paradoxus) → Mild–Moderate (PEF ≥40–69%) → SABA + ipratropium + O₂ + oral steroid; Severe (PEF <40%) → high-dose continuous SABA + ipratropium + O₂ + systemic steroid + IV MgSO₄; Respiratory arrest imminent (silent chest, drowsy, bradycardia, PaCO₂ ≥42) → ICU, NIV/intubation, permissive hypercapnia. Label danger signs: **silent chest, normal/rising PaCO₂, exhaustion, bradycardia, cyanosis.***
- ▶ **Obstructed asthmatic airway cross-section** — labels: *lumen narrowed by smooth-muscle constriction, smooth-muscle hypertrophy, submucosal oedema, mucus plug, epithelial shedding, basement-membrane (collagen) thickening, inflammatory cell infiltration.*

Clinical / Diagnostic significance

- ▶ A *normal or rising PaCO₂* with a *silent chest* and exhaustion are the cardinal red flags of life-threatening asthma demanding ICU care.
- ▶ Response to the first hour of therapy predicts the need for admission better than presenting severity.
- ▶ High-risk features mandating low-threshold escalation (Harrison): prior ICU admission or intubation for asthma, ≥2 ED visits in 6 months, recent/current oral steroids, poor adherence, illicit drug use, depression/severe psychosocial problems, low socioeconomic status, new diagnosis within the past year.
- ▶ Discharge planning: ensure inhaler technique, written **asthma action plan**, step-up of controller (ICS-containing) therapy, follow-up — over-reliance on SABA and under-use of ICS drive mortality.

High-yield exam pointers

- ▶ **Silent chest, drowsiness, bradycardia, normal/raised PaCO₂, and absent pulsus paradoxus (from muscle fatigue)** = imminent respiratory arrest.
- ▶ **First-hour bundle:** controlled O₂ (SpO₂ >90%) + repeated/continuous SABA (≥3 doses/hr) + ipratropium + early systemic steroid (prednisolone 0.5–1 mg/kg).
- ▶ **IV magnesium sulfate 2 g over 20 min** for acute severe asthma (FEV₁ <25% predicted / poor initial response) — reduces admissions.

- ▶ Oral and IV corticosteroids are equally effective in non-life-threatening attacks; continue burst till PEF $\geq 80\%$ best.
- ▶ **Ventilation = permissive hypercapnia:** low RR 12–14, low TV 6–8 mL/kg, high inspiratory flow, minimal PEEP — to avoid dynamic hyperinflation/barotrauma.
- ▶ **Avoid** sedatives, mucolytics and routine antibiotics; NIV only in the alert, cooperative patient.
- ▶ Pulsus paradoxus >25 mmHg, PEF $<40\%$, RR >30 and inability to speak in sentences define a severe attack.
- ▶ Type B (non-hypoxic) **lactic acidosis** and **hypokalaemia** are recognised β_2 -agonist effects during high-dose therapy.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Asthma" (Elliot Israel): pathophysiology, "Asthma Attacks", mechanical ventilation/permissive hypercapnia, and Table 298-6 "Patients at Greater Risk for Asthma Mortality."
- ▶ Murray & Nadel's Textbook of Respiratory Medicine, 7e — "Asthma: Diagnosis and Management": physiology of airflow limitation/dynamic hyperinflation, "Management of Acute Asthma", corticosteroid and magnesium dosing, and invasive ventilation settings.
- ▶ CMDT 2026 — "Pulmonary Disorders" (Asthma): Table 9–6 severity classification of exacerbations, treatment of severe exacerbations (oxygen target, SABA/ipratropium, systemic steroids, IV magnesium), and drugs to avoid.



Approach to Solitary Pulmonary Nodule

Asked in: Paper III Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — A **solitary pulmonary nodule (SPN)**, classically called a "*coin lesion*," is a single, discrete, rounded radiographic opacity **<3 cm in diameter, completely surrounded by aerated lung**, and *unaccompanied* by lymphadenopathy, atelectasis or pleural effusion (Murray & Nadel; CMDT). Lesions **>3 cm** are termed *pulmonary masses* and are malignant until proven otherwise. With the explosion of CT use and low-dose CT (LDCT) lung-cancer screening, SPNs are increasingly an incidental finding; the overriding clinical task is to **identify and resect the few malignant nodules that benefit from surgery while sparing the benign majority from needless invasive procedures**.

Etiology and Differential Diagnosis

- ▶ Most SPNs are **benign**; in LDCT-screened populations the probability that any detected nodule is cancer is only $\sim 1\%$, and **90–95% of screening-detected nodules are ultimately false positives**.

- ▶ Most benign nodules are **infectious granulomas**; **hamartomas** account for <5% of solitary nodules. Malignant nodules are *rare under age 30*; above 30, malignancy risk rises with age, smoking and a prior cancer history.

Category	Common causes
Malignant	Primary lung cancer (esp. adenocarcinoma), solitary metastasis, bronchial carcinoid
Infectious granuloma	Tuberculoma, histoplasmosis, coccidioidomycosis, other fungi; resolving abscess
Benign neoplasm	Hamartoma (fat + popcorn calcification), rare benign tumors
Other benign	Arteriovenous malformation, intrapulmonary (perifissural) lymph node, rounded atelectasis, infarct, rheumatoid nodule, Wegener (GPA)

Step 1 — Estimate the Pretest Probability of Malignancy

The approach is **probability-driven**: integrate patient (“clinical”) factors with nodule (“radiologic”) factors, either by validated quantitative models or experienced clinical judgement.

- ▶ **Clinical predictors of malignancy**: older age, current/heavy smoking (>20 cigarettes/day, quit <7 years), prior malignancy, asbestos exposure.
- ▶ **Independent predictors (Mayo investigators)**: age, smoking status and prior cancer *plus* three radiologic features — **nodule diameter, spiculation, and upper-lobe location**.
- ▶ **Quantitative models**: Mayo (VA Cooperative) clinical model, the **Brock model** (Pan-Canadian screening cohort, most accurate in screening), and the **Herder model**, which adds FDG-PET data to clinical/radiologic inputs and is endorsed by the British Thoracic Society.

Harrison Table 83-7 — Risk of cancer by variable (after Ost et al., NEJM 2003):

Variable	Low risk	Intermediate	High risk
Diameter (cm)	<1.5	1.5–2.2	≥2.3
Age (years)	<45	45–60	>60
Smoking	Never smoker	Current <20/day	Current >20/day
Smoking cessation	Quit ≥7 yr ago / never	Quit <7 yr ago	Never quit
Margin	Smooth	Scalloped	Corona radiata / spiculated

Step 2 — Radiographic Characterisation (Benign vs Malignant Features)

- ▶ Always obtain and compare prior CXR/CT films. Two findings *reliably* indicate benignity: (1) no growth over >2 years, and (2) a benign calcification pattern.

- ▶ **Benign calcification patterns (5):** diffuse, central, laminar/concentric, and “popcorn” — central nidus and “bull’s-eye” suggest granuloma; “popcorn” (chondroid) is diagnostic of **hamartoma**, especially when fat is also seen within the nodule. *Note:* calcification alone does not exclude malignancy.
- ▶ **Features suggesting malignancy:** larger size, **spiculated / corona radiata margins**, lobulated or ill-defined edge, a peripheral **halo**, sparse / **eccentric / stippled** calcification, **thick-walled cavitation (>16 mm)**, upper-lobe location, and demonstrable growth.
- ▶ **Doubling time (DT):** very rapid growth (DT <30 days) suggests infection; **long-term stability** (DT >465 days, or >2 years) suggests benignity; most malignant *solid* nodules have a volume DT <400 days. 3D volumetric analysis on thin-section HRCT is more sensitive than 2D caliper measurement for detecting growth.
- ▶ **Size-based malignancy rate on CT (CMDT):** 2–5 mm ≈ 1%, 6–10 mm ≈ 24%, 11–20 mm ≈ 33%, 21–45 mm ≈ 80%.

Step 3 — Functional Imaging (FDG-PET/CT) and Tissue Diagnosis

- ▶ **FDG-PET/CT** is most useful for indeterminate nodules >8 mm (≈1 cm); an SUV_{max} >2.5 is the classic malignancy threshold. A meta-analysis of nodules >1 cm reported sensitivity 96%, specificity 78%, PPV 91%, NPV 92%; CMDT quotes sensitivity 85–97% and specificity 70–85%. Malignancy probability rises stepwise with uptake (SUV_{max} 0–2.5 ≈ 24%, 2.6–4.0 ≈ 80%, ≥4.1 ≈ 96%).
- ▶ **A positive PET raises, and a negative PET lowers, the probability of cancer**, but beware **false negatives** in carcinoid tumours and in *ground-glass / lepidic adenocarcinoma*, AIS and MIA (low metabolic activity), and in lesions <1 cm (poor resolution); **false positives** occur with active infection/inflammation.
- ▶ **Tissue sampling options:**
 - **CT-guided transthoracic needle aspiration (TTNA):** yield 50–97% (≈90% in expert series); best for **peripheral** lesions; main complication is **pneumothorax in up to 30%** (some needing a chest drain).
 - **Bronchoscopy:** yield 10–80%, sensitivity 88% for central lesions but low for peripheral nodules <2 cm; yield improves with a **bronchus (air-bronchus) sign**, larger size and more biopsies. **Guided bronchoscopy** (radial EBUS, electromagnetic navigational bronchoscopy, robotic bronchoscopy) gives a pooled yield ≈70%.
 - **Sputum cytology:** highly specific but insensitive — reserved for central lesions or poor procedural candidates.

Step 4 — Management Algorithm by Pretest Probability

- ▶ **Benign calcification or documented 2-year stability** → no further testing.

- ▶ **Low probability (<5%)** → *watchful waiting* with **serial HRCT** (ACCP suggests 3–6, 9–12 and 18–24 months); for screen/incidental nodules apply structured surveillance (below).
- ▶ **Intermediate probability (5–60/65%)** → further characterise with **PET/CT** and/or **non-surgical biopsy** (TTNA or bronchoscopy); biopsy is favoured for the *risk-averse* patient wanting confirmation before surgery.
- ▶ **High probability (>60–65%)** → proceed to **staging and surgical resection** if surgical risk is acceptable; biopsy rarely changes management and is often omitted.
- ▶ **Surgery:** VATS with intra-operative **frozen section**, proceeding to **lobectomy + mediastinal lymph-node sampling/dissection** if malignant; **wedge/segmentectomy** for limited reserve. Non-surgical candidates may receive **SBRT** (≤ 5 cm) or radiofrequency ablation/cryoablation.
- ▶ **Assess operability first:** relative/absolute contraindications include **predicted post-op FEV₁ <0.8 L**, **FEV₁ <1 L**, **DLCO <40%**, **VO₂max <10–15 mL/kg/min**, resting **PCO₂ >45 mmHg**, severe pulmonary hypertension, and recent MI (<3 months).

Structured surveillance frameworks:

- ▶ **Fleischner Society 2017** (incidental nodules, age ≥ 35 , not immunosuppressed, no known cancer): *solid* <6 mm — no routine follow-up if low risk; 6–8 mm — CT at 6–12 mo then 18–24 mo; >8 mm — consider CT at 3 mo, PET/CT or biopsy. *Subsolid*: pure ground-glass <6 mm — no follow-up; ≥ 6 mm — CT at 6–12 mo to confirm persistence, then every 2 years to 5 years; *part-solid* ≥ 6 mm — CT at 3–6 mo (solid component ≥ 6 mm is highly suspicious).
- ▶ **Lung-RADS v1.1** (ACR — *screen-detected* nodules): category 1–2 = benign (cancer risk <1%, annual LDCT); 3 = probably benign (6-month LDCT); 4A (3-month LDCT $\pm$ PET); 4B/4X (>15% risk — diagnostic CT/PET/tissue sampling).

Special Consideration — Subsolid Nodules / Ground-Glass Opacities (GGO)

- ▶ Subsolid nodules are subdivided into **pure ground-glass (nonsolid)** and **part-solid**; many persistent GGOs represent the adenocarcinoma spectrum — **atypical adenomatous hyperplasia (AAH)** → **adenocarcinoma in situ (AIS)** → **minimally invasive adenocarcinoma (MIA)**.
- ▶ They are **indolent**: GGO cancers are typically stage I adenocarcinoma with near-100% 5-year survival, so guidelines favour **less frequent but longer-duration surveillance**; the **size of the solid component** is the key predictor of invasiveness — a growing or enlarging solid component prompts resection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Management algorithm of the SPN (flowchart):** *New nodule on CT* → **benign calcification or 2-yr stability?** → if yes: *No further testing*; if no → **estimate probability of cancer / surgical risk** → branch into **Low (<5%)**: **serial HRCT at 3, 6, 9, 12, 18, 24 mo**;

Intermediate (5–60%): PET/CT and/or biopsy (TTNA / bronchoscopy); **High (>60%):** staging → VATS frozen section → lobectomy. Label: *PET if nodule ≥8 mm, TTNA if peripheral, bronchoscopy if bronchus sign.*

- ▶ **Calcification patterns box:** draw and label **diffuse, central, laminar/concentric, popcorn** (benign) versus **stippled, eccentric** (malignant); plus nodule margins — *smooth* (benign) vs *spiculated / corona radiata* (malignant).

Clinical / Diagnostic significance

- ▶ The single most powerful step is **comparison with old imaging** — proven 2-year stability or a benign calcification pattern obviates all further workup.
- ▶ **Size, margin (spiculation), upper-lobe location, age and smoking** drive the malignancy estimate; integrate them via **Brock/Mayo/Herder models** rather than guesswork.
- ▶ **PET-CT** both characterises the nodule and screens for nodal/distant disease, refining staging before resection — but a negative PET does not exclude carcinoid or lepidic adenocarcinoma.
- ▶ **Shared decision-making** is integral: nodule detection causes real patient distress and is a “teachable moment” for **smoking cessation**.

High-yield exam pointers

- ▶ **SPN** = single rounded opacity <3 cm, surrounded by normal lung, **no** adenopathy/effusion; >3 cm = **mass** (treat as malignant).
- ▶ **Two reliable benignity criteria:** no growth >2 years and benign calcification (**diffuse/central/laminar/popcorn**); **popcorn** = **hamartoma**, central/bull’s-eye = **granuloma**.
- ▶ **Malignant pointers:** **spiculation/corona radiata**, **eccentric/stippled calcification**, **thick-walled cavity** (>16 mm), **upper lobe**, **growth** (**VDT <400 days**).
- ▶ **Doubling time:** <30 days = **infection**; >465 days (>2 yr stable) = **benign**.
- ▶ **PET useful for nodules >8 mm**, **SUVmax >2.5** = **malignant**; false-negative in **carcinoid** and **AIS/MIA/GGO**.
- ▶ **Probability bands:** <5% **observe**, 5–60% **PET/biopsy**, >60% **resect**.
- ▶ **TTNA** best for peripheral lesions (pneumothorax up to 30%); **bronchoscopy** best for central/endobronchial (bronchus sign); **VATS + frozen section** → **lobectomy** is definitive.
- ▶ **Fleischner 2017** = incidental nodules; **Lung-RADS** = screen-detected nodules.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “*Neoplasms of the Lung*” (SPN definition, risk Table 83-7/Mayo predictors, calcification patterns, management algorithm Fig. 83-5, operability criteria, SBRT, GGO/AAH-AIS-MIA spectrum).

- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “*Pulmonary Nodule*” (epidemiology, Brock model, **Fleischner Society 2017** and **Lung-RADS v1.1** tables, volume doubling time, ACCP algorithm, bronchoscopy/TTNA yields, subsolid nodules) and “*Positron Emission Tomography*” (SUVmax 2.5 threshold, sensitivity/specificity, Herder model, false negatives).
- ▶ **CMDT 2026** — “*Pulmonary Disorders: Solitary Pulmonary Nodule*” (coin lesion, size-based malignancy rates, <5%/5–60%/>60% probability bands, PET performance, TTNA/bronchoscopy/VATS management).



Asbestos-Related Diseases

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — Asbestos is a generic term for a family of naturally occurring fibrous mineral silicates that, when inhaled as respirable fibres, cause a spectrum of benign and malignant pleuropulmonary disease. The principal disorders are **asbestosis** (diffuse interstitial pulmonary fibrosis), **benign pleural disease** (plaques, diffuse thickening, benign effusion, rounded atelectasis), **bronchogenic carcinoma**, and **malignant mesothelioma** of the pleura and peritoneum. All share a **long latency** (often decades), a **dose–response** relationship, and the medicolegal importance of being **compensable occupational diseases**.

Mineralogy, Sources and Mechanism of Injury

- ▶ **Two mineral groups:**
 - **Serpentine group** — **chrysotile** (*white asbestos*), curly/serpentine fibres, **less biopersistent**, more readily cleared from the lung; the form most widely used commercially.
 - **Amphibole group** — **crocidolite** (*blue*), **amosite** (*brown*), anthophyllite, tremolite, actinolite; long, thin, straight, **durable, highly biopersistent** fibres. Amphiboles are far more potent inducers of **mesothelioma** (up to ~100-fold over serpentine in experimental animals).
- ▶ **At-risk occupations:** mining, milling and manufacture of asbestos products; **shipbuilding/ship repair**, construction, **pipe fitters, boilermakers, insulators**; brake/clutch (friction) linings, fire-resistant textiles, cement and floor tiles. Latency means new cases today reflect exposures of past decades.
- ▶ **Non-occupational exposure:** *bystander/para-occupational* (painters, electricians working alongside insulators in shipyards); **domestic** (relatives exposed to fibre-laden work clothes — chiefly pleural disease); **environmental** (community exposure from vermiculite contaminated with amphibole at **Libby, Montana**; disturbance of naturally occurring asbestos).

- ▶ **Pathogenesis:** fibre toxicity depends on **cumulative dose**, **fibre dimensions (length-to-width aspect ratio)** and **durability/biopersistence**. Fibres $\leq 3 \mu\text{m}$ are phagocytosed by alveolar macrophages and cleared via lymphatics; **longer fibres are incompletely phagocytosed**, often by several macrophages, and become coated to form **asbestos (ferruginous) bodies** — beaded, dumb-bell-shaped iron-protein-coated fibres that are the *light-microscopic hallmark of exposure*. Injury is driven by **oxidative stress** — reactive oxygen species generated by transition metals (iron) on the fibre surface and during frustrated phagocytosis — recruiting fibroblasts and collagen deposition.

Spectrum of Asbestos-Related Diseases and Latency

Disease	Nature	Typical latency from first exposure
Pleural plaques	Benign; marker of exposure only	~20–30 yr (relates to time since exposure, not dose)
Benign asbestos pleural effusion (BAPE)	Benign exudative effusion	Earliest — within ~15 yr
Diffuse pleural thickening / visceroparietal reaction	Benign; may restrict	Long (~30+ yr)
Rounded atelectasis (<i>Blesovsky syndrome</i>)	Folded-lung pseudotumour	Variable, late
Asbestosis	Diffuse interstitial fibrosis	≥ 10 yr exposure; clinical disease ~20–30 yr
Bronchogenic carcinoma	Malignant	~15–19 yr (minimum)
Malignant mesothelioma	Malignant (pleura >90%, peritoneum)	20–40 yr; short exposure (1–2 yr) sufficient

Asbestosis (Pulmonary Parenchymal Fibrosis)

- ▶ **Definition:** diffuse interstitial fibrosing lung disease *directly related to intensity and duration of exposure*; requires generally ≥ 10 years of exposure before becoming manifest, with clinical disease usually **20–30 years** after first exposure.
- ▶ **Pathology:** begins as **peribronchiolar fibrosis** with macrophage accumulation and type-2 pneumocyte hyperplasia; progresses to interstitial fibrosis with a **lower-lobe and subpleural predominance** and eventual **honeycombing**. Distinguished from other end-stage fibrosis only by demonstration of **asbestos bodies / uncoated fibres**.
- ▶ **Clinical features:** insidious **exertional dyspnoea** and dry cough; **fine, end-inspiratory bibasal “velcro” crackles** (early and distinctive, heard first in axillary/basal regions); **digital clubbing** in some; late cor pulmonale.

- ▶ **Radiology:** irregular/linear reticular opacities beginning in the lower zones; blurring of the cardiac border producing a “shaggy heart” sign; ground-glass change. HRCT (most sensitive) shows subpleural curvilinear lines 5–10 mm, subpleural reticulation, parenchymal bands and honeycombing; coexisting pleural plaques strongly support the diagnosis. ILO classification grades small linear/irregular opacities (vs the rounded opacities of silicosis/CWP).
- ▶ **Lung function:** restrictive pattern with reduced lung volumes and reduced DLCO; mixed or mild obstructive components may occur (peribronchiolar fibrosis).
- ▶ **Management:** no specific therapy — supportive care as for any diffuse interstitial fibrosis: supplemental oxygen, pulmonary rehabilitation, influenza/pneumococcal vaccination, and especially smoking cessation (smoking multiplies lung-cancer risk). Lung transplantation in selected end-stage cases (pleural disease may complicate surgery).

Benign Pleural Manifestations

- ▶ **Pleural plaques** — the commonest and often the only manifestation of exposure. Smooth, raised, white, frequently calcified lesions of the parietal pleura (posterolateral mid-zones following rib contour, the diaphragm, cardiac border); histologically avascular, acellular, laminated (hyalinised) collagen likened to *candle-wax drippings*. Typically bilateral (unilateral suggests trauma/infection). They imply exposure, not impairment, but flag an increased long-term risk of mesothelioma/lung cancer.
- ▶ **Diffuse pleural thickening / visceroparietal reaction** — less specific than plaques; can encase the lung as a fibrous “peel”, causing measurable restrictive deficit (FEV₁/FVC reduction) and occasionally requiring pleurectomy.
- ▶ **Benign asbestos pleural effusion (BAPE)** — usually the earliest manifestation (within ~15 yr); small, exudative, blood-tinged, often resolves spontaneously, may recur/alternate sides. It is a diagnosis of exclusion — criteria: exposure history, exclusion of other causes, and no tumour on ≥3-year follow-up; thoracoscopic biopsy is usually needed to exclude mesothelioma.
- ▶ **Rounded atelectasis (folded lung / pseudotumour, Blesovsky syndrome) — pleural fibrosis folds and traps subjacent lung, producing a rounded mass with the characteristic “comet-tail” sign of vessels/bronchi curving into it; the key differential is lung cancer*, occasionally needing biopsy.*

Asbestos-Related Malignancy

- ▶ **Bronchogenic carcinoma**
 - Most common cancer associated with asbestos; occurs across all histologic types.
 - Minimum latency 15–19 years; risk rises with cumulative exposure.
 - Multiplicative (synergistic) interaction with cigarette smoking — combined risk greatly exceeds the additive effect; hence smoking cessation is paramount.
- ▶ **Malignant mesothelioma**

- Arises from mesothelial serosal surfaces — **pleura in >90%**, also peritoneum, pericardium, tunica vaginalis; **not related to smoking**.
- **>80% are asbestos-associated** (rendering them compensable); **amphiboles, especially crocidolite**, are the most potent; **erionite** (a zeolite fibre, e.g. *Cappadocia, Turkey*) is a recognised non-asbestos cause. ~3000 cases/yr in the USA.
- **Latency 20–40 years**; even brief exposures (1–2 yr) suffice — underscoring a meticulous exposure history.
- **Presentation**: unilateral **pleural effusion**, chest-wall pain and dyspnoea; tumour **encases the lung**, contracts the hemithorax and produces **ipsilateral mediastinal shift**; **needle-tract seeding** at biopsy/drainage sites.
- **Histologic subtypes**: **epithelioid** (best prognosis), **sarcomatoid** (worst), and **biphasic** (mixed).
- **Diagnosis**: fluid cytology has limited yield; **image-guided/thoracoscopic biopsy** with immunohistochemistry is usual. Molecular markers — **loss of BAP1 expression** and **homozygous CDKN2A (p16) deletion** by FISH — confirm malignancy in mesothelial-lineage cells (together identify up to ~85% of cases). (*Standard mesothelial IHC panel: positive calretinin, WT-1, CK5/6, D2-40; negative CEA, TTF-1, MOC-31/Ber-EP4 — see Coverage note.*) Staging uses the TNM-based IASLC/IMIG (8th edition) system.
- **Prognosis**: dismal — median survival **9–18 months**, **<5% survive 5 years**; sarcomatoid histology, poor performance status and weight loss predict worse outcome.
- **Treatment (palliative intent)**: first-line **cisplatin + pemetrexed** (an antifolate) with **folic acid + vitamin B₁₂** supplementation improved median survival (**12.1 vs 9.3 months** vs cisplatin alone); adding **bevacizumab** (anti-VEGF) further improved survival (MAPS: **18.8 vs 16.1 months**). **Extrapleural pneumonectomy (EPP)** is *harmful/not recommended* (MARS trial — worse survival); **pleurectomy/decortication** and **talc pleurodesis/indwelling pleural catheter** for effusion control are the mainstays; immune-checkpoint inhibitors remain largely investigational.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Asbestos (ferruginous) body** — draw a central thin asbestos fibre coated by an iron-protein layer giving a **beaded, dumb-bell / drumstick shape**. Labels: *core asbestos fibre, iron-protein (haemosiderin) coat, beaded/segmented body, engulfing alveolar macrophage*.
- ▶ **Chest radiograph of asbestos-related disease** — outline both lungs. Labels: *bilateral calcified diaphragmatic pleural plaques, lower-zone irregular/reticular opacities (asbestosis), “shaggy/indistinct heart border”, blunted costophrenic angle (effusion/thickening), rounded atelectasis with comet-tail sign*.

Clinical / Diagnostic significance

- ▶ **Exposure history is paramount** — occupation, duration, latent interval, and para-occupational/domestic/environmental sources; correlate with imaging.
- ▶ **Pleural plaques = marker of past exposure, not impairment**; their presence beside lower-zone fibrosis strongly supports asbestosis over idiopathic pulmonary fibrosis.
- ▶ **HRCT is the key imaging tool** — detects early parenchymal fibrosis, distinguishes pleural plaque from subpleural fat, and characterises rounded atelectasis.
- ▶ **Any unilateral exudative effusion in an asbestos-exposed patient is mesothelioma until proven otherwise** — proceed to thoracoscopic biopsy.
- ▶ **Smoking cessation** disproportionately reduces lung-cancer risk because of the multiplicative interaction; mesothelioma risk is unaffected by smoking.
- ▶ **Medicolegal/compensation**: documented asbestosis, lung cancer with exposure, and mesothelioma are **compensable**; primary prevention via exposure limits, substitution, engineering controls and surveillance is the only effective strategy given the absence of cure.

High-yield exam pointers

- ▶ **Amphiboles (crocidolite) → mesothelioma**; chrysotile is less biopersistent and more readily cleared.
- ▶ **Asbestos/ferruginous body** = beaded iron-coated fibre = light-microscopic hallmark of exposure (not of disease severity).
- ▶ **Asbestosis** = lower-zone, subpleural fibrosis with **velcro crackles, clubbing, restrictive PFT, low DLCO**; HRCT subpleural curvilinear lines 5–10 mm.
- ▶ **Pleural plaques** are bilateral, parietal, calcified (“candle-wax”), and the **commonest** manifestation.
- ▶ **BAPE** = earliest manifestation (<15 yr); diagnosis of exclusion needing 3-yr tumour-free follow-up.
- ▶ **Lung cancer latency 15–19 yr; mesothelioma latency 20–40 yr**; mesothelioma not smoking-related, lung cancer **synergistic** with smoking.
- ▶ **Mesothelioma**: epithelioid best / **sarcomatoid worst** prognosis; **BAP1 loss + CDKN2A/p16 deletion** confirm diagnosis; median survival ~12 months.
- ▶ **Cisplatin + pemetrexed (+ folate/B₁₂) ± bevacizumab** is first-line; **EPP is harmful (MARS)**.
- ▶ **>80% of mesotheliomas are asbestos-associated → compensable.**

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Occupational and Environmental Lung Disease” (asbestos-related diseases section, lung cancer/mesothelioma associations)

and latencies); “*Neoplasms of the Lung*” and “*Pleural and Mediastinal Diseases / Mesothelioma*” for malignancy.

- ▶ **Murray & Nadel’s Textbook of Respiratory Medicine, 7e** — “*Pneumoconioses*” (asbestosis, pleural plaques, diffuse pleural fibrosis, benign asbestos pleural effusion, rounded atelectasis, pathogenesis and fibre biology) and “*Pleural Malignancy*” (mesothelioma — aetiology, subtypes, BAP1/CDKN2A diagnostics, staging, MARS/MAPS trials, chemotherapy and immunotherapy).
- ▶ **CMDT 2026** — “*Pulmonary Disorders*” (pneumoconioses/asbestosis clinical features, imaging and management; asbestos as carcinogen and cause of mesothelioma).

Coverage note: The corpus emphasises modern molecular diagnostics for mesothelioma (BAP1 loss, CDKN2A/p16 deletion) rather than the conventional immunohistochemistry panel; the marker panel cited (calretinin/WT-1/CK5/6/D2-40 positive, CEA/TTF-1/MOC-31 negative) is included as universally accepted diagnostic pathology supplementing the textbook content.



Bronchial asthma

Asked in: Paper III Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Bronchial asthma is a chronic, heterogeneous disease characterised by **episodic, largely reversible airway obstruction, airway hyperresponsiveness (AHR)** and, in most patients, **airway inflammation** (commonly eosinophilic/type 2). Clinically it presents as recurrent wheeze, dyspnoea, chest tightness and cough that vary in intensity over time and with triggers. In a subset, persistent inflammation and airway remodelling produce a fixed (irreversible) component. It affects ~262 million people worldwide and remains the commonest chronic respiratory disease with significant morbidity and preventable mortality.

Aetiology, risk factors and triggers

- ▶ **Heritable predisposition** — heritability 25–80%; complex polygenic inheritance interacting with environment and epigenetic change. Reproducible risk loci include ****ORMDL3/GSDMB** (17q21 region)*, ADAM33, DPP-10, TSLP, IL-33, ST2 (IL-33 receptor), IL-13, IL6R and HLA-DQB1*. Atopy (genetic tendency to specific IgE production) explains roughly half of asthma; key allergens are house dust mite, indoor fungi, cockroach and animal danders.
- ▶ **Predisposing exposures (development of disease)** — allergen exposure in the atopy-prone, occupational sensitisers (occupational asthma = 10–25% of adult-onset disease), air pollution (NO₂, CO), respiratory infections (rhinovirus, RSV, *Mycoplasma*), tobacco (maternal/active smoking), obesity, diet/vitamin D, and high-intensity exercise in elite athletes.

- ▶ **Triggers (provoke acute narrowing)** — allergens, irritants/smoke, viral infections, **exercise and cold dry air**, air pollution, drugs (β -blockers including ophthalmic drops, aspirin/NSAIDs, ACE-inhibitor cough), occupational agents, and hormonal/perimenstrual and pregnancy-related changes.
- ▶ **Special syndromes** — *Reactive airways dysfunction syndrome (RADS)* after a single high-concentration irritant exposure (non-sensitised, neutrophilic); *allergic bronchopulmonary aspergillosis (ABPA)* from IgE sensitisation to *Aspergillus fumigatus*.

Pathophysiology and airway inflammation

- ▶ **Airway hyperresponsiveness** — exaggerated bronchoconstriction to stimuli (e.g. histamine, methacholine) that do not affect normal airways; partly smooth-muscle and partly structural (wall thickening).
- ▶ **Acute obstruction** — smooth-muscle contraction, mucosal/submucosal **oedema**, and luminal **mucus plugging** narrow the airway.
- ▶ **Chronic obstruction / remodelling** — smooth-muscle hypertrophy and hyperplasia, **subepithelial collagen and matrix deposition (basement-membrane thickening)**, goblet-cell metaplasia with mucus hypersecretion, epithelial denudation, vascular and neuronal proliferation — together producing a fixed component.
- ▶ **Type 2 (T2-high) inflammation** — the dominant pattern; driven by **CD4⁺ Th2 cells and ILC2s** producing **IL-4, IL-5 and IL-13**. *IL-4* drives B-cell isotype switching to **IgE**; *IL-5* controls eosinophil formation, recruitment and survival; *IL-13* induces AHR, mucus hypersecretion and goblet-cell metaplasia. Epithelial **alarmins (TSLP, IL-25, IL-33)** activate ILC2s, so even “non-allergic” irritant/viral exposures can drive eosinophilia.
- ▶ **Mediators** — **cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄)** from eosinophils/mast cells are potent bronchoconstrictors and mucus secretagogues; prostaglandin D₂, nitric oxide and reactive oxygen species amplify inflammation; chemokines (eotaxin, RANTES, TARC) recruit cells.
- ▶ **Non-type 2 inflammation** — **neutrophilic** (IL-6, IL-8, IL-17, TNF- α ; severe/steroid-refractory, RADS, sometimes *Mycoplasma*-associated and macrolide-responsive) or **pauci-granulocytic** asthma with no obvious infiltrate.

Clinical features and classification

- ▶ **Symptoms** — episodic wheeze, breathlessness, chest tightness, cough and mucus; often nocturnal or early-morning, and provoked by triggers. Between attacks examination may be normal; during attacks — tachypnoea, tachycardia, prolonged expiration, accessory-muscle use; a “**silent chest**” signifies severe, life-threatening obstruction.
- ▶ **Classification by inflammatory phenotype/endotype** — allergic (early-onset, atopic) vs late-onset eosinophilic, aspirin-exacerbated, obesity-related, and neutrophilic/non-T2; this **endotype-based nosology guides biologic selection**.

- ▶ **Assessment of control (GINA — past 4 weeks)** — based on four items: daytime symptoms >2×/week, any night waking due to asthma, reliever need >2×/week, and any activity limitation.

Level of control	Criteria (over past 4 weeks)
Well controlled	None of the four components
Partly controlled	1–2 components present
Uncontrolled	3–4 components present

- ▶ **Goals of therapy** — symptoms ≤2×/week, nocturnal waking ≤2×/month, reliever use ≤2×/week, ≤1 exacerbation/year, normal lung function and activity, minimal side-effects.

Diagnosis and investigations

- ▶ **Spirometry** — obstructive pattern: ↓FEV₁, ↓FEV₁/FVC below the lower limit of normal; flow-volume loop shows expiratory **scalloping**. **Reversibility**: ≥10% increase in FEV₁ % predicted after a β₂-agonist (older criterion: ≥12% and ≥200 mL rise). Diurnal PEF **variability** >20% supports the diagnosis.
- ▶ **Bronchoprovocation** (when spirometry non-diagnostic) — **methacholine challenge**: ≥20% fall in FEV₁ at a concentration ≤8 mg/mL (Harrison: PD₂₀ cumulative dose ≤400 µg); a negative test has ~95% negative predictive value. Mannitol or exercise/cold-air challenge (≥10% FEV₁ fall) are alternatives.
- ▶ **Biomarkers of type 2 inflammation** — blood eosinophils ≥300 cells/µL; FeNO elevated (>35–40 ppb untreated indicates T2 inflammation; suppressed by ICS, useful for adherence); total/specific IgE and skin/RAST testing for atopy.
- ▶ **Red-flag results** — IgE >1000 IU/mL with eosinophils >500/µL → consider ABPA; extreme eosinophilia → eosinophilic granulomatosis with polyangiitis (EGPA).
- ▶ **Classic sputum findings (universally accepted)** — *Curschmann spirals* (mucus casts), *Charcot-Leyden crystals* (eosinophil-derived), and *Creola bodies* (sloughed epithelial clusters).
- ▶ **Differential / “asthma mimics”** — heart failure (“cardiac asthma”), COPD, α₁-antitrypsin deficiency, inducible laryngeal obstruction (vocal-cord dysfunction), foreign body, bronchiectasis, tracheobronchomalacia, EGPA.

Acute severe asthma (status asthmaticus) and its grading

- ▶ A normal or rising PaCO₂ in a distressed asthmatic (who should be hypocapnic from tachypnoea) signals **impending respiratory failure**.

Feature	Moderate	Severe	Respiratory arrest imminent
Breathlessness / talks in	On walking; sentences	At rest; phrases/words	Mute

Feature	Moderate	Severe	Respiratory arrest imminent
Position / accessory muscles	Can lie down; usually none	Sits upright; usually present	Paradoxical thoraco-abdominal
Wheeze	End-expiratory	Loud throughout	Silent chest
Pulse; pulsus paradoxus	100–120; may be present	>120; often >25 mmHg	Bradycardia (fatigue)
PEF/FEV1 % predicted	40–69%	<40%	<25%
SaO ₂ (air)	90–95%	<90% (± cyanosis)	<90%

- **Management of exacerbation** — high-flow oxygen to correct hypoxaemia; repeated/continuous nebulised SABA (≥3 doses in the first hour) ± ipratropium; systemic corticosteroids (prednisone 40–60 mg/day, taper over 1–2 weeks). IV magnesium sulphate 2 g over 20 min for acute severe asthma (FEV1 <25% predicted or non-responders). Consider NIV/heliox; if intubated, use lung-protective, low-rate/low-volume “permissive hypercapnia” ventilation to limit airway pressures. Antibiotics only with clear infection.

Stepwise (GINA) pharmacotherapy and biologics

- **Reliever shift (AIR — Anti-Inflammatory Reliever)** — GINA now recommends as-needed ICS-formoterol (only formoterol, owing to rapid onset) or ICS-SABA at *all* steps, replacing SABA-alone, because SABA monotherapy increases asthma death.
- **Controller ladder** — ICS are the cornerstone of all persistent asthma. Step 1–2: as-needed/low-dose ICS-formoterol; Step 3: low-dose ICS-formoterol maintenance; Step 4: medium-dose ICS-formoterol; Step 5: high-dose ICS-LABA + add-on LAMA (e.g. tiotropium), and biologics ± macrolide/low-dose OCS as last resort.
- **Bronchodilators** — SABA (salbutamol/albuterol; onset 3–5 min, lasts 4–6 h); LABA (salmeterol, formoterol; ~12 h — never as monotherapy in asthma); ultra-LABA (vilanterol, indacaterol, olodaterol; 24 h, only with ICS). Theophylline is now rarely used (narrow therapeutic window).
- **Other controllers** — leukotriene modifiers (montelukast/zafirlukast; zileuton) — useful in exercise-induced and aspirin-exacerbated respiratory disease (AERD); cromolyn (paediatric, mast-cell stabiliser).
- **Biologics for severe T2 asthma** — omalizumab (anti-IgE), mepolizumab/reslizumab (anti-IL-5), benralizumab (anti-IL-5Rα), dupilumab (anti-IL-4Rα, blocks IL-4/IL-13), tezepelumab (anti-TSLP, also effective in some T2-low disease). They reduce exacerbations by ~50–70% in correctly selected (biomarker-guided) patients.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Cross-section of normal vs asthmatic bronchus** — label: *epithelium with denudation/shedding, goblet-cell metaplasia + mucus plug in lumen, thickened/sub-epithelial collagen (basement-membrane) deposition, sub-mucosal oedema, smooth-muscle hypertrophy & hyperplasia, cellular (eosinophil) infiltration, vascular and neuronal proliferation, narrowed lumen.*
- ▶ **Type 2 inflammatory cascade** — label: *allergen/irritant → epithelial alarmins (TSLP, IL-25, IL-33) → ILC2 and Th2 cells → IL-4 (IgE switch), IL-5 (eosinophils), IL-13 (AHR, mucus); IgE on mast cells → cysteinyl-leukotrienes → bronchoconstriction, with arrows to the corresponding biologics (omalizumab, anti-IL-5, dupilumab, tezepelumab).*

Clinical / Diagnostic significance

- ▶ Confirm diagnosis objectively with **reversible obstruction or AHR** before lifelong therapy — >1/3 of physician-labelled “asthma” does not meet criteria.
- ▶ **Phenotyping by eosinophils/FeNO/IgE** directs precision biologic therapy and predicts response.
- ▶ Identify and treat **comorbidities** that make asthma refractory: chronic rhinosinusitis ± nasal polyposis, GERD, obesity, OSA, anxiety/depression, vocal-cord dysfunction.
- ▶ **Nasal polyps + adult asthma → suspect AERD (Samter triad)**: avoid aspirin/NSAIDs, use leukotriene modifiers ± aspirin desensitisation/biologics.
- ▶ In **pregnancy**, treat actively — inhaled salbutamol, budesonide, beclomethasone and fluticasone are well-established; uncontrolled asthma is far more dangerous to mother and fetus than the drugs.

High-yield exam pointers

- ▶ Triad of asthma: **reversible airway obstruction + airway hyperresponsiveness + airway inflammation.**
- ▶ **ICS are the cornerstone**; SABA-only treatment increases mortality — GINA now uses ICS-formoterol as reliever (AIR) at every step.
- ▶ **Reversibility** = $\geq 10\%$ rise in FEV1 % predicted (or $\geq 12\%$ and ≥ 200 mL); **PEF diurnal variability** $> 20\%$.
- ▶ Key T2 cytokines: **IL-4 (IgE), IL-5 (eosinophils), IL-13 (AHR/mucus)**; alarmins = TSLP, IL-25, IL-33.
- ▶ **ABPA**: IgE > 1000 IU/mL, eosinophils $> 500/\mu\text{L}$, central bronchiectasis — treat with itraconazole + steroids.
- ▶ Acute severe asthma red flags: **silent chest, pulsus paradoxus > 25 mmHg, normal/rising PaCO_2 , bradycardia.**

- ▶ Acute treatment: O₂ + nebulised SABA + ipratropium + systemic steroids; IV MgSO₄ 2 g in severe cases.
- ▶ Biologics by endotype: omalizumab (IgE), mepolizumab/benralizumab (IL-5/IL-5R), dupilumab (IL-4Rα), tezepelumab (TSLP).
- ▶ High asthma-death risk: prior ICU/intubation, ≥2 ED visits in 6 months, recent OCS, psychosocial problems.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Asthma” (pathophysiology, type 2/non-type 2 inflammation, genetics, diagnosis, GINA/NAEPP step therapy, biologics, status asthmaticus, AERD, pregnancy).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Asthma: Pathogenesis and Phenotypes” (T2-high/T2-low endotypes, ILC2/Th2 biology).
- ▶ **CMDT 2026** — “Pulmonary Disorders” (Asthma) (GINA control classification, exacerbation severity grading table, methacholine/PEF criteria, acute management including IV magnesium).



Acute Respiratory Distress Syndrome — Causes, Pathophysiology, Diagnostic Criteria and Management

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Acute respiratory distress syndrome (ARDS) is a clinical syndrome of rapid-onset severe dyspnoea, refractory hypoxaemia and bilateral pulmonary infiltrates caused by diffuse, increased-permeability (non-cardiogenic) pulmonary oedema arising from direct or indirect lung injury. The pathological substrate is **diffuse alveolar damage (DAD)**, and the physiological hallmarks are intrapulmonary shunting, reduced lung compliance and increased dead space. First described by *Ashbaugh* and colleagues in 1967, it is currently defined by the **Berlin criteria (2012)** and complicates ~10% of ICU admissions, with hospital mortality of 35–46%.

Etiology / Causes

Over 80% of cases arise from a few disorders — **pneumonia and sepsis (~40–60%)**, aspiration of gastric contents, trauma, multiple transfusions and drug overdose. Causes are classified by mechanism of injury:

Direct (pulmonary) lung injury	Indirect (extrapulmonary) lung injury
Pneumonia — bacterial, viral (influenza, COVID-19)	Sepsis (commonest single cause)

Direct (pulmonary) lung injury	Indirect (extrapulmonary) lung injury
Aspiration of gastric contents	Severe trauma — multiple fractures, flail chest, head trauma
Pulmonary contusion	Multiple blood transfusions (>15 units/24 h; TRALI)
Toxic inhalation injury	Acute pancreatitis
Near-drowning	Cardiopulmonary bypass
Reperfusion injury (post-lung transplant)	Drug overdose; burns

- ▶ **Predisposing/severity modifiers:** older age, **chronic alcohol abuse** (relative risk ~2.0, and higher mortality), active or passive cigarette smoke, and severity of critical illness — trauma patients with an **APACHE II score ≥ 16** have a 2.5-fold increased risk. The presence of **more than one risk factor** multiplies the risk.
- ▶ ARDS arising from **direct** lung injury carries nearly **twice** the mortality of indirect causes; trauma-associated ARDS has the best prognosis and end-stage liver disease the worst.

Pathophysiology

The natural history evolves through **three overlapping phases** (exudative → proliferative → fibrotic).

- ▶ **Exudative phase (day 0–7):** injury to **alveolar capillary endothelium** and **type I pneumocytes** disrupts the tight alveolar barrier, allowing **protein-rich exudate** into the interstitium and alveoli. Pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF- α) and lipid mediators (**leukotriene B4**) recruit **neutrophils**, which release proteases, reactive oxygen species and **neutrophil extracellular traps (NETs)**. Condensed plasma proteins, debris and inactivated surfactant form **hyaline membranes** (the histological correlate of DAD). Microvascular injury causes obliteration by **microthrombi**.
- ▶ **Physiological consequences:** alveolar flooding and dependent atelectasis cause **right-to-left intrapulmonary shunt** → **hypoxaemia refractory to oxygen**, **reduced compliance** (“stiff lungs”, increased work of breathing), and **increased dead space** from microvascular occlusion → **hypercapnia** and **pulmonary hypertension**. Loss/inactivation of **surfactant** promotes further alveolar collapse; **hypoxia impairs alveolar Na^+/K^+ -ATPase-dependent fluid clearance**.
- ▶ **Proliferative phase (day 7–21):** organisation of exudate, **type II pneumocyte proliferation** (synthesising new surfactant and differentiating into type I cells), and a shift from neutrophil- to lymphocyte-predominant infiltrate. Most patients begin to recover here.
- ▶ **Fibrotic phase (>2–3 weeks):** in a subset, alveolar and interstitial **fibrosis**, acinar disruption with **bullae**, and intimal fibroproliferation causing vascular occlusion and pulmonary hypertension; predicts higher mortality and risk of pneumothorax.

- **Important nuances:** DAD is found in only ~50% of ARDS at biopsy/autopsy. Latent-class analysis identifies two **subphenotypes** — a **hypoinflammatory** and a **hyperinflammatory** (high IL-6/IL-8, low protein C, vasopressor-dependent, higher mortality) phenotype that respond differently to PEEP, fluids and statins. Mechanical ventilation itself propagates injury — **ventilator-induced lung injury (VILI)** via **volutrauma** (overdistension), **barotrauma**, **atelectrauma** (cyclic opening/closing) and **biotrauma** (cytokine release driving multi-organ failure).

Diagnostic criteria — Berlin definition (2012)

All four must be satisfied; severity is graded by oxygenation on PEEP/CPAP ≥ 5 cmH₂O.

Domain	Requirement
Timing	Within 1 week of a known insult or new/worsening respiratory symptoms
Chest imaging	Bilateral opacities (CXR or CT) not fully explained by effusion, lobar/lung collapse or nodules
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload ; if no risk factor, objective testing (e.g. echocardiography) to exclude hydrostatic oedema
Oxygenation (PaO ₂ /FiO ₂ on PEEP ≥ 5)	Mild 200–300 mmHg · Moderate 100–200 mmHg · Severe ≤ 100 mmHg

- The Berlin definition **abolished the term “acute lung injury (ALI)”** and removed the pulmonary-artery wedge-pressure requirement (≤ 18 mmHg of the older AECC definition).
- **Proposed updates (2023) / new global definition (2024):** allow diagnosis in **non-intubated** patients on **high-flow nasal oxygen** (≥ 30 L/min) or NIV/CPAP, permit **SpO₂/FiO₂ (S/F) ratios** (≤ 315 if SpO₂ $\leq 97\%$) and **lung ultrasound** as imaging, easing diagnosis in resource-limited settings.
- **Key differentials:** cardiogenic pulmonary oedema (look for cardiomegaly, effusions, vascular redistribution; BNP/echocardiography), bilateral pneumonia, diffuse alveolar haemorrhage, acute interstitial pneumonia and neurogenic pulmonary oedema.

Management strategies

Mortality reduction stems chiefly from **lung-protective ventilation and meticulous supportive critical care** — there is **no proven pharmacotherapy that reduces mortality**.

- **Treat the precipitating cause** — source control, antibiotics for sepsis/pneumonia; ICU “bundle” care (VTE, GI and aspiration prophylaxis, minimised sedation, enteral nutrition, infection prevention).

- ▶ **Lung-protective ventilation (cornerstone, Evidence A):** the ARDSNet (ARMA) trial showed low tidal volume 6 mL/kg predicted body weight with plateau pressure ≤ 30 cmH₂O reduced mortality (31% vs 40%) versus 12 mL/kg. Target SpO₂ 88–95%, pH ≥ 7.30 (permissive hypercapnia), and the lowest FiO₂ (aim < 0.6) to avoid oxygen toxicity. **Driving pressure (P_{plat} – PEEP)** may be the strongest predictor of survival.
- ▶ **PEEP / open-lung strategy (Evidence B):** PEEP is titrated (PEEP–FiO₂ table) to recruit atelectatic lung, reduce atelectrauma and lower FiO₂; **higher PEEP is safe and improves oxygenation in severe ARDS** but no trial shows a clear mortality benefit. **Routine recruitment manoeuvres are not recommended** (harmful when combined with high PEEP).
- ▶ **Prone positioning (Evidence B):** the PROSEVA trial showed prolonged proning (> 16 h/day) in severe ARDS (PaO₂/FiO₂ < 150) reduced 28-day mortality (16% vs 33%). Requires an experienced team; contraindicated in unstable spinal injury.
- ▶ **Conservative fluid management:** FACTT trial — conservative fluids/diuresis (CVP < 4 or PAOP < 8 mmHg) gave more ventilator-free and ICU-free days without increasing shock or dialysis. **Pulmonary artery catheters are not routinely indicated.** Transfuse to Hb ≥ 7 g/dL only.
- ▶ **Neuromuscular blockade (selective):** early cisatracurium $\times 48$ h improved survival in severe ARDS (ACURASYS 90-day mortality 31.6% vs 40.7%) but the confirmatory ROSE trial (with light sedation control) showed no benefit — reserve for **ventilator dyssynchrony** despite deep sedation.
- ▶ **Corticosteroids:** not routinely advised historically, but the DEXA-ARDS trial (dexamethasone 20 mg/day $\times 5$ then 10 mg/day $\times 5$) increased ventilator-free days (12.3 vs 7.5) and lowered 60-day mortality (21% vs 36%); **2024 ATS guidelines** give a **conditional recommendation** for corticosteroids, most useful within **< 14 days**, in severe CAP, and in COVID-19.
- ▶ **ECMO (rescue):** CESAR favoured referral to an ECMO centre; EOLIA showed a non-significant mortality reduction (35% vs 46%, with high crossover) — ECMO is a **salvage option for very severe, refractory ARDS**, not first-line.
- ▶ **Therapies NOT recommended / ineffective:** surfactant replacement, **inhaled nitric oxide / epoprostenol** (transiently improve oxygenation, no survival benefit; iNO risks renal dysfunction — rescue only), β_2 -agonists (salbutamol — harmful), high-frequency oscillatory ventilation, statins (except possibly the hyperinflammatory subphenotype), and immunonutrition/ ω -3 supplements.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Time-course of ARDS (three phases):** an x-axis “Day 0 $\rightarrow$ 2 $\rightarrow$ 7 $\rightarrow$ 14 $\rightarrow$ 21” with overlapping bands labelled Exudative (alveolar oedema, neutrophils, hyaline membranes), Proliferative (interstitial inflammation, type II pneumocyte proliferation, early fibrosis) and Fibrotic (fibrosis, bullae).

- ▶ **Injured alveolus (exudative phase):** label alveolar capillary, damaged endothelium, injured type I pneumocyte, type II pneumocyte, protein-rich oedema fluid in alveolus, hyaline membrane, migrating neutrophil with proteases/ROS/NETs, activated macrophage, platelet–fibrin microthrombus, and inactivated surfactant — contrasted with a normal alveolus.

Clinical / Diagnostic significance

- ▶ **Bedside diagnosis** hinges on excluding **cardiogenic oedema** — echocardiography/BNP when no clear ARDS risk factor; CT shows characteristic **dependent, heterogeneous** consolidation guiding lung-protective ventilation.
- ▶ **Mortality (LUNG SAFE):** mild 34.9%, moderate 40.3%, severe 46.1%; most deaths (>80%) are from **sepsis and non-pulmonary multi-organ failure**, not refractory hypoxaemia — emphasising that survival depends on holistic critical care.
- ▶ **Complications:** ventilator-associated pneumonia (30–65%), **barotrauma** (pneumothorax/pneumomediastinum, 12–13%), and **ICU-acquired weakness**.
- ▶ **Recovery:** survivors usually regain near-normal lung function by 6–12 months, but **persistent exercise limitation, muscle weakness, depression and PTSD** are common — warranting post-ICU follow-up.

High-yield exam pointers

- ▶ **Berlin triad:** acute (≤ 1 week) + bilateral opacities + non-cardiogenic oedema; severity by $\text{PaO}_2/\text{FiO}_2$ on PEEP ≥ 5 (Mild ≤ 300 , Moderate ≤ 200 , Severe ≤ 100).
- ▶ **Pathology = diffuse alveolar damage;** phases = **exudative** $\rightarrow$ **proliferative** $\rightarrow$ **fibrotic**.
- ▶ **Two cornerstones with mortality benefit:** **low tidal volume** (6 mL/kg PBW, $\text{P}_{\text{plat}} \leq 30$) and **prone positioning in severe ARDS** (PROSEVA).
- ▶ **Conservative fluids** (FACTT) $\rightarrow$ more ventilator-free days; PA catheter not routine.
- ▶ **VILI mechanisms:** volutrauma, barotrauma, atelectrauma, biotrauma.
- ▶ **Cisatracurium** (ACURASYS+, ROSE–) and **ECMO** (EOLIA) are selective/rescue, not routine.
- ▶ **No drug reliably cuts mortality;** corticosteroids (dexamethasone) are a **conditional** option in early ARDS.
- ▶ **Commonest causes:** **sepsis and pneumonia;** commonest cause of death: **multi-organ failure**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Acute Respiratory Distress Syndrome” (etiology, Berlin criteria, three-phase pathophysiology,

ARDSNet/PROSEVA/ACURASYS/ROSE, evidence-based recommendations, prognosis) and “Mechanical Ventilatory Support”.

- ▶ **Murray & Nadel’s Textbook of Respiratory Medicine, 7e** — “Acute Respiratory Distress Syndrome” (AECC→Berlin evolution, DAD/neutrophil and NET pathobiology, subphenotypes, VILI, detailed ventilation/PEEP/proning/NMB/ECMO trial data, DEXA-ARDS, long-term outcomes).
- ▶ **CMDT 2026** — “Pulmonary Disorders: ARDS” (current management, conservative fluid targets, 2024 ATS corticosteroid recommendation, prognosis).



Complications of Bronchiectasis

Asked in: Paper III Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Bronchiectasis is an *irreversible* dilation of the medium-to-large airways (cylindrical/tubular, varicose, or cystic/saccular) driven by Cole’s “vicious cycle/vortex” of impaired mucociliary clearance, chronic infection, transmural neutrophilic inflammation and progressive airway-wall destruction. Although recurrent suppurative infection is the defining feature, the clinical burden of the disease comes largely from its **complications**, which are best grouped as pulmonary, cardiovascular, systemic/extrapulmonary and microbiological. These determine quality of life, lung-function decline and mortality, and several severity scores are built around them.

Overview — complications grouped by system

System	Key complications
Airway / pulmonary	Acute infective exacerbations; chronic bacterial colonisation (esp. <i>Pseudomonas aeruginosa</i>); haemoptysis (incl. massive/life-threatening); progressive airflow obstruction → chronic respiratory failure; recurrent pneumonia, lung abscess, empyema; pneumothorax
Microbiological	Antimicrobial resistance from repeated courses; superinfection with non-tuberculous mycobacteria (NTM); <i>Aspergillus</i> — ABPA, mucoid impaction, aspergilloma/chronic pulmonary aspergillosis
Cardiovascular	Chronic hypoxaemic pulmonary hypertension → cor pulmonale (right-heart failure); excess cardiovascular and cerebrovascular events
Systemic / extrapulmonary	Secondary (AA) amyloidosis; IgA nephropathy; anaemia of chronic disease; weight loss/cachexia;

System	Key complications
	digital clubbing; reduced QOL, fatigue, depression, sleep-disordered breathing
Functional / prognostic	Frequent-exacerbator phenotype; accelerated FEV ₁ decline; increased hospitalisation and ~2-fold excess mortality

Pulmonary and airway complications

- ▶ **Acute exacerbations** are the commonest and most important clinical event. They are characterised by a change in sputum — *increased volume and purulence* — with worsening cough/dyspnoea; classical signs of infection (fever, new infiltrates) may be absent. Commonly implicated organisms are *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Moraxella catarrhalis*. The **frequent-exacerbator phenotype** (≥ 3 exacerbations/year) is the strongest predictor of future exacerbations and carries poorer QOL, more hospitalisations and higher, exacerbation-proportional mortality.
- ▶ **Chronic colonisation / Pseudomonas aeruginosa infection* — *P. aeruginosa colonises damaged airways, forms biofilms (exopolysaccharide glycocalyx, quorum sensing) and evades host defences. It is a marker of disease severity, frequent exacerbation, accelerated decline and confers an approximately three-fold increased risk of death**.
- ▶ **Antimicrobial resistance** — recurrent infection with repeated courses of antibiotics drives multidrug resistance, sometimes forcing combinations of independently toxic agents.
- ▶ **Haemoptysis** — the **most common complication**; recurrent infection injures superficial bronchial-mucosal vessels causing bleeding that ranges from streaking to **massive, life-threatening haemoptysis** (bleeding is from the high-pressure **bronchial arterial** circulation). Discussed separately below.
- ▶ **Progressive airflow obstruction and chronic respiratory failure** — mild-to-moderate obstruction overlaps with COPD; FEV₁ in non-CF bronchiectasis declines at ~50–55 mL/year (vs 20–30 mL/year in healthy controls), eventually causing chronic hypoxaemia/hypercapnia and end-stage respiratory failure requiring long-term oxygen or transplantation.
- ▶ **NTM superinfection** — *Mycobacterium avium* complex (MAC) and *M. abscessus* both **cause and complicate** bronchiectasis; bronchiectasis is the best-recognised predisposing condition for pulmonary NTM. NTM may be a coloniser or true pathogen, and chronic macrolide monotherapy risks inducing **macrolide-resistant NTM** — hence NTM must be excluded before long-term macrolides are started.
- ▶ **Aspergillus-related disease** — damaged/central airways may develop **ABPA** (immune-mediated, mucoid impaction, central bronchiectasis) or, within residual cavities (e.g., post-TB), an **aspergilloma/chronic pulmonary aspergillosis** causing recurrent haemoptysis, weight loss and fatigue.

- ▶ **Suppurative spread** — necrotising infection of bronchiectatic lung can produce **recurrent pneumonia, lung abscess, parenchymal scarring, pneumatocles and empyema**; pneumothorax occurs in cystic disease and in connective-tissue-associated bronchiectasis (e.g., Marfan syndrome).

Massive haemoptysis — recognition and management (high-yield)

- ▶ Defined by life-threatening volume/rate; the airway, not exsanguination, is the immediate threat, so the priorities are **airway protection and gas exchange**.
- ▶ **Stepwise management**: secure the airway (often **intubation**, with the bleeding lung dependent / lateral decubitus to protect the non-bleeding lung); resuscitate and correct coagulopathy; **localise the source** with chest CT-angiogram and/or bronchoscopy; achieve haemostasis.
- ▶ **Definitive control**: **bronchial artery embolisation** is first-line for control; bronchoscopic measures (balloon tamponade, topical vasoconstrictors, laser) may temporise; **surgical resection** is reserved for refractory or localised disease.

Cardiovascular, renal and systemic complications

- ▶ **Pulmonary hypertension and cor pulmonale** — chronic hypoxaemia, parenchymal destruction and vascular remodelling raise pulmonary arterial pressure; sustained pressure load produces **right-ventricular hypertrophy and failure (cor pulmonale)** — a recognised late sequela of chronic suppurative/fibrotic lung disease (e.g., post-tuberculous bronchiectasis).
- ▶ **Secondary (AA) amyloidosis** — long-standing suppuration with sustained serum amyloid-A (acute-phase) elevation can deposit AA fibrils in kidney, liver and spleen, classically presenting as nephrotic-range proteinuria and renal failure; a classic, now-uncommon complication of chronic neglected bronchiectasis.
- ▶ **IgA nephropathy** — chronic bronchiectasis is among the systemic conditions associated with mesangial IgA deposition; usually clinically silent but occasionally causes glomerular disease.
- ▶ **Systemic burden** — anaemia of chronic disease, **weight loss/cachexia**, fatigue and **digital clubbing**; patients carry excess **cardiovascular, cerebrovascular and malignancy risk**, gastro-oesophageal reflux, sleep-related complications, and high rates of anxiety/depression with markedly reduced quality of life (captured by the QOL-B instrument).

Prognosis and severity-scoring tools

- ▶ Bronchiectasis confers an approximately **two-fold excess mortality** versus age/sex-matched controls.
- ▶ Validated multidimensional scores predict mortality and hospitalisation:
 - **FACED score** — FEV₁, Age, Chronic colonisation (*P. aeruginosa*), radiographic Extension (number of lobes), Dyspnoea (mMRC).

- **Bronchiectasis Severity Index (BSI)** — incorporates the above plus **prior hospitalisation and exacerbation frequency**.
- (The E-FACED adds the Exacerbation dimension to FACED.)
- ▶ The strongest adverse prognostic markers are chronic *P. aeruginosa* infection, frequent exacerbations, lower FEV₁, greater radiographic extent and higher dyspnoea grade.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Cole's "vicious vortex" of bronchiectasis (link to complications):** draw a four-node cycle — label *Impaired mucociliary clearance / ciliary dysfunction* → *Chronic bacterial infection & biofilm (Pseudomonas)* → *Transmural neutrophilic inflammation (elastase, proteases, ROS)* → *Airway-wall destruction & dilation* — with outward arrows to the major complications: **Haemoptysis, Exacerbations, Respiratory failure, Cor pulmonale, Amyloidosis**.
- ▶ **Cross-section of a bronchiectatic airway:** label *dilated lumen with retained mucus*, *destroyed wall (loss of elastin, smooth muscle, cartilage)*, *hypertrophied/eroded bronchial arteries (source of haemoptysis)*, *peribronchial inflammation, adjacent pulmonary artery*; alongside, sketch the CT "**signet-ring sign**" (airway:vessel diameter ≥ 1.5) and "**tram-track**" dilated airways.

Clinical / Diagnostic significance

- ▶ **HRCT** is the diagnostic standard and quantifies disease extent (a FACED/BSI input); look for tram-tracks, signet-ring sign, lack of tapering, tree-in-bud and cystic change.
- ▶ **Sputum surveillance** (bacterial, AFB/NTM, fungal cultures) is essential — isolating *P. aeruginosa* or NTM changes prognosis and therapy; exclude NTM before chronic macrolides and obtain an ECG to exclude long QT before macrolide therapy.
- ▶ Work up the **underlying cause** (sweat chloride/CFTR, immunoglobulins, α_1 -antitrypsin, nasal NO/ciliary studies, *Aspergillus* IgE/IgG + eosinophils, autoantibodies) because cause-specific therapy (IgG replacement, ABPA steroids/antifungals, CFTR modulators) modifies complications.
- ▶ Management aimed at the vicious cycle — **airway clearance** (physiotherapy, oscillatory PEP/flutter, hypertonic saline), treating exacerbations (7–14 day antibiotics), long-term suppressive/macrolide therapy for frequent exacerbators, pulmonary rehabilitation, and vaccination (influenza, pneumococcal, COVID, RSV) — reduces exacerbations and lung-function decline. *Note: DNase (dornase) helps in CF but is not recommended (possibly harmful) in non-CF bronchiectasis.*

High-yield exam pointers

- ▶ **Haemoptysis is the commonest complication;** massive haemoptysis arises from eroded bronchial arteries — manage by airway protection + **bronchial artery embolisation**.

- ▶ Chronic **Pseudomonas** colonisation = severity marker, faster decline, ~3× **mortality**; FEV₁ falls 50–55 mL/yr in non-CF disease.
- ▶ **Frequent-exacerbator phenotype** (≥3/yr) predicts future exacerbations, hospitalisation and death.
- ▶ Late systemic complications: **cor pulmonale**, **secondary (AA) amyloidosis**, IgA nephropathy, anaemia, cachexia, clubbing.
- ▶ NTM both causes and complicates bronchiectasis; beware macrolide-resistant NTM — exclude NTM before chronic macrolides.
- ▶ **ABPA / aspergilloma** are *Aspergillus*-related complications; aspergilloma in old cavities causes recurrent haemoptysis.
- ▶ Severity/prognosis scores: **FACED** (FEV₁, Age, Colonisation, Extension, Dyspnoea), **E-FACED**, and **BSI**; overall ~2× excess mortality.
- ▶ Exacerbation = increased sputum **volume** + **purulence** (fever/infiltrate often absent).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Bronchiectasis” (complications: haemoptysis, antimicrobial resistance, FEV₁ decline, NTM); “Nontuberculous Mycobacterial Infections”; “Tuberculosis” (post-TB bronchiectasis, pulmonary hypertension, aspergilloma); “Glomerular Diseases” (IgA nephropathy association); “Lung Abscess” / “Pneumonia” (empyema, pneumatoceles, abscess).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Bronchiectasis” (vicious vortex, biofilms, *Pseudomonas* ~3× mortality, frequent-exacerbator phenotype, FACED/BSI scores, ~2× excess mortality, cardiovascular/cerebrovascular/GERD/malignancy morbidity).
- ▶ **CMDT 2026** — “Bronchiectasis” (haemoptysis as commonest complication and its management; *Pseudomonas* as severity marker; ≥3 exacerbations/year and mortality) and “Allergic Bronchopulmonary Aspergillosis”.

Coverage note: The dedicated bronchiectasis chapters describe haemoptysis, exacerbations/colonisation, lung-function decline and excess mortality in detail. **Secondary (AA) amyloidosis** and **cor pulmonale** are universally accepted classical complications of chronic suppurative bronchiectasis; in this corpus they are grounded indirectly (amyloidosis via the systemic AA mechanism; pulmonary hypertension explicitly in the post-tuberculous lung-disease section) rather than stated verbatim within the bronchiectasis chapters.



Describe etiology, clinical features, GOLD criteria in Chronic Obstructive Pulmonary Disease (COPD) and treatment of COPD exacerbation

Asked in: Paper III Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Chronic obstructive pulmonary disease (COPD) is a heterogeneous, preventable and treatable disease state characterised by **persistent respiratory symptoms and chronic airflow obstruction that is not fully reversible and is usually progressive**, arising from airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases. It encompasses three overlapping processes in varying proportion: **emphysema** (anatomic destruction of alveoli with airspace enlargement), **chronic bronchitis** (chronic cough and phlegm, clinically defined) and **small airway disease** (narrowed, reduced bronchioles). Diagnosis requires **spirometry**. Globally COPD affects an estimated 480 million people and is the third to fourth leading cause of death worldwide.

Etiology and risk factors

- ▶ **Cigarette smoking** — the dominant risk factor in the developed world; causes a dose-dependent (pack-year) accelerated decline in FEV1 (≈ 66 mL/yr in men, 54 mL/yr in women vs ≈ 30 and 22 mL/yr in quitters). Only $\sim 15\%$ of FEV1 variability is explained by pack-years, implying additional host factors; $\sim 15\%$ of smokers develop disabling disease. Cigar/pipe, **vaping and inhaled cannabis** are emerging concerns.
- ▶ **Biomass fuel smoke** — combustion of wood/dung for cooking in poorly ventilated dwellings; the leading cause in the developing world, especially in **women** and never-smokers.
- ▶ **Occupational exposures (VGDF)** — vapours, gases, dusts, fumes; coal mining, gold mining and cotton-textile dust are implicated (coal dust independently causes emphysema).
- ▶ **$\alpha 1$ -antitrypsin ($\alpha 1$ AT) deficiency** — the proven genetic cause; the **PiZ** phenotype (ZZ or Z/null) gives severe deficiency (~ 1 in 3000), serum $\alpha 1$ AT < 11 $\mu\text{mol/L}$ (~ 50 mg/dL); accounts for $\sim 1\%$ of COPD and causes early-onset, lower-zone **panlobular emphysema**.
- ▶ **Other genetics** — > 80 GWAS loci including *HHIP* (chr 4), the chr 15 cluster (nicotinic acetylcholine receptor, *IREB2*) and *FAM13A* (Wnt/ β -catenin).
- ▶ **Airway hyperresponsiveness / asthma, respiratory infections** (childhood pneumonia, tuberculosis-associated airflow limitation, HIV), **air pollution**, and **abnormal lung development / early-life passive smoke exposure** (maternal smoking, low maximal attained lung function).

Pathology and pathogenesis

- ▶ **Large airways** — mucus-gland enlargement, goblet-cell hyperplasia and squamous metaplasia $\rightarrow$ cough and sputum (chronic bronchitis).

- ▶ **Small airways (≤ 2 mm)** — goblet-cell metaplasia, smooth-muscle hypertrophy, fibrosis, mucus plugging and luminal narrowing; this is the **major site of increased airflow resistance** and the earliest lesion.
- ▶ **Parenchyma (emphysema)** — destruction of respiratory bronchioles, alveolar ducts and alveoli. Pathologic types: **centrilobular** (upper-lobe, smoking-related), **panlobular** (lower-lobe, $\alpha 1$ AT deficiency) and **paraseptal** (subpleural).
- ▶ **Disease mechanisms** — four interrelated events: chronic inhalational injury in susceptible hosts → inflammatory/immune cell recruitment → **protease–antiprotease imbalance** (the *elastase:antielastase* hypothesis; neutrophil elastase, MMP-12) and **oxidant–antioxidant imbalance** (oxidant inactivation of HDAC2, NRF2/SOD3 dysfunction) → structural cell death (ceramide, mTOR/Rtp801, senescence) → **ineffective repair** of elastin and matrix → airspace enlargement.

Pathophysiology

- ▶ **Airflow obstruction** — chronically reduced FEV1 and FEV1/FVC ratio that does not normalise after bronchodilator (fixed obstruction).
- ▶ **Hyperinflation** — air trapping ($\uparrow$ residual volume, $\uparrow$ RV/TLC), then $\uparrow$ TLC; flattens the diaphragm, shortening fibres and increasing work of breathing.
- ▶ **Gas exchange** — **V/Q mismatch** causes hypoxaemia (shunt minimal, hence corrected by modest O_2). P_{aO_2} usually stays near normal until FEV1 $< 50\%$ predicted; P_{aCO_2} rises only when FEV1 $< 25\%$ predicted. Sustained pulmonary hypertension → **cor pulmonale** typically when FEV1 $< 25\%$ and $P_{aO_2} < 55$ mmHg.

Clinical features

- ▶ **Symptoms** — the classic triad of **chronic cough, sputum production and progressive exertional dyspnoea**; symptoms often precede presentation by years. Arm work above shoulder level is poorly tolerated.
- ▶ **Signs** — early examination may be normal. Advanced: prolonged expiration, expiratory wheeze, **barrel chest**, poor diaphragmatic excursion, accessory-muscle use, **tripod posture**, pursed-lip breathing, cyanosis, cachexia (poor prognostic sign) and signs of cor pulmonale (raised JVP, pedal oedema). **Digital clubbing is NOT a feature** of COPD and mandates a search for another cause (especially lung cancer).
- ▶ **Two classic phenotypes** (most patients overlap):

Feature	Type A — “Pink Puffer” (emphysema-predominant)	Type B — “Blue Bloater” (bronchitis-predominant)
Main symptom	Severe dyspnoea, onset after ~50 yr; scant cough	Chronic productive cough, frequent infective exacerbations; onset 30s–40s
Build	Thin, recent weight loss, distressed, accessory-muscle use	Overweight, cyanotic, comfortable at rest, peripheral oedema
Chest	Quiet, no adventitious sounds	Noisy — rhonchi, wheezes
Pao ₂ / Paco ₂	Near normal (65–75 / 35–40 mmHg)	↓Pao ₂ (45–60), ↑Paco ₂ (50–60 mmHg)
Haemoglobin	Normal	Elevated (secondary polycythaemia)
CXR	Hyperinflation, flat diaphragms, ↓vascular markings	“Dirty lungs”, ↑interstitial markings, diaphragms not flat
Dlco / cor pulmonale	Reduced Dlco; late cor pulmonale	Normal Dlco; early, marked cor pulmonale

Diagnosis and GOLD criteria

- ▶ **Diagnostic requirement** — post-bronchodilator FEV₁/FVC <0.70 on spirometry confirms persistent airflow obstruction (some authorities prefer the lower limit of normal / Z-score to reduce mis-classification).
- ▶ **GOLD spirometric grades** (severity of obstruction, all require FEV₁/FVC <0.70):

Grade	Severity	Post-bronchodilator FEV ₁ (% predicted)
GOLD 1	Mild	≥80%
GOLD 2	Moderate	50–79%
GOLD 3	Severe	30–49%
GOLD 4	Very severe	<30%

- ▶ **GOLD “ABE” assessment tool** — combines symptom burden with exacerbation risk to guide therapy. **Symptoms:** mMRC ≥2 or CAT ≥10 = high; **Exacerbation risk:** ≥2 moderate exacerbations or ≥1 leading to hospitalisation in the past year = high.
 - **Group A** — low symptoms, low risk → a bronchodilator.
 - **Group B** — high symptoms, low risk → LABA + LAMA.
 - **Group E** — high exacerbation risk (any symptoms) → LABA + LAMA; add ICS if blood eosinophils ≥300/μL.

- ▶ **mMRC dyspnoea scale:** 0 (breathless only on strenuous exertion) to 4 (too breathless to leave the house/dress).
- ▶ **Other assessment** — ABG (ventilatory failure = $\text{Paco}_2 > 45$ mmHg), Dlco (reduced in emphysema), CBC (eosinophils guide ICS; raised Hct = chronic hypoxaemia), chest CT (defines emphysema pattern, screens for cancer), serum $\alpha 1\text{AT}$ in all COPD/early-onset disease, 6-minute walk and the multidimensional **BODE index** (Body-mass index, Obstruction, Dyspnoea, Exercise capacity) — a better predictor of mortality than FEV1 alone.

Treatment of COPD exacerbation

- ▶ **Definition** — an acute worsening of respiratory symptoms (increased dyspnoea, cough, sputum volume/purulence) beyond day-to-day variation, usually over < 14 days. Strongest predictor = a prior exacerbation.
- ▶ **Precipitants** — respiratory infection (viral in $> 50\%$; bacteria — *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*), air pollution, non-adherence; consider **pulmonary embolism** (increased incidence) and pneumothorax mimics.
- ▶ **Indications for hospital admission** — respiratory acidosis/hypercapnia, new or worsening hypoxaemia, severe underlying COPD, serious comorbidity (e.g. heart failure), frequent-exacerbator phenotype, inadequate home support.
- ▶ **Management:**
 - **Controlled oxygen** — target SpO_2 88–92%; recheck ABG at 30–60 min for CO_2 retention. Hypoxaemia is more dangerous than hypercapnia — never withhold needed O_2 .
 - **Bronchodilators** — aggressive short-acting β_2 -agonist (salbutamol) + short-acting muscarinic antagonist (ipratropium), usually nebulised initially.
 - **Systemic glucocorticoids** — prednisone 40 mg orally for 5 days (0.5 mg/kg/day; 5 days non-inferior to 10–14 days) — shortens recovery, improves lung function and reduces relapse; watch for hyperglycaemia.
 - **Antibiotics** — for moderate/severe exacerbations, guided by the **Anthonisen criteria** (increased dyspnoea + increased sputum volume + increased sputum purulence; greatest benefit when all three present, or when ventilated), for 5–7 days. Choice per local susceptibility; cover *Pseudomonas* (e.g. piperacillin-tazobactam, levofloxacin) when risk factors present.
 - **Non-invasive positive-pressure ventilation (NIPPV)** — first-line for acute respiratory acidosis ($\text{Paco}_2 > 45$ mmHg and $\text{pH} \leq 7.35$); reduces mortality, need for intubation, complications and length of stay.
 - **Invasive mechanical ventilation** — for severe distress, refractory hypoxaemia/hypercapnia or acidosis despite NIPPV, impaired consciousness, respiratory arrest or haemodynamic instability; beware **auto-PEEP** — allow adequate expiratory time.

- ▶ **Prognosis** — mechanical ventilation in an exacerbation carries 17–49% in-hospital mortality; ~20% are re-hospitalised within 30 days, 45% within a year, and ~20% die within the year after discharge. Influenza, pneumococcal, COVID-19 and RSV vaccination plus smoking cessation reduce future exacerbations.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Emphysema subtypes / CT patterns** — three labelled lung-acinus panels: (A) **Centrilobular** — dilated airspaces around the respiratory bronchiole, *upper-lobe, smoking*; (B) **Panlobular** — uniform acinar destruction, *lower-lobe, α 1AT deficiency*; (C) **Paraseptal** — subpleural airspaces along pleural margins. Label respiratory bronchiole, alveolar duct, alveolus, pleura.
- ▶ **GOLD ABE assessment grid** — Y-axis “Exacerbation history” (≥ 2 moderate or ≥ 1 hospitalisation = high), X-axis “Symptoms” (mMRC/CAT). Boxes labelled A, B, E; side column labelled GOLD 1–4 with FEV1 thresholds (≥ 80 , 50–79, 30–49, < 30).

Clinical / Diagnostic significance

- ▶ **Spirometry** (post-bronchodilator FEV1/FVC < 0.70) is mandatory — clinical features alone over- and under-diagnose COPD.
- ▶ Distinguish from **asthma** (reversible obstruction), **bronchiectasis** (recurrent pneumonia, clubbing, hemoptysis), **cystic fibrosis** and central airway obstruction.
- ▶ **Three interventions improve survival** — smoking cessation, long-term oxygen in chronic hypoxaemia (Pao₂ ≤ 55 mmHg, or ≤ 59 with cor pulmonale/erythrocytosis; ≥ 15 h/day), and lung volume reduction (surgical/endobronchial valve) in selected upper-lobe emphysema; triple inhaled therapy reduces mortality in selected patients.
- ▶ **Blood eosinophil count** individualises ICS use; clubbing or hemoptysis should prompt evaluation for **lung cancer**.

High-yield exam pointers

- ▶ COPD = persistent symptoms + non-fully-reversible airflow obstruction; diagnosis needs post-bronchodilator FEV1/FVC < 0.70 .
- ▶ GOLD grades 1–4 by FEV1 %predicted (≥ 80 / 50–79 / 30–49 / < 30); management by ABE groups using mMRC/CAT + exacerbation history.
- ▶ α 1AT deficiency $\rightarrow$ early-onset **panlobular**, lower-zone emphysema; serum < 11 μ mol/L (~ 50 mg/dL), PiZ; IV augmentation ~ 60 mg/kg weekly.
- ▶ **Centrilobular** = upper-lobe, smoking; **panlobular** = lower-lobe, α 1AT.
- ▶ **Pink puffer** (emphysema, thin, normal gases) vs **blue bloater** (bronchitis, cyanotic, hypercapnic, cor pulmonale).

- ▶ Exacerbation: **prednisone 40 mg × 5 days**, antibiotics 5–7 days by **Anthonisen criteria**, O₂ target 88–92%, NIPPV when pH ≤ 7.35 & PaCO₂ > 45.
- ▶ **Clubbing** is **NOT** part of COPD — investigate for malignancy.
- ▶ **BODE index** predicts mortality better than FEV₁ alone.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — “Chronic Obstructive Pulmonary Disease” (definition, pathology/pathogenesis, GOLD spirometric grades [Table 303-1] and ABE tool, exacerbation management).
- ▶ Murray & Nadel's Textbook of Respiratory Medicine, 7e — “COPD: Pathogenesis and Natural History” and “COPD: Diagnosis and Management” (GOLD classification figure, Anthonisen criteria, corticosteroid/antibiotic dosing, LTOT thresholds, BODE).
- ▶ CMDT 2026 — “Pulmonary Disorders” (pink puffer/blue bloater Table 9-7, diagnostic tests, hospitalised-exacerbation regimen, NIPPV).



Pathogenesis of Bronchiectasis

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Bronchiectasis is an *irreversible*, abnormal dilatation (ectasia) and destruction of the bronchial wall, involving the lung focally or diffusely. It is classically categorised morphologically as **cylindrical/tubular** (commonest), **varicose**, or **cystic/saccular**. It is not a single disease but the common structural end-point of many insults, the great majority operating through a self-perpetuating “**vicious cycle**” (Cole) of impaired mucociliary clearance → microbial colonisation → chronic neutrophilic inflammation → airway-wall destruction. The pathogenesis must therefore be understood as the interaction of a **predisposing host/structural defect**, **microbial persistence**, and an **unresolved inflammatory (protease-driven) response**.

Normal defences whose failure permits bronchiectasis

- ▶ The airway is continuously protected by the **mucociliary escalator**, an effective **cough**, **secretory IgA**, and epithelial **antimicrobial peptides** (lysozyme, secretory leukocyte protease inhibitor, defensins, cathelicidin), backed by resident/recruited phagocytes (macrophages, neutrophils) and T-effector lymphocytes.
- ▶ Airway patency normally depends on **negative intrapleural pressure** transmitted via interstitial *tethering*, plus the **cartilaginous rings** of large/medium bronchi.
- ▶ Bronchiectasis develops when one or more of these are compromised — by an inherited/structural defect, immunodeficiency, mechanical obstruction, fibrotic traction, or an overwhelming/repeated infection — allowing the vicious cycle to be established.

Three fundamental mechanical mechanisms (traction, pulsion, weakness)

- ▶ **Traction bronchiectasis** — *retractile (centrifugal) forces* of a fibrosing/scarring parenchyma pull the airways open. Seen with idiopathic pulmonary fibrosis, post-radiation fibrosis, sarcoidosis and post-tuberculous scarring.
- ▶ **Pulsion bronchiectasis** — intense *intraluminal* inflammation and mucoid impaction balloon the airway from within; the prototype is **allergic bronchopulmonary aspergillosis (ABPA)**, where an immune reaction to *Aspergillus* lodged in central airways, with thick mucoid plugs, dilates the proximal bronchi.
- ▶ **Weakness of the airway wall** — loss of structural integrity, either *acquired* (post-infectious destruction of elastin/muscle/cartilage with regional volume loss) or *congenital* — e.g. **Mounier-Kuhn syndrome** (tracheobronchomegaly from atrophy of airway *elastic fibres*), **Williams-Campbell syndrome** (absent cartilage in segmental/subsegmental bronchi), Marfan syndrome, relapsing polychondritis. Weak, collapsible airways also cripple the cough mechanism, impeding secretion clearance and feeding the infective cycle.

The “vicious cycle / vicious vortex” — the central engine of pathogenesis

- ▶ The most widely cited mechanism (Cole) is a **self-amplifying cycle**: a susceptible airway with **poor mucociliary clearance** → **microbial colonisation/infection** of the bronchial tree → **chronic inflammation** → **airway-wall damage** → still poorer clearance → perpetuation.
- ▶ A single severe infection (*Bordetella pertussis*, *Mycoplasma pneumoniae*, measles, adenovirus, necrotising bacterial pneumonia) can initiate the cycle by causing the index airway injury; thereafter the process becomes self-sustaining and *infection-independent of the original trigger*.
- ▶ Recent reframing as a “**vicious vortex**” (a tetrad in which each factor perpetuates the other three):
 - ▶ **Airway epithelial & ciliary dysfunction with mucus hypersecretion**
 - ▶ **Chronic infection**, itself driving further mucus hypersecretion
 - ▶ **Inflammation** causing permanent airway injury and dilatation
 - ▶ **Resultant bronchiectatic airways** with impaired mucociliary clearance, which feed back into (1)–(3).
- ▶ Certain organisms — especially ***Pseudomonas aeruginosa**, *nontuberculous mycobacteria (NTM, mainly Mycobacterium avium complex)* and *Aspergillus** — preferentially colonise damaged airways and evade host defence, accelerating the vortex.

Cellular & molecular mediators — the protease–antiprotease imbalance

- ▶ The dominant inflammatory cell is the **neutrophil**, recruited by epithelial- and macrophage-derived chemokines/cytokines — **interleukin-8 (IL-8)**, **macrophage inflammatory protein-2 (MIP-2)**, **TNF- α** — with a prominent **Th17** axis.
- ▶ Activated/necrotic neutrophils release **neutrophil elastase**, **matrix metalloproteinases (MMPs)**, other proteases and **reactive oxygen species** that directly digest the airway wall, producing the classic 1950s-described pathology: **small-airway wall inflammation with larger-airway destruction and dilatation, and loss of elastin, smooth muscle and cartilage**.
- ▶ **Neutrophil elastase** is pivotal — it causes *ciliary dysfunction*, *mucous-gland hyperplasia* and *mucus hypersecretion* (worsening clearance), and **disables host defence**: it cleaves **Fc γ receptors** and **complement receptor 1** from neutrophils and digests **immunoglobulin** and **complement** off bacterial surfaces → impaired **opsonisation** and bacterial killing. It also inhibits **efferocytosis** (macrophage clearance of apoptotic neutrophils) by cleaving phosphatidylserine, so inflammation fails to resolve.
- ▶ Normally, **antiproteases** — chiefly **α 1-antitrypsin** — neutralise neutrophil elastase and enhance bacterial killing; a **protease–antiprotease imbalance** (excess elastase or **α 1-antitrypsin deficiency**) tips the balance toward wall destruction (bronchiectasis $\pm$ emphysema). Necrotic neutrophils also liberate highly viscous **DNA**, increasing sputum viscosity and inspissation.

Microbial colonisation and biofilms

- ▶ Mere colonisation is *insufficient* for bronchiectasis (smokers' chronic bronchitis carries a similar flora — *H. influenzae*, *S. pneumoniae*, *Moraxella* — without bronchiectasis); an *additional* host/structural disturbance is required to establish chronic transmural infection.
- ▶ **Biofilms** are central to chronicity: *P. aeruginosa* attaches to the airway surface and grows within an **exopolysaccharide matrix** (**glycocalyx / alginate**) that shields it from immune cells and antibiotics. Behaviour is coordinated by **quorum sensing** (cell–cell signalling), and biofilm-embedded bacteria can survive antibiotic concentrations up to **1000 $\times$ the MIC**.
- ▶ Chronic *P. aeruginosa* infection (often a mucoid, alginate-producing phenotype) is a marker of severe disease — more exacerbations, faster FEV₁ decline and roughly **three-fold increased mortality**.

Aetiology-specific pathways (mapping cause → mechanism)

Pattern / Cause	Mechanism in pathogenesis
Focal (foreign body, tumour, broncholith, extrinsic node compression)	Localised airway obstruction → distal stasis, infection, post-obstructive dilatation
Diffuse — infection (post-pertussis/measles/adenovirus; TB, NTM/MAC; necrotising pneumonia)	Direct wall destruction initiating the vicious cycle

Pattern / Cause	Mechanism in pathogenesis
Cystic fibrosis	CFTR anion-channel defect → reduced $\text{Cl}^-/\text{HCO}_3^-$ & water secretion → depleted periciliary/airway-surface liquid , ciliary collapse, viscid mucus, defective bacterial killing (low ASL pH) → relentless neutrophilic infection
Primary ciliary dyskinesia (Kartagener's)	Structural/functional ciliary defect → primary mucociliary clearance failure
Immunodeficiency (CVID, hypogammaglobulinaemia, IgG-subclass/IgA deficiency, HIV)	Recurrent infection from defective humoral defence → cycle
$\alpha 1$ -antitrypsin deficiency	Loss of antiprotease screen → unopposed elastase wall damage
ABPA & autoimmune/CTD (RA, Sjögren)	Immune-mediated bronchial-wall injury (pulsion / inflammatory)
Fibrosis (IPF, post-radiation), aspiration, Mounier-Kuhn/Williams-Campbell	Traction / recurrent chemical injury / congenital wall weakness

- **Anatomic distribution offers aetiological clues:** *upper zones* — CF, TB, sarcoid; *mid zones* — NTM/MAC and PCD; *lower zones* — idiopathic, chronic aspiration, hypogammaglobulinaemia, $\alpha 1$ -antitrypsin deficiency, CTD; *central airways* — ABPA, Mounier-Kuhn, Williams-Campbell.
- Up to 25–50% of referred cases remain **idiopathic** after full workup.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **“Vicious vortex” wheel diagram** — a central airway with four arrows forming a closed loop, labelled: (1) *Epithelial & ciliary dysfunction + mucus hypersecretion* → (2) *Chronic infection (Pseudomonas/NTM, biofilm)* → (3) *Neutrophilic inflammation (elastase, MMPs, ROS, IL-8, TNF- α , Th17)* → (4) *Airway-wall destruction & dilatation (loss of elastin, smooth muscle, cartilage)* → back to (1). Add a side-box: *predisposing defect — impaired MCC / immunodeficiency / obstruction / wall weakness / fibrotic traction*.
- **Cross-sectional airway comparison** — label: *normal bronchus* (intact epithelium, cilia, smooth muscle, cartilage, basement membrane) vs *bronchiectatic airway* (loss of cilia, goblet-cell/mucous-gland hyperplasia, mucus/biofilm plug, neutrophil infiltrate, destroyed muscle & cartilage, dilated thickened wall). Include the three morphological types: *cylindrical, varicose, cystic/saccular*.

Clinical / Diagnostic significance

- Explains the cardinal clinical picture: **chronic productive cough with copious purulent sputum, recurrent infective exacerbations, haemoptysis** (erosion of dilated bronchial vessels — the commonest complication), crackles, wheeze and **digital clubbing**.

- ▶ Rationalises a **mechanism-directed workup**: sweat chloride/CFTR genetics (CF), immunoglobulins ± vaccine-challenge (CVID), α 1-antitrypsin level/phenotype, nasal NO/ciliary studies (PCD), *Aspergillus* IgE/IgG + eosinophils (ABPA), RF/autoantibodies (CTD), and sputum culture including mycobacteria.
- ▶ **HRCT** is the diagnostic gold standard — *signet-ring sign* (broncho-arterial diameter ratio ≥ 1.5), tram-track lines, lack of tapering, airways within 1 cm of pleura, wall thickening, and *tree-in-bud* (small-airway secretions).
- ▶ The protease-driven, *Pseudomonas*/biofilm-sustained cycle is the **therapeutic target**: airway clearance/hygiene, treat exacerbations, long-term **macrolides** (anti-inflammatory + anti-quorum-sensing/biofilm action), inhaled antibiotics for *Pseudomonas*, and disease-specific therapy (CFTR modulators in CF, steroids ± itraconazole in ABPA, immunoglobulin replacement in CVID). Untreated, FEV₁ declines ~50–55 mL/year (vs 20–30 mL/year normally), comparable to COPD.

High-yield exam pointers

- ▶ Bronchiectasis = **irreversible** bronchial dilatation; morphology = **cylindrical** > **varicose** > **cystic**.
- ▶ Central mechanism = **Cole's vicious cycle**, modernised as the “**vicious vortex**” tetrad.
- ▶ Three mechanical routes = **traction**, **pulsion** (ABPA), **weakness** (Mounier-Kuhn / Williams-Campbell).
- ▶ Key effector = **neutrophil elastase** → ciliary dysfunction, mucus hypersecretion, impaired opsonisation/efferocytosis; balanced by **α 1-antitrypsin** (protease–antiprotease imbalance).
- ▶ Wall pathology = **loss of elastin, smooth muscle and cartilage**.
- ▶ ****Pseudomonas aeruginosa*** (*mucoïd/alginate, biofilm, quorum sensing*) = *chronicity* + ~3× *mortality*; MIC survival up to 1000×*.
- ▶ **Focal** = **obstruction**; **diffuse** = **systemic/infectious**; distribution clues — upper (CF/TB), mid (NTM/PCD), lower (aspiration/immunodeficiency/AAT), central (ABPA/Mounier-Kuhn).
- ▶ 25–50% remain idiopathic; CF/CFTR variants and NTM are increasingly recognised drivers.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Bronchiectasis” (etiology, pathogenesis & pathology, vicious-cycle hypothesis, protease/ α 1-antitrypsin role) and “Cystic Fibrosis” (CFTR/airway-surface-liquid mechanism).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Bronchiectasis” (traction/pulsion/weakness framework, vicious vortex tetrad, neutrophil-elastase/efferocytosis biology, biofilms & quorum sensing, aetiology-specific pathways and anatomic distribution).

- CMTD 2026 — “Bronchiectasis” (current causes, microbiology, diagnostic criteria and management framing).



Discuss clinical features, diagnosis and management of Pulmonary Thromboembolism

Asked in: Paper III May 2022 — RGUHS MD General Medicine

Definition / Introduction — Pulmonary thromboembolism (PE) is the lodgement, in the pulmonary arterial circulation, of thrombus that has usually embolised from a deep-venous thrombosis (DVT) of the lower limbs; together DVT and PE constitute **venous thromboembolism (VTE)**. When a DVT detaches from its site of formation it travels through the vena cava, right atrium and right ventricle to obstruct the pulmonary arteries, producing acute PE. PE is termed “*the great masquerader*” because its symptoms and signs are non-specific, and it remains a major cause of cardiovascular death, chronic disability and emotional distress. Notably, many patients with PE have no demonstrable DVT because the leg thrombus has already embolised entirely to the lungs.

Classification (severity stratification) of PE

Risk stratification is central because it directs both prognosis and the intensity of therapy.

Category	Proportion	Defining features	Prognosis
Massive (high-risk) PE	5–10%	Systemic arterial hypotension ; extensive thrombosis affecting <i>at least half</i> the pulmonary vasculature; dyspnoea, syncope, hypotension, cyanosis are hallmarks; may present in cardiogenic shock	Can die from multisystem organ failure
Submassive (intermediate-risk) PE	20–25%	RV dysfunction despite <i>normal</i> systemic arterial pressure; right heart failure plus elevated cardiac biomarkers (troponin) signals high risk of deterioration	Guarded; needs close monitoring
Low-risk PE	65–75%	Normotensive, normal RV function and haemodynamics	Excellent prognosis

- ▶ **DVT classification:** Lower-extremity DVT usually begins in the **calf** and may propagate proximally to the popliteal, femoral and iliac veins. Leg DVT is **~10 times** more common than upper-extremity DVT (the latter often precipitated by pacemakers, defibrillators or indwelling central venous/PICC catheters).

Pathophysiology (to anchor the clinical features)

- ▶ **Gas exchange:** the commonest abnormalities are **arterial hypoxaemia** and a widened **alveolar–arterial O₂ gradient**; anatomical and physiological **dead space increase** because ventilated lung is not perfused.
- ▶ **Increased pulmonary vascular resistance** from mechanical obstruction and from platelet-released vasoconstrictors (e.g. **serotonin**); **alveolar hyperventilation** (irritant-receptor reflex), **increased airway resistance** (bronchoconstriction) and **decreased compliance** (oedema, haemorrhage, surfactant loss).
- ▶ **RV failure cascade:** rising pulmonary artery pressure raises RV wall tension → **RV dilation, stretch and dysfunction** with release of **brain natriuretic peptide (BNP)**. The interventricular **septum bulges into the LV**, impairing LV filling. High RV wall tension compresses the **right coronary artery**, causing **RV microinfarction** with **troponin** release. LV underfilling lowers cardiac output and systemic pressure → circulatory collapse and death.

Clinical features

- ▶ **PE — most common symptom is unexplained breathlessness (dyspnoea).** Suspect PE when overt congestive heart failure or pneumonia fails to improve with standard therapy.
- ▶ **Pulmonary infarction** usually indicates a *small, peripheral* PE; it is *exquisitely painful* (pleuritic) because the thrombus lodges near the pleural nerves, and may cause haemoptysis.
- ▶ **DVT — most common symptom is a cramp or “charley horse” in the lower calf** that persists and intensifies over days. Physical signs may be only mild calf tenderness; massive DVT presents with marked thigh swelling, tenderness and erythema.
- ▶ **Phlegmasia cerulea dolens** — the most serious form of DVT — produces a diffusely oedematous, cyanotic limb.
- ▶ **May-Thurner syndrome** — recurrent left thigh oedema (especially in young women) from right iliac artery compression of the left iliac vein.
- ▶ **Superficial venous thrombosis** — erythema, tenderness and a *“palpable cord”*; visible chest-wall veins are *Urschel’s sign*; carries risk of extension to the deep system.

Diagnosis

Clinical probability first — apply the *Wells point-score* (validated in ambulatory, not hospitalised, patients). Patients with **low** probability of DVT or **low-to-moderate** probability of PE proceed to D-

dimer; a normal D-dimer rules out VTE without imaging. **High** clinical likelihood → *skip D-dimer and image directly*.

Wells score — PE	Points
Signs/symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilisation >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Haemoptysis	1.0
Cancer	1.0

High clinical likelihood of PE if score exceeds 4. (For DVT: low if ≤0, moderate 1–2, high ≥3.)

Blood tests

- **Quantitative plasma D-dimer (ELISA)**: sensitivity >95% for PE; an excellent “*rule-out*” test when pretest probability is low, but **not specific** (also raised in MI, pneumonia, sepsis, cancer, post-operative state, pregnancy) — hence rarely useful in hospitalised patients.
- **Age-adjusted D-dimer**: for patients >50 years with low/intermediate probability, the upper limit of normal = $\text{age} \times 10 \text{ ng/mL}$ (e.g. 700 ng/mL at age 70); reduces unnecessary CT angiograms. *Does not apply to suspected DVT.*
- **Cardiac biomarkers**: troponin rises with RV microinfarction; BNP/NT-proBNP rises with myocardial stretch.

ECG — sinus tachycardia is commonest; the classic **S1Q3T3** pattern (S in I, Q in III, inverted T in III) is *specific but insensitive*; RV strain produces **T-wave inversion in V1–V4**, the most common abnormality of a large PE.

Imaging

Modality	Key diagnostic point
CT pulmonary angiography (CTPA)	<i>Principal</i> test for PE; visualises intraluminal filling defects; RV/LV diameter ratio >1 indicates increased 30-day mortality; defines alternative lung diagnoses
Venous ultrasonography	First-line for DVT; primary criterion is loss of vein compressibility ; thrombus is homogeneous, central, low echogenicity
Chest X-ray	Often near-normal; classic signs — Westermarck’s sign (focal oligoemia), Hampton’s hump (pleural-

Modality	Key diagnostic point
	based triangular density of infarction), Palla's sign (enlarged right descending pulmonary artery)
V/Q lung scan	Second-line (for those unable to receive contrast); high probability = ≥ 2 segmental perfusion defects with normal ventilation (~90% certain)
Echocardiography	Not reliable to <i>diagnose</i> PE (most echos normal) but detects mimics (MI, tamponade, dissection); best indirect sign is McConnell's sign — RV free-wall hypokinesis with normal/hyperkinetic RV apex
MR (venography/angiography)	When US/pelvic imaging equivocal; unreliable for small segmental/subsegmental PE
Invasive pulmonary angiography / contrast phlebography	Reserved for non-diagnostic CT or when an interventional procedure (catheter thrombolysis/embolectomy) is planned

Management / Treatment

Risk-stratify, then treat. Haemodynamic instability, RV dysfunction on echo, RV enlargement on CT, and troponin elevation portend high risk despite anticoagulation. Normotension with normal RV → secondary prevention (anticoagulation); normotension with RV hypokinesis → individualised therapy; hypotension → primary therapy (thrombolysis/embolectomy).

Anticoagulation — the cornerstone. Three strategies: (1) parenteral UFH/LMWH/fondaparinux bridged to warfarin; (2) parenteral agent for 5 days then switch to **dabigatran** (direct thrombin inhibitor) or **edoxaban** (anti-Xa); (3) **oral monotherapy** with **rivaroxaban** or **apixaban** (anti-Xa) with a loading phase.

Agent	Regimen (normal renal function)
Unfractionated heparin (UFH)	Bolus 80 U/kg, then 18 U/kg/h infusion; target aPTT 60–80 s (anti-Xa 0.3–0.7 U/mL)
Enoxaparin (LMWH)	1 mg/kg SC twice daily; no routine monitoring
Fondaparinux	Weight-based once-daily SC; reduce in renal impairment; <i>does not cause HIT</i>
Warfarin	Start 5 mg, titrate to INR 2.0–3.0; overlap parenteral agent ≥ 5 days until two INRs ≥ 1 day apart are therapeutic
Rivaroxaban	15 mg twice daily $\times$ 3 weeks, then 20 mg once daily with dinner
Apixaban	10 mg twice daily $\times$ 1 week, then 5 mg twice daily

Agent	Regimen (normal renal function)
Dabigatran / Edoxaban	After 5 days parenteral: dabigatran 150 mg bid / edoxaban 60 mg once daily

- ▶ **Heparin-induced thrombocytopenia (HIT):** use IV direct thrombin inhibitors **argatroban** (hepatic) or **bivalirudin** (renal), or subcutaneous fondaparinux.
- ▶ **Reversal of bleeding:** protamine sulfate for heparin/LMWH; **idarucizumab** for dabigatran; **andexanet alfa** / **prothrombin complex concentrate** for anti-Xa DOACs (watch for rebound thrombosis).
- ▶ **DOAC cautions:** avoid in pregnancy/breast-feeding; **warfarin** (not DOACs) is standard for antiphospholipid syndrome; uncertain in ESRD/cirrhosis.

Massive (high-risk) PE

- ▶ **Volume:** cautious 500 mL normal saline (over-filling worsens RV ischaemia and septal shift).
- ▶ **Vasoactives:** **norepinephrine** (raises systemic pressure) + **dobutamine** (raises RV inotropy, lowers filling pressures); consider **veno-arterial ECMO**.
- ▶ **Systemic fibrinolysis:** FDA-approved 100 mg tPA (**alteplase**) IV over 2 h; effective up to 14 days post-PE; major bleeding ~10%, intracranial haemorrhage 2–3%. Contraindications: intracranial disease, recent surgery, trauma.
- ▶ **Catheter-directed therapy** (pharmacologic, mechanical or pharmacomechanical, e.g. ultrasound-facilitated low-dose thrombolysis — lower bleeding) and **surgical pulmonary embolectomy** for selected patients.

Adjuncts and special situations

- ▶ **IVC filter** (preferably retrievable) — only for (1) active bleeding precluding anticoagulation, or (2) recurrent VTE despite intensive anticoagulation.
- ▶ **Cancer-associated VTE:** LMWH monotherapy or a DOAC (apixaban/edoxaban; avoid DOAC in GI cancer), continued until cancer-free.
- ▶ **Duration:** ESC 2019 abandons the “*provoked/unprovoked*” dichotomy; extended anticoagulation for first PE with no identifiable, persistent, or minor transient risk factor.
- ▶ **CTEPH** develops in ~2% of acute PE — follow survivors with pulmonary hypertension by echocardiography; treat with **pulmonary thromboendarterectomy** (operative mortality 1–5% at expert centres).
- ▶ **Prevention:** low-dose UFH or LMWH is the commonest in-hospital prophylaxis (see Table 290-7 regimens by surgical/medical risk).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology of PE (flow diagram):** label — *Embolus in pulmonary artery* → ↑ RV pressure overload → ↑ RV wall tension → RV dysfunction + RV ischaemia/infarction → septal shift compressing LV → ↓ LV preload → ↓ cardiac output → ↓ systemic & coronary perfusion → circulatory collapse.
- ▶ **Integrated diagnostic algorithm:** label — *Suspect DVT/PE* → assess clinical likelihood (Wells) → low/not-high: D-dimer (normal = stop; high = image) vs high: image directly → CTPA / venous ultrasound / V/Q scan → treat.

Clinical / Diagnostic significance

- ▶ A normal/near-normal chest X-ray with profound hypoxaemia is itself a clue to PE.
- ▶ RV/LV ratio >1 on CT and troponin/BNP elevation identify the submassive group needing escalated monitoring (not just routine anticoagulation).
- ▶ McConnell's sign and S1Q3T3 are high-yield bedside/echo pointers to a large PE.
- ▶ The age-adjusted D-dimer is a practical tool that safely reduces CTPA use in older outpatients.
- ▶ Post-PE syndrome (persistent dyspnoea, fatigue, reduced exercise capacity, RV dysfunction) affects ~half of survivors — warrants follow-up.

High-yield exam pointers

- ▶ Most common symptom: PE = **unexplained dyspnoea**; DVT = **calf cramp**/"charley horse."
- ▶ PE severity classes: massive 5–10%, submassive 20–25%, low-risk 65–75%.
- ▶ D-dimer sensitivity >95%, a *rule-out* test only; age-adjusted cut-off = age × 10 ng/mL (>50 yrs).
- ▶ ECG: S1Q3T3 (specific, insensitive); commonest abnormality is T-inversion V1–V4.
- ▶ CXR triad: Westermarck's sign, Hampton's hump, Palla's sign.
- ▶ Echo indirect sign of PE: McConnell's sign.
- ▶ UFH: bolus 80 U/kg, infusion 18 U/kg/h, target aPTT 60–80 s; warfarin target INR 2–3.
- ▶ Massive PE: alteplase 100 mg IV over 2 h; ICH risk 2–3%; vasopressor norepinephrine + inotrope dobutamine.
- ▶ IVC filter indications: bleeding precluding anticoagulation OR recurrent VTE despite anticoagulation.
- ▶ CTEPH in ~2% → pulmonary thromboendarterectomy.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 290 "Deep-Venous Thrombosis and Pulmonary Thromboembolism" (Samuel Z. Goldhaber). Coverage note: the chapter fully supports clinical features, diagnosis and management as written. PESI/sPESI prognostic scoring

and the Wells DVT sub-criteria are referenced only via Table 290-2; the PE Wells table reproduced above is verbatim from the source. Standard universally-accepted points (e.g. haemoptysis/pleuritic pain with pulmonary infarction) are consistent with the text.



Discuss Pulmonary Rehabilitation Post Severe COVID Pneumonia

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — *Pulmonary rehabilitation (PR)* is a comprehensive, multidisciplinary, patient-centred intervention—built on a thorough assessment followed by patient-tailored therapies that include, but are not limited to, **exercise training, education and behaviour change**—designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote long-term adherence to health-enhancing behaviours (ATS/ERS definition). Survivors of **severe COVID-19 pneumonia** frequently leave hospital with prolonged dyspnoea, profound deconditioning, ICU-acquired weakness, impaired exercise capacity and psychological morbidity, so they constitute a logical—though relatively new—indication for PR. Although disease-specific COVID PR protocols are still evolving and largely expert-opinion based, the well-validated framework of PR (derived chiefly from COPD and post-exacerbation/post-ICU rehabilitation) is directly applicable.

Rationale — the systemic legacy of severe COVID pneumonia

- ▶ **Pulmonary:** severe COVID pneumonia causes ARDS with bilateral ground-glass opacities/consolidation; survivors of severe acute pulmonary injury may have **persisting respiratory impairment** (residual fibrosis, reduced diffusing capacity, exertional hypoxaemia and breathlessness).
- ▶ **Critical-illness sequelae:** prolonged mechanical ventilation, sedation and immobility produce ICU-acquired weakness, **skeletal-muscle deconditioning and debility related to hospitalisation and critical illness**, which explicitly warrant rehabilitation.
- ▶ **Recovery is slow:** ~80% of symptomatic infections resolve within 2 weeks, but **severe disease often needs several months** for recovery, and a subset develop persisting/recurring symptoms.
- ▶ **Long COVID** (a chronic condition present ≥ 3 months after infection): commonest features are **fatigue (32%), smell/taste disorder (22%), dyspnoea (16%), headache (12%), memory impairment (11%), hair loss (10%) and sleep disorder (10%)** — fatigue, cognitive deficits, cough, dyspnoea and chest pain dominate.
- ▶ **Extrapulmonary:** persisting cardiac injury, thromboembolic risk (PE/DVT), encephalopathy/ICU delirium, and high rates of anxiety, depression, post-traumatic symptoms and sleep disturbance — all of which PR is designed to address.

Definition, goals and evidence base of PR

- ▶ PR provides improvements in dyspnoea, exercise tolerance and health status **exceeding those of any other therapy for COPD, despite no direct effect on lung function** — explained by treating the *systemic* manifestations (limb-muscle dysfunction, deconditioning, fear of dyspnoea-producing activity, poor pacing/coping). The same systemic-illness logic applies after severe COVID pneumonia.
- ▶ **Goals:** increase exercise tolerance, reduce dyspnoea and fatigue, reduce anxiety/depression, increase self-efficacy and self-management, improve health-related quality of life (QOL), and reduce health-care utilisation.
- ▶ **Proven benefits of PR (RCT/Cochrane level):**

Improved	Reduced
Exercise capacity (endurance, strength, peak workload), balance	Dyspnoea
Functional/ADL & physical-activity performance	Fatigue
Self-efficacy, self-management, disease knowledge	Anxiety / depression
Quality of life	Urgent health-care use & hospitalisations
Survival (when delivered after hospitalisation for COPD exacerbation)	Health-care costs

- ▶ Cochrane data (COPD): exercise training increased **6-minute walk distance by 43.9 m** (95% CI 32.6–55.6), increased maximal exercise capacity by 6.8 W, and improved SGRQ by a mean of –6.9 units (exceeding the 4-unit MCID). Following a hospitalised COPD exacerbation, post-discharge PR reduces mortality (~42% relative reduction; Lindenauer *JAMA* 2020 — PR within 90 days of discharge, HR 0.63) — the evidence template for offering early PR to severe-COVID-pneumonia survivors.

Patient assessment, candidacy and pre-rehab screening

- ▶ **Referral triggers** relevant after severe COVID: severe dyspnoea/fatigue, decreased exercise tolerance/low physical-activity levels, difficulty with ADLs, impaired health status, and **recovery from an acute event requiring hospitalisation**.
- ▶ **Pre-enrolment evaluation:** medical history, examination, record review, and baseline assessment of exercise capacity, symptoms and health status; screen specifically for **persisting cardiac injury, arrhythmia, residual VTE/anticoagulation status, and exertional desaturation** (pulse oximetry) before prescribing exercise.
- ▶ **Absolute contraindications:** unstable angina or arrhythmia; unstable bone fracture; **communicable infectious disease** (i.e. the patient must be past the infectious period for COVID-19 before joining group/centre-based PR); unstable psychiatric condition posing harm.

- ▶ **Relative contraindications:** severe cognitive impairment, lack of motivation, severe progressive neurological disease, severe anaemia, and severe debilitating fatigue that would prevent participation.
- ▶ Patients with a **wide range of impairment benefit**, including those needing supplemental oxygen — so even oxygen-dependent COVID survivors are candidates.

Core components of the programme

Component	Content
Exercise training (<i>cornerstone</i>)	Lower- & upper-limb aerobic (cycling/walking), resistance (weights/bands/machines), interval training; balance training; adjuncts — neuromuscular electrical stimulation (NMES), whole-body vibration, yoga/Tai Chi
Education / self-management	Disease & medication/inhaler education, oxygen and (where relevant) NIV use, exacerbation recognition + written action plan , pacing & energy conservation
Psychosocial support	Coping/relaxation, anxiety & depression management, cognitive-behavioural techniques; refer significant psychiatric illness onward
Nutritional support	Assessment of body composition/BMI; supplementation (esp. if low fat-free mass) combined with resistance training to rebuild muscle
Breathing training & airway clearance	Pursed-lip breathing (inhale through nose, exhale over 4–6 s through pursed lips), body-forward positioning, inspiratory-muscle training (selected cases), chest physiotherapy/PEP devices for sputum
Physical-activity promotion	Coaching, pedometers/accelerometers, tele-coaching to translate gains into daily activity and sustain long-term behaviour change

- ▶ Exercise is the cornerstone because severe respiratory illness causes **skeletal-muscle dysfunction** (loss of muscle mass/strength, reduced type-I fibres, mitochondrial/capillary loss) that is *reversible with training* — the key therapeutic target after a deconditioning ICU stay.
- ▶ Education beyond exercise has not been shown to add to traditional outcomes, but improves engagement, completion and self-management — important in this anxious, symptom-burdened group.

Exercise prescription and delivery settings

- ▶ Prescription (typical, individualised to baseline field-test capacity):

Modality	Frequency	Intensity	Duration
Endurance (aerobic)	3–5×/week (ideal)	60–80% of maximal work rate	20–60 min/session
Interval training	3–4×/week	80–100% of maximal work rate	45–60 min total
Resistance training	2–3×/week	Fraction of 1-repetition maximum	progressed as tolerated

- ▶ **Interval training** (e.g. 20–30 s high-intensity alternating with 30–40 s low-intensity/rest) gives gains comparable to continuous training and **suits patients with severe dyspnoea or markedly limited capacity** — a practical option for the most deconditioned COVID survivors.
- ▶ **Supplemental oxygen** for resting/exertional hypoxaemia maintains safety and allows higher training intensity; optimise any bronchodilator therapy first.
- ▶ Most programmes run **8–12 weeks**. **Settings**: outpatient/community (most evidence; usually 2–3 sessions/week over 6–8 weeks), **inpatient** (for complex/nursing-dependent patients; 5–6 days/week for 2–6 weeks), and **home-based/tele-rehabilitation**.
- ▶ **COVID-specific delivery**: interest in **home-based PR and tele-rehabilitation** rose during the pandemic because most centre-based programmes were suspended (inability to maintain social distancing); home confinement itself worsened functional status. **Optimal rehabilitation strategy for COVID-19 survivors is not yet defined**, but expert-panel physiotherapy recommendations (e.g. Thomas *et al*, acute-hospital physiotherapy management of COVID-19) and home-exercise recommendations have been published, supporting a staged, individualised, symptom-titrated approach with monitoring for **post-exertional symptom worsening**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Flow diagram** — “From severe COVID pneumonia to recovery via PR”: boxes/labels — Severe COVID pneumonia (ARDS) → ICU / mechanical ventilation → ICU-acquired weakness + deconditioning + persisting dyspnoea/hypoxaemia + long-COVID fatigue/cognitive symptoms → Referral & baseline assessment (6MWT, mMRC, SpO₂, HADS, screen cardiac/VTE) → Multidisciplinary PR (Exercise training [aerobic/resistance/interval] + Education/self-management + Psychosocial + Nutrition + Breathing/airway clearance + Physical-activity promotion) → Outcomes: ↑exercise capacity & QOL, ↓dyspnoea/anxiety, ↑self-efficacy → Long-term maintenance (home/tele-rehab).
- ▶ **“Wheel of PR components”**: central hub labelled *Pulmonary Rehabilitation*, six spokes labelled — *Exercise training (cornerstone)*, *Education / self-management*, *Psychosocial support*, *Nutritional support*, *Breathing training & airway clearance*, *Physical-activity promotion*.

Clinical / Diagnostic significance

- ▶ **Outcome assessment** (mandatory minimum domains = exercise capacity, dyspnoea, health status): field tests — **6-minute walk test (6MWT)** and **incremental shuttle walk test**; **cardiopulmonary exercise testing** where available; exertional dyspnoea by **Borg/VAS**; symptom burden by **modified MRC (mMRC)** score; QOL by **Chronic Respiratory Questionnaire (CRQ)**, **St George's Respiratory Questionnaire (SGRQ)**, **COPD Assessment Test (CAT)**; mood by **Hospital Anxiety and Depression Scale (HADS)**; plus muscle strength (dynamometry), timed up-and-go and sit-to-stand tests, and body composition.
- ▶ **Safety/monitoring** during exercise: continuous pulse oximetry for desaturation, heart-rate/Borg-guided intensity, and vigilance for cardiac symptoms (given COVID myocardial injury) and post-exertional fatigue.
- ▶ **Investigations that guide rehab** in severe-COVID survivors: serial spirometry and **DLCO** (restrictive/diffusion defects), **HRCT** for residual fibrosis/ground-glass change, echocardiography/troponin if cardiac injury suspected, and D-dimer/imaging for residual VTE.
- ▶ **Maintenance**: short-term gains decline after the programme unless exercise continues; home-based and “booster” PR, tele-rehabilitation, activity diaries and pedometers help sustain benefit.

High-yield exam pointers

- ▶ **ATS/ERS definition** of PR (comprehensive intervention: assessment → tailored therapies including exercise training, education, behaviour change) — write it verbatim.
- ▶ **Exercise training is the cornerstone**; PR improves dyspnoea/exercise/QOL **despite no change in FEV₁** because it treats systemic/skeletal-muscle dysfunction.
- ▶ **Prescription numbers**: endurance 3–5×/week at **60–80% max work rate, 20–60 min**; resistance 2–3×/week; programme 8–12 weeks.
- ▶ **6MWD improves by ~44 m** with PR (Cochrane); post-hospitalisation PR **improves survival** (Lindenauer *JAMA* 2020, HR 0.63) — rationale for early post-COVID rehab.
- ▶ **Six core components**: exercise, education/self-management, psychosocial, nutrition, breathing/airway clearance, physical-activity promotion.
- ▶ **Long COVID** = symptoms ≥3 months; commonest = **fatigue 32%, smell/taste 22%, dyspnoea 16%**.
- ▶ **Absolute contraindications**: unstable angina/arrhythmia, unstable fracture, **communicable infectious disease** (wait out the COVID infectious period), unstable psychiatric illness.
- ▶ Settings: outpatient (most evidence), inpatient (complex), **home/tele-rehabilitation (expanded during COVID)**; optimal COVID-specific protocol still expert-opinion based.
- ▶ Outcome tools: 6MWT, mMRC/Borg, CRQ/SGRQ/CAT, HADS.

SOURCE & COVERAGE

- ▶ **Murray & Nadel's Textbook of Respiratory Medicine** — “Pulmonary Rehabilitation” (definition/ATS-ERS, components, exercise prescription, settings, outcomes, COVID-19 home-based/tele-rehabilitation and post-critical-illness rehabilitation; post-exacerbation PR survival).
- ▶ **Harrison's Principles of Internal Medicine, 22e** — “SARS-CoV-2 and COVID-19” (severe disease/ARDS, mechanical ventilation, recovery timeline, persisting respiratory/cardiac impairment, long COVID, neuropsychiatric sequelae).
- ▶ **CMDT 2026** — “Viral & Rickettsial Infections” (COVID-19: long COVID prevalence and symptom frequencies, convalescent management).

Coverage note: As flagged in the spec, the corpus does not contain a dedicated *post-severe-COVID* PR protocol; COVID-specific guidance in the sources is limited and expressly described as **expert-opinion based with “optimal strategies unknown.”** This answer therefore applies the validated PR framework (Murray, COPD/post-exacerbation/post-ICU and non-COPD evidence) to the severe-COVID survivor, using COVID-specific epidemiology and sequelae from Harrison/CMDT. Exercise-prescription numbers, the proven-benefit data and contraindications are COPD-derived (the established evidence base) and are extrapolated to the COVID context; the caution regarding post-exertional symptom worsening reflects standard current practice rather than a corpus-quoted COVID protocol.



Pulmonary Embolism: Risk Factors and Management

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — Pulmonary embolism (PE) is occlusion of the pulmonary arterial tree by material — most often a thrombus that has detached from a deep vein and embolised through the right heart. Together with deep-venous thrombosis (DVT) it constitutes **venous thromboembolism (VTE)**, the third commonest cardiovascular cause of death. PE is a “*great masquerader*” with non-specific presentation, so management hinges on a structured diagnostic and risk-stratification pathway followed by anticoagulation, with reperfusion reserved for high-risk disease.

Risk factors (enumerate)

The substrate is **Virchow's triad** — venous stasis, hypercoagulability and endothelial injury/inflammation — with inflammation now recognised as a central trigger.

Category	Examples
Inherited (genetic) thrombophilia	Factor V Leiden (activated protein C resistance — commonest); prothrombin gene mutation;

Category	Examples
	deficiencies of antithrombin, protein C, protein S (rare)
Acquired thrombophilia	Antiphospholipid syndrome (APS — venous <i>and</i> arterial thrombosis; often warrants lifelong anticoagulation)
Stasis / immobility	Bed-rest, post-operative state, stroke, long-haul air travel (“ <i>economy-class syndrome</i> ”), sedentary lifestyle (prolonged television watching)
Surgery / trauma	Major orthopaedic surgery (hip/knee replacement, hip fracture), pelvic/long-bone fracture, major general surgery
Malignancy	Active cancer (lung, brain, pancreas, leukaemia); erythropoiesis-stimulating agents; chemotherapy
Hormonal	Oestrogen-containing contraceptives, postmenopausal HRT, pregnancy and the first 6–12 weeks postpartum, high-dose fertility injections
Inflammation-linked illness (Table 290-1)	Inflammatory bowel disease (ulcerative colitis, Crohn’s), rheumatoid arthritis, psoriasis, type-2 diabetes/metabolic syndrome, pneumonia, sepsis, acute coronary syndrome, acute stroke
Other comorbid	Obesity, cigarette smoking, systemic hypertension, COPD, chronic kidney disease, elevated LDL/lipoprotein(a), air pollution, blood transfusion, indwelling central venous catheters/PICC (upper-limb DVT)

- ▶ Carotid plaque **doubles** incident VTE risk; VTE, MI and stroke share inflammation, hypercoagulability and endothelial injury, and each more than doubles the risk of the others.
- ▶ **Non-thrombotic** PE (relevant to the differential and to “embolism” broadly): fat (long-bone fracture), air (neurosurgery, central lines), amniotic fluid (labour), tumour, septic emboli (right-sided endocarditis), talc (IV drug use), bone-cement (arthroplasty).

Classification and risk stratification (drives management)

Class	Frequency	Definition	Prognosis
Massive (high-risk)	5–10%	Systemic hypotension (SBP <90 mmHg ≥15 min or drop ≥40 mmHg); thrombus ≥50% of pulmonary vasculature; syncope,	High mortality

Class	Frequency	Definition	Prognosis
		cyanosis, cardiogenic shock	
Submassive (intermediate-risk)	20–25%	Normotensive but RV dysfunction (echo/CT) $\pm$ troponin/BNP rise	Risk of abrupt deterioration
Low-risk	65–75%	Normotensive, normal RV, normal biomarkers	Excellent

- **Clinical probability** — *Wells score* (PE): signs/symptoms of DVT 3, alternative diagnosis less likely 3, HR >100 = 1.5, immobilisation/surgery within 4 weeks 1.5, prior PE/DVT 1.5, haemoptysis 1, cancer 1 (PE-likely if >4). *PERC* rule can exclude PE in very-low-risk patients meeting all 8 criteria.
- **Mortality prognostication** — *Simplified PESI* (*sPESI*): age >80, cancer, chronic cardiopulmonary disease, pulse ≥ 110 , SBP <100, SaO₂ <90% (each = 1). Score 0 = low 30-day mortality (consider outpatient/early discharge); ≥ 1 = higher risk. *Hestia criteria* also screen for home-treatment eligibility.

Diagnostic approach (essential before treatment)

- **D-dimer ELISA**: sensitivity >95%; a normal value rules out PE in low/intermediate pretest probability. Use **age-adjusted cut-off** (age $\times$ 10 ng/mL) in patients >50 years; unhelpful in inpatients (frequently raised).
- **CT pulmonary angiography (CTPA)** — principal/gold-standard imaging; an RV:LV diameter ratio >1 predicts increased 30-day mortality. **V/Q scan** when contrast is contraindicated. **Compression venous ultrasound** for DVT.
- **ECG**: sinus tachycardia (commonest), *S1Q3T3*, T-inversion V1–V4 (RV strain). **CXR**: often normal; *Westermarck's sign* (oligaemia), *Hampton's hump* (infarct), *Palla's sign* (enlarged descending pulmonary artery). **Echo**: *McConnell's sign* (RV free-wall hypokinesis with apical sparing). **Troponin/BNP** raised in ~25% — risk markers.

Management — anticoagulation (cornerstone)

Anticoagulation prevents clot propagation and recurrence while endogenous fibrinolysis dissolves existing thrombus; start empirically when clinical suspicion is high and bleeding risk low, before confirmation. **DOACs are first-line** for most patients.

Drug	Regimen (normal renal function)
Unfractionated heparin (UFH)	80 U/kg bolus then 18 U/kg/h; target aPTT 60–80 s (anti-Xa 0.3–0.7 U/mL). Preferred if unstable, renal failure, or reperfusion may be needed

Drug	Regimen (normal renal function)
Enoxaparin (LMWH)	1 mg/kg SC twice daily (no monitoring unless obese/CKD)
Dalteparin / Tinzaparin	200 U/kg od (or 100 U/kg bid) / 175 U/kg od
Fondaparinux	Weight-based SC od (5/7.5/10 mg for <50/50–100/>100 kg); does not cause HIT
Rivaroxaban	15 mg bid × 3 weeks → 20 mg od (oral monotherapy)
Apixaban	10 mg bid × 1 week → 5 mg bid (oral monotherapy)
Edoxaban	After ≥5 days parenteral → 60 mg od (30 mg if CrCl 15–50 or <60 kg)
Dabigatran	After ≥5 days parenteral → 150 mg bid (direct thrombin inhibitor)
Warfarin	Overlap with parenteral ≥5 days until INR ≥2 on two readings; target INR 2.0–3.0

- ▶ Heparin-induced thrombocytopenia (HIT) suspected/proven: use **argatroban** (hepatic) or **bivalirudin** (renal) — IV direct thrombin inhibitors — or **fondaparinux**.
- ▶ Reversal: protamine for heparin/LMWH; **idarucizumab** for dabigatran; **andexanet alfa** (or PCC) for anti-Xa DOACs; vitamin K/FFP/PCC for warfarin.
- ▶ DOACs are contraindicated in **pregnancy/lactation**; **warfarin** (not DOAC) remains standard for APS.

Management of high-risk (massive) and intermediate-risk PE

- ▶ Supportive care (massive PE): cautious volume — only ~500 mL normal saline (excess fluid worsens RV wall stress and septal shift); **noradrenaline** (vasopressor of choice) plus **dobutamine** (inotrope); **veno-arterial ECMO** or percutaneous RV assist for refractory shock.
- ▶ Systemic thrombolysis — indicated for massive PE without contraindication: **alteplase 100 mg IV over 2 h** (bolus 0.6 mg/kg, max 50 mg over 15 min if cardiac arrest imminent). Major bleeding ~10%, intracranial haemorrhage 2–3%. *Absolute contraindications*: prior intracranial haemorrhage, structural cerebrovascular lesion/neoplasm, ischaemic stroke <3 months, active bleeding, recent significant head trauma/surgery.
- ▶ Intermediate-risk (submassive) PE: routine thrombolysis is **controversial** — in *PEITHO*, tenecteplase reduced haemodynamic collapse (2.6% vs 5.6%) but increased intracranial bleeding (2.0% vs 0.2%) with no survival benefit; preferred strategy is anticoagulation with **close monitoring**, reserving rescue thrombolysis for deterioration.

- ▶ **Catheter-directed therapy** (pharmacologic, mechanical, or pharmacomechanical/ultrasound-facilitated low-dose thrombolysis) — lower bleeding than systemic lysis; for high-risk patients or intermediate-risk at risk of collapse.
- ▶ **Surgical pulmonary embolectomy** — when thrombolysis is contraindicated/failed, or for clot-in-transit/mobile intracardiac thrombus.
- ▶ **IVC filter** — only two firm indications: (1) active bleeding precluding anticoagulation, (2) recurrent VTE despite therapeutic anticoagulation. Use **retrievable** filters and remove when anticoagulation resumes.

Special situations and duration of anticoagulation

- ▶ **Minimum 3 months** for all PE. Continued (extended/indefinite) anticoagulation is decided by recurrence risk vs bleeding risk (ESC 2019 abandons the “provoked/unprovoked” dichotomy):

Recurrence risk after stopping	Examples
Low (<3%/yr)	Major surgery/trauma (transient) → stop at 3 months
Intermediate (3–8%/yr)	Minor surgery, hospitalisation, pregnancy/oestrogen, long-haul flight, IBD, no identifiable factor
High (>8%/yr)	Active cancer, antiphospholipid syndrome → indefinite anticoagulation

- ▶ **Cancer-associated VTE**: LMWH or a DOAC (apixaban/edoxaban; avoid DOAC if GI/luminal cancer) until cancer-free.
- ▶ **Pregnancy**: weight-adjusted LMWH is preferred (UFH peri-delivery); warfarin, DOACs and fondaparinux are contraindicated. Thrombolysis only for life-threatening PE.
- ▶ **Isolated subsegmental PE with no DVT and low recurrence risk**: surveillance without anticoagulation is acceptable.

Prevention (prophylaxis)

- ▶ **Universal in-hospital VTE prophylaxis** unless contraindicated: UFH 5000 U SC bid/tid or enoxaparin 40 mg od (or dalteparin/fondaparinux 2.5 mg od) for medical and high-risk surgical patients.
- ▶ **Major orthopaedic surgery**: aspirin 81 mg, rivaroxaban 10 mg od, apixaban 2.5 mg bid, dabigatran, LMWH or warfarin; extended prophylaxis after hip/knee replacement.
- ▶ **Mechanical** (intermittent pneumatic compression ± graduated stockings) when anticoagulation is contraindicated; early ambulation always.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Acute PE management algorithm** — boxes/labels: *Suspected PE* → *assess for hypotension/shock/arrest*; if YES → *supportive care* (O_2 , fluids 500 mL, noradrenaline + dobutamine) + *systemic thrombolysis / embolectomy*; if NO → *confirm with CTPA* → *risk-stratify* (sPESI, RV function, troponin): **Low** → **anticoagulate (DOAC) ± early discharge**; **Intermediate** → **anticoagulate + monitor**; **High/massive** → **reperfusion**.
- ▶ **Pathophysiology of PE** — labels: *Pulmonary artery obstruction* → $\uparrow$ PVR / $\uparrow$ RV afterload → *RV wall tension* $\uparrow$ → *RV dilatation & dysfunction* → *interventricular septal shift* → $\downarrow$ LV filling → $\downarrow$ cardiac output → $\downarrow$ coronary perfusion → *RV ischaemia/microinfarction* (troponin $\uparrow$) → *circulatory collapse*.

Clinical / Diagnostic significance

- ▶ Empirical anticoagulation before confirmation in high pretest probability prevents early recurrent (often fatal) PE.
- ▶ Haemodynamics — **not** clot bulk on imaging — predict mortality; many “saddle emboli” are stable and recover on anticoagulation alone.
- ▶ **Post-PE syndrome** (persistent dyspnoea, fatigue, RV dysfunction in ~50%) and **CTEPH** (~2% of PE) warrant follow-up echocardiography at ~6 weeks/6 months; CTEPH is treated by **pulmonary thromboendarterectomy** (mortality 1–5% at expert centres) ± balloon pulmonary angioplasty.

High-yield exam pointers

- ▶ **Virchow’s triad** = stasis + hypercoagulability + endothelial injury/inflammation.
- ▶ Commonest inherited thrombophilia = **factor V Leiden**; APS = lifelong warfarin (not DOAC).
- ▶ **Wells** = pretest probability; **sPESI** = 30-day mortality; **PESI 0 / sPESI 0** = candidate for outpatient therapy.
- ▶ **CTPA** = investigation of choice; **age-adjusted D-dimer** ($\text{age} \times 10$) in >50 years.
- ▶ ECG **S1Q3T3** & T-inversion V1–V4; **McConnell’s sign** on echo; **Westermarck / Hampton’s hump** / **Palla** on CXR.
- ▶ **DOACs first-line**; UFH preferred if unstable/renal failure/reperfusion likely.
- ▶ **Massive PE** → alteplase 100 mg over 2 h; noradrenaline + dobutamine; ECMO; **submassive** → anticoagulate + monitor (PEITHO).
- ▶ **Minimum 3 months** anticoagulation; **active cancer & APS** → indefinite.
- ▶ **IVC filter** only when anticoagulation contraindicated or recurrence despite it.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Deep-Venous Thrombosis and Pulmonary Thromboembolism*” (risk factors/Table 290-1, classification, diagnosis, anticoagulation Table 290-4, thrombolysis, IVC filter, ESC duration tables, prophylaxis Table 290-7).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “*Pulmonary Thromboembolism: Presentation and Diagnosis*” and “*Pulmonary Thromboembolism: Prophylaxis and Treatment*” (sPESI, PEITHO, anticoagulant treatment table, catheter-directed/surgical reperfusion, pregnancy, prophylaxis).
- ▶ **CMDT 2026** — “*Pulmonary Disorders: Pulmonary Venous Thromboembolism*” (Wells/PERC, risk stratification, current treatment and thrombolysis).



Hospital-Acquired Pneumonia

Asked in: Paper III Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Hospital-acquired pneumonia (HAP) is an infection of the pulmonary parenchyma that becomes clinically and radiographically apparent **more than 48 hours after admission** in a patient who was **not intubated** at the time pneumonia developed, and which was neither present nor incubating on admission. The 2016 IDSA/ATS guidelines re-defined HAP and **ventilator-associated pneumonia (VAP)** as *mutually exclusive* entities — VAP is pneumonia arising >48 h after endotracheal intubation, so HAP by current usage refers to the **non-ventilated** patient. The older umbrella term *health care-associated pneumonia (HCAP)* has been **discontinued** because it neither reliably predicted resistant pathogens nor improved outcomes, while encouraging overuse of broad-spectrum antibiotics. HAP is among the most common and most lethal nosocomial infections.

Epidemiology and burden

- ▶ HAP is the **third most prevalent hospital-acquired infection** after surgical-site and gastrointestinal infections; roughly **96,000–110,000 cases per year** in the United States, affecting about **0.5–2% of all hospitalised patients** (~0.6% point prevalence among non-ventilated inpatients).
- ▶ It is **two- to threefold more frequent than VAP**; ~70% of all nosocomial pneumonia is acquired *outside* the ICU.
- ▶ Risk is highly condition-dependent: ~13% of non-ICU stroke patients and ~1% of surgical patients (up to 5.8% after lobar pulmonary resection, ~3% after major abdominal surgery) develop HAP/postoperative pneumonia. *Cardiothoracic and upper-abdominal surgery* carry the greatest risk.

- ▶ HAP carries substantial attributable burden: **excess mortality** ~2–14%, **excess length of stay** ~2.5–15.9 days, and **excess cost** ~\$30,000–40,000 per case.

Pathogenesis and risk factors

Three sequential mechanisms are required (each maps to a prevention target):

- ▶ **Oropharyngeal colonisation** with pathogenic organisms — hospitalised patients rapidly replace normal flora with **gram-negative bacilli**; driven chiefly by **antibiotic selection pressure**, cross-infection, severe illness and malnutrition.
- ▶ **Aspiration (microaspiration)** of these contaminated secretions into the lower respiratory tract — favoured by impaired consciousness (anaesthesia, opioids, sedatives), dysphagia, stroke, and impaired cough from pain/sedation.
- ▶ **Compromise of host defences** — failure of laryngeal protection, mucociliary clearance, secretory IgA/lysozyme/lactoferrin, alveolar macrophages and surfactant proteins; aggravated by immune senescence and malnutrition.
- ▶ Less common routes: **large-volume gastric aspiration**, **haematogenous spread**, and **inhalation of contaminated aerosols** (the usual route for nosocomial *Legionella*).
- ▶ Key modifiable risks: **gastric acid suppression** (PPIs/H₂-blockers promote gastric bacterial overgrowth), nasogastric/endotracheal tubes, supine positioning, prolonged or broad-spectrum antibiotics, COPD, advanced age, diabetes and cerebrovascular disease.

Microbiology

HAP pathogens resemble those of VAP far more than CAP (atypicals are rare), with a higher proportion of **multidrug-resistant (MDR)** organisms than CAP but slightly lower than VAP. Pathogens are unidentified in **50–90%** of cases because adequate lower-respiratory samples are hard to obtain in non-intubated patients.

Group	Approx. share	Representative organisms
Gram-negative bacilli (total)	~35%	—
• Non-fermenters	~20%	<i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> spp., <i>Stenotrophomonas maltophilia</i>
• Enteric GNB	~15%	<i>E. coli</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>Enterobacter</i> (incl. ESBL/carbapenemase producers)
<i>Staphylococcus aureus</i>	~15%	MSSA ~10%, MRSA ~6%
Other bacteria	—	<i>Streptococcus</i> spp., <i>H. influenzae</i> , rarely <i>S. pneumoniae</i> ; <i>Legionella</i> (water-supply clusters)

Group	Approx. share	Representative organisms
Respiratory viruses	>20%	Rhinovirus, influenza, parainfluenza (often co-infection)
Fungi	Uncommon	<i>Aspergillus</i> (severely immunocompromised)

- ▶ **Anaerobes** (*Prevotella*, *Peptostreptococcus*, *Fusobacterium*, *Bacteroides*) are more common in non-ventilated HAP than VAP due to macroaspiration, but usually as part of polymicrobial infection; specific anti-anaerobe therapy is seldom needed.
- ▶ *Candida* recovered from respiratory secretions of non-ventilated patients represents colonisation, **not** a true pathogen.

Diagnosis

- ▶ **Clinical/radiographic criteria (2016 IDSA/ATS):** a **new or progressive radiographic opacity** *plus* clinical evidence of infection — typically ≥ 2 of: fever/hypothermia, leukocytosis/leukopenia, **purulent secretions**, and **decline in oxygenation**; with cough, dyspnoea or new delirium.
- ▶ HAP is frequently **over-diagnosed** — fever, infiltrate and abnormal sounds may instead reflect heart failure, atelectasis, ARDS, pulmonary embolism, pulmonary haemorrhage, or drug reaction. A **good frontal + lateral film** (or CT, the most sensitive) outperforms a portable radiograph; ~35% labelled HAP lack confirmatory radiographic findings.
- ▶ **Microbiological work-up:** obtain **blood cultures from two sites** (positive in 15–20%) and a respiratory sample to allow targeted therapy and de-escalation. The **non-invasive** route (expectorated/induced sputum, nasotracheal or endotracheal aspirate) is preferred over invasive bronchoscopy, which adds risk in a non-intubated, hypoxic patient.
- ▶ **Quantitative culture thresholds** (mainly extrapolated from VAP): endotracheal aspirate 10^6 CFU/mL, BAL $<10^4$ CFU/mL and protected-specimen brush / blind bronchial sampling $<10^3$ CFU/mL indicate colonisation $\rightarrow$ antibiotics may be withheld below threshold.
- ▶ **Adjuncts:** rapid nasal MRSA PCR (high negative predictive value) helps *de-escalate* anti-MRSA cover; procalcitonin/CRP are *not* recommended to establish the diagnosis but can guide *duration*; the CPIS is not recommended.

Treatment

Therapy is **empirical first**, started promptly (delay increases mortality), then **de-escalated/targeted** once cultures return. Empirical choice rests on **three factors** (time of onset alone does *not* predict MDR risk): (1) **IV antibiotic use within 90 days**, (2) **the local unit antibiogram**, and (3) **disease severity** (need for ventilation or septic shock = “high mortality risk”).

Clinical category	Empirical regimen
Not high mortality risk, no MRSA risk	One anti-pseudomonal agent — piperacillin–tazobactam 4.5 g IV q6h <i>or</i> cefepime 2 g IV q8h <i>or</i> levofloxacin 750 mg IV daily <i>or</i> imipenem 500 mg q6h / meropenem 1 g q8h
Not high risk, with MRSA risk	Above anti-pseudomonal + anti-MRSA: vancomycin 15 mg/kg q8–12h (trough 15–20) <i>or</i> linezolid 600 mg q12h
High mortality risk / IV antibiotics in prior 90 days	Two anti-pseudomonal agents from <i>different classes</i> (β -lactam + aminoglycoside [amikacin 15–20 mg/kg, <i>or</i> gentamicin/tobramycin 5–7 mg/kg] <i>or</i> fluoroquinolone; add polymyxin B/ colistin for carbapenem-resistant GNB) + anti-MRSA agent

- ▶ **MRSA cover** is indicated for prior MRSA, IV antibiotics in 90 days, or treatment in a unit where >20% of *S. aureus* are MRSA (or rate unknown). **Double gram-negative cover** is favoured where >10% of GNB resist the candidate monotherapy, or with structural lung disease (bronchiectasis, cystic fibrosis).
- ▶ **Drug pearls:** Daptomycin must NOT be used for pneumonia (inactivated by surfactant); linezolid is preferred over vancomycin for high-MIC MRSA/renal impairment; oxacillin/nafcillin/cefazolin are definitive for MSSA. Newer agents (ceftazidime–avibactam, ceftolozane–tazobactam, imipenem–relebactam, meropenem–vaborbactam, cefiderocol) extend cover against resistant *Pseudomonas*, carbapenem-resistant Enterobacterales and *Acinetobacter*.
- ▶ **PK/PD optimisation** (extended/continuous infusion of β -lactams, weight-based dosing, therapeutic drug monitoring) improves survival. **Inhaled antibiotics** are reserved as adjuncts for MDR gram-negatives susceptible only to aminoglycosides or polymyxins.
- ▶ **Duration:** a 7-day course is standard and as effective as longer regimens (even for non-fermenting GNB), lengthened only for complications (empyema, necrotising pneumonia) or inadequate initial therapy; procalcitonin trends can guide stopping.

Prevention

- ▶ **General:** rigorous **hand hygiene** (alcohol-based rubs), antibiotic stewardship, oral care/dysphagia screening (especially stroke patients), avoiding unnecessary PPIs/H₂-blockers, minimising sedating opioids/benzodiazepines, optimal pain control, and **early mobilisation**.
- ▶ **VAP-specific (also applicable to ventilated HAP), bundled for $\geq 95\%$ compliance:** avoid intubation / use NIV; minimise ventilation duration via **daily sedation interruption and weaning protocols**; **head-of-bed elevation 30–45°**; **subglottic secretion drainage** with specialised tubes; maintain **cuff pressure >20 cm H₂O**; avoid reintubation; drain ventilator-circuit condensate.

- ▶ **Selective oral / digestive decontamination (SOD/SDD)** reduces VAP and (SDD) mortality in low-resistance ICUs but risks selecting resistant flora; routine **chlorhexidine oral care** is now questioned (no mortality benefit, possible harm).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis schematic of HAP:** a vertical arrow chain — *Hospital admission* → *Oropharyngeal colonisation with gram-negative bacilli / S. aureus* → *Microaspiration past glottis (supine, sedation, dysphagia, NG/ET tube)* → *Impaired host defence (cough, mucociliary clearance, IgA, macrophages, surfactant)* → *Bacterial proliferation in alveoli* → *Pneumonia*. Side-branches labelled: *gastric overgrowth (raised pH/PPI), contaminated aerosols* → *Legionella, haematogenous spread*. Annotate matching prevention at each step (oral care, head-up 30–45°, sedation holds, hand hygiene).
- ▶ **Empirical antibiotic decision tree:** root *Suspected HAP* → branch on **MRSA risk and mortality/MDR risk** into the three boxes — labels: “One anti-pseudomonal”, “Anti-pseudomonal + Vancomycin/Linezolid”, “Two anti-pseudomonal + anti-MRSA”; footnote labels *MRSA threshold >20%, GNB resistance >10%, de-escalate at 48–72 h on cultures, duration 7 days*.

Clinical / Diagnostic significance

- ▶ Distinguishing HAP from its mimics (heart failure, atelectasis, ARDS, PE) prevents unnecessary broad-spectrum antibiotics and resistance amplification.
- ▶ **Inappropriate initial empirical therapy** is a major driver of excess mortality — hence early, antibiogram-guided broad cover, followed by **disciplined de-escalation** once susceptibilities (and a negative nasal MRSA PCR) are available.
- ▶ Non-ventilated HAP has **better host immunity, fewer MDR pathogens and lower mortality** than VAP, permitting **monotherapy in a larger proportion** of cases.
- ▶ Knowledge of the **unit-specific antibiogram** is the single most useful tool for rational empirical prescribing.

High-yield exam pointers

- ▶ HAP = pneumonia >48 h after admission in a non-ventilated patient; VAP = >48 h after intubation; the two are **mutually exclusive** (2016 IDSA/ATS); HCAP is obsolete.
- ▶ **Third commonest nosocomial infection**; 2–3× more frequent than VAP; pathogens unidentified in 50–90%.
- ▶ Triad of pathogenesis: **colonisation** → **aspiration** → **impaired host defence**; commonest mechanism is **microaspiration of contaminated oropharyngeal secretions**.
- ▶ Core pathogens: **P. aeruginosa, S. aureus (MSSA/MRSA), enteric & non-fermenting GNB**; viruses >20%; atypicals rare.

- ▶ Diagnose by **new infiltrate** + **≥2 clinical criteria**; obtain **blood cultures** (positive 15–20%) and a respiratory sample; **non-invasive sampling preferred**.
- ▶ Empirical therapy keyed to (1) **prior IV antibiotics ≤90 d**, (2) **local antibiogram**, (3) **severity**; **MRSA cover** if unit MRSA >20%, double GNB cover if resistance >10%.
- ▶ **Vancomycin trough 15–20 / linezolid 600 mg q12h** for MRSA; **never daptomycin** (surfactant-inactivated); **treat for 7 days**.
- ▶ Prevention: **head-up 30–45°**, **sedation holds**, **weaning protocols**, **subglottic drainage**, **hand hygiene**, **oral care**, **avoid unnecessary PPIs** — delivered as **care bundles**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Pneumonia*” (HAP/VAP sections, including IDSA/ATS empirical-therapy tables and quantitative-culture thresholds) and “*Infections Acquired in Health Care Facilities*”.
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “*Hospital-Acquired Pneumonia*” (epidemiology, microbiology, diagnosis, empirical-therapy table, prevention) and “*Ventilator-Associated Pneumonia*” (prevention bundles, SDD/SOD).
- ▶ **CMDT 2026** — “*Pulmonary Disorders: Nosocomial Pneumonia (Hospital-Acquired & Ventilator-Associated)*” (MDR/MRSA/Pseudomonas risk-factor tables and current empirical regimens).



Hypersensitivity pneumonitis

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Hypersensitivity pneumonitis (HP), also called **extrinsic allergic alveolitis**, is an immunologically-mediated inflammatory and/or fibrotic interstitial lung disease (ILD) caused, in susceptible individuals, by repeated **inhalation of organic antigens or low-molecular-weight chemical sensitizers** that are small enough to deposit in distal airways and alveoli. Sensitization, manifest as specific circulating **IgG** (precipitins), is *necessary but not sufficient* — many heavily exposed people are sensitized yet never develop disease. It is one of the commonest diagnoses at ILD referral centres, and — paradoxically — smokers are at *reduced* risk of developing HP (though smoking worsens prognosis once disease exists).

Etiology — Offending Antigens

More than 200 inciting exposures are described, grouped into **microbes**, **animal proteins** and **chemical sensitizers**; named after the setting of exposure (e.g. “farmer’s lung”). Despite exhaustive search, **no antigen is identified in up to 50% of chronic HP** at tertiary centres.

Category	Disease (eponym)	Antigen / source
Microbial	Farmer's lung	Thermophilic actinomycetes (<i>Saccharopolyspora rectivirgula</i> , <i>Thermoactinomyces vulgaris</i>); moldy hay, silage, grain
	Bagassosis	Thermophilic actinomycetes; moldy sugarcane (bagasse)
	Humidifier / air-conditioner lung	Actinomycetes, <i>Aureobasidium</i> , <i>Candida</i> , <i>Klebsiella</i> ; contaminated water reservoirs
	Hot-tub lung	<i>Mycobacterium avium</i> complex; contaminated hot-tub water/mold
	Summer-type HP (Japan)	<i>Trichosporon cutaneum</i> ; residential mold
	Suberosis	<i>Penicillium glabrum</i> ; moldy cork dust
	Malt/mushroom/cheese-washer's lung	<i>Aspergillus</i> , <i>Penicillium</i> ; barley, compost, cheese
Animal protein	Bird fancier's / pigeon breeder's lung	Avian "bloom", droppings, feathers, serum proteins; also duvet/feather-bedding lung
	Poultry / laboratory worker's lung	Chicken serum proteins; rat urine, serum, fur
Chemical	Chemical worker's lung	Isocyanates (toluene/diphenylmethane diisocyanate); polyurethane foam, paints, varnish
	Detergent worker's lung	<i>Bacillus subtilis</i> enzymes

Pathogenesis

- ▶ HP is an **immune-mediated** response to inhaled antigen, dominated by dysregulated **TH1 and TH17** responses; granuloma formation is driven by Th1/macrophage cytokines (IFN- γ , TNF- α , IL-18).
- ▶ A combination of **type III (immune-complex; precipitating IgG)** and, predominantly, **type IV (cell-mediated, delayed-type) hypersensitivity** operates. In acute disease BAL shows a **neutrophil influx peaking ~48 h** after exposure, followed by a **CD4⁺-then-CD8⁺ lymphocytic alveolitis**.

- ▶ **Innate immunity** also contributes — Toll-like receptors and **MyD88** signalling drive neutrophil recruitment.
- ▶ **Host susceptibility / genetics**: only a minority of exposed persons fall ill. Associations include polymorphisms in **TAP1** and **MHC class II** (antigen processing/presentation). Chronic (fibrotic) HP shares genetic overlap with IPF — the **MUC5B promoter variant (rs35705950)** and **short telomeres / telomere-related gene mutations** predict fibrosis and reduced survival.
- ▶ **Fibrotic HP** reflects a shift toward a profibrotic Th2 phenotype with loss of effector-T-cell function; bone-marrow-derived fibrocytes contribute.

Classification

- ▶ **Traditional (now discouraged)**: acute / subacute / chronic — a *time-based* scheme that lacks prognostic precision (subacute overlaps both).
- ▶ **Current (ATS/JRS/ALAT 2020)**: stratified by fibrosis on HRCT/histology into **nonfibrotic (inflammatory)** vs **fibrotic HP** — because radiographic fibrosis (reticulation, traction bronchiectasis, honeycombing) consistently predicts poor outcome. Each is further coded by whether the antigen is identifiable, indeterminate or unidentifiable.

Clinical Features

Feature	Nonfibrotic (acute) HP	Fibrotic (chronic) HP
Onset vs exposure	Symptoms 4–8 h after exposure; resolve in 24–48 h, recur on re-exposure	Insidious; temporal link to exposure often lost
Symptoms	Flu-like — fever, chills, malaise, myalgia + cough, dyspnoea	Progressive exertional dyspnoea, dry cough, weight loss, fatigue, clubbing
Examination	May be normal; bibasilar crackles, inspiratory “squeaks/squawks” (bronchiolitis), tachypnoea	Velcro inspiratory crackles , squawks, hypoxaemia, signs of right-heart strain
Reversibility	Usually fully reversible with antigen removal	Often irreversible , may progress despite avoidance (mirrors IPF)

Diagnosis & Investigations

No single test confirms HP; diagnosis integrates clinical, radiologic and histopathologic data in a **multidisciplinary discussion (MDD)** — now the gold standard (histology alone is not). A **compatible exposure history** is the single strongest predictor.

- ▶ **HRCT (essential)** — *nonfibrotic*: diffuse **ground-glass opacities**, poorly-defined **centrilobular nodules**, mid-upper zone, with **mosaic attenuation and expiratory air-trapping** (small-airway disease). Coexisting infiltrative + obstructive lobules produce the **“headcheese” sign** (highly

specific). *Fibrotic*: reticulation, traction bronchiectasis, honeycombing — but with **relative basal sparing** (unlike IPF).

- ▶ **PFT** — restrictive, obstructive or mixed pattern (so pattern is not diagnostic); **reduced DL_{CO}**, especially in fibrotic disease; isolated exertional desaturation may be the earliest sign. Used to monitor progression.
- ▶ **Serum precipitins / specific IgG** — supportive but neither sensitive nor specific (high false-positives in exposed-but-healthy people; e.g. 87% of control bird fanciers positive — so *not* a screening test; false-negatives if the panel omits the relevant antigen).
- ▶ **Bronchoalveolar lavage (BAL)** — a marked **lymphocytosis** (>30%, classically >50%) is characteristic of HP; less prominent in fibrotic disease and in smokers. The **CD4:CD8 ratio** is **variable** — classically described as low/<1 (CD8 predominance) in contrast to sarcoidosis, but it is inconsistent and of limited diagnostic value.
- ▶ **Lung biopsy** (transbronchial, **cryobiopsy**, or surgical/VATS) — reserved for diagnostic uncertainty. Classic histology is the “**triad of four**”: ① bronchiolocentric **lymphoplasmacytic interstitial infiltrate**, ② **poorly-formed, loose non-caseating granulomas** (cf. the well-formed granulomas of sarcoidosis), ③ foci of **organizing pneumonia**; multinucleate giant cells ± cholesterol clefts.
- ▶ **HP Study Group clinical prediction rule** — **6 predictors**: (1) exposure to a known HP antigen (*strongest*), (2) positive serum precipitins, (3) recurrent symptoms, (4) symptoms **4–8 h after exposure**, (5) inspiratory crackles, (6) weight loss.

Differential Diagnosis

- ▶ **Nonfibrotic HP** ↔ viral/atypical pneumonia, **organic dust toxic syndrome (ODTS)** — ODTS follows heavy organic-dust exposure but needs *no* prior sensitization and lacks specific IgG; asthma; drug reaction; inhalational fever.
- ▶ **Fibrotic HP** ↔ IPF, NSIP, connective-tissue-disease ILD, **sarcoidosis** (well-formed granulomas, hilar adenopathy, multi-organ), pleuroparenchymal fibroelastosis.

Treatment

- ▶ **Antigen avoidance is the mainstay** and the only intervention shown to improve clinical course and survival — remove birds/mold, improve ventilation, source-control of water systems (humidity <60%), respirators/ventilated helmets (may be inadequate in the sensitized), and occupational change where needed. Identifying *and* avoiding the antigen improves survival (median 8.8 vs 4.9 years).
- ▶ **Glucocorticoids** — for severe nonfibrotic or symptomatic disease: **prednisone 0.5–1 mg/kg/day** (max 60 mg/day) for ~1–2 weeks (CMDT: ~2 weeks), then taper over weeks (total ~3 months). They *accelerate symptom resolution* but do not alter long-term outcome.

- ▶ **Steroid-sparing immunosuppressants** — azathioprine or mycophenolate mofetil in progressive/fibrotic disease (reduce steroid dose; fewer adverse events); **rituximab** in refractory cases.
- ▶ **Antifibrotics** — **nintedanib** (INBUILD trial: slowed FVC decline in progressive fibrosing ILDs including HP) and **pirfenidone** for progressive fibrotic HP.
- ▶ **Supportive & advanced** — supplemental O₂, pulmonary rehabilitation, vaccination, smoking cessation; **lung transplantation** for end-stage fibrotic disease (outcomes better than IPF, low recurrence risk).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **HRCT axial section of nonfibrotic HP** — label: *diffuse ground-glass opacity, centrilobular nodules, mosaic attenuation / air-trapping, “headcheese” sign, mid–upper zone predominance.*
- ▶ **Pathogenesis flow diagram** — label: *Inhaled antigen → deposition in distal airways/alveoli → sensitization (specific IgG) → Type III immune complex + Type IV (TH1/TH17) delayed hypersensitivity → neutrophilic then lymphocytic alveolitis → poorly-formed non-caseating granulomas → (with persistent exposure / Th2 shift, MUC5B, short telomeres) → fibrosis (honeycombing).*

Clinical / Diagnostic significance

- ▶ **Occupational/avocational history is decisive** — HP cannot be managed without identifying and removing the source; recognition of an index case is a *sentinel event* signalling others at risk (outbreak investigation).
- ▶ **Distinguish from IPF** — bronchiolocentric fibrosis, upper/mid-zone predominance with basal sparing, BAL lymphocytosis and mosaic attenuation favour HP; this matters because antifibrotic and avoidance strategies, and transplant outcomes, differ.
- ▶ **Prognostic markers of poor outcome**: older age, male sex, baseline crackles, low FVC and DL_{CO}, HRCT fibrosis/honeycombing, MUC5B variant, short telomeres, smoking, no identifiable antigen, pulmonary hypertension; the **ILD-GAP index** and a **≥10% FVC decline over 6–12 months** predict mortality.

High-yield exam pointers

- ▶ HP = **extrinsic allergic alveolitis**; antigen-induced ILD of alveoli + small airways; **IgG sensitization necessary but not sufficient.**
- ▶ **Smokers have lower risk** of developing HP but worse prognosis once it develops.
- ▶ Classic eponyms: **Farmer’s lung** (*S. rectivirgula*), **Bird fancier’s/pigeon breeder’s lung** (avian proteins), **Hot-tub lung** (MAC), **Bagassosis**, **Summer-type HP** (*Trichosporon*, Japan), **Suberosis** (cork).

- ▶ New classification: **nonfibrotic vs fibrotic** (replaces acute/subacute/chronic).
- ▶ Mechanism: **Type III + Type IV** hypersensitivity; TH1/TH17; symptoms **4–8 h** post-exposure.
- ▶ HRCT: **centrilobular nodules + GGO + mosaic air-trapping**; “**headcheese**” sign; fibrotic HP spares lung bases (unlike IPF).
- ▶ BAL: **lymphocytosis** (often >50%); histology = “**triad of four**” with **poorly-formed non-caseating granulomas**.
- ▶ HP Study Group rule strongest predictor = **known antigen exposure**.
- ▶ Treatment: **antigen avoidance** (mainstay) > glucocorticoids (**prednisone 0.5–1 mg/kg/day**) > azathioprine/MMF > **nintedanib/pirfenidone** > transplant.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia” (Akuthota & Wechsler); and “Occupational and Environmental Lung Disease”.
- ▶ **Murray & Nadel’s Textbook of Respiratory Medicine, 7e** — “Hypersensitivity Pneumonitis” (Johannson & Fernández Pérez) — classification, immunopathogenesis/genetics, “triad of four” histology, headcheese sign, ILD-GAP prognostication, ATS/JRS/ALAT 2020 diagnostic algorithm and management.
- ▶ **CMDT 2026** — “Pulmonary Disorders: Hypersensitivity Pneumonitis” — causes table, clinical findings and corticosteroid regimen.
- ▶ *Coverage note:* sources differ on BAL **CD4:CD8 ratio** (Harrison: typically <1; Murray: variable/often elevated and not recommended) — answered as “variable, of limited value,” which is faithful to both.



Inflammatory Mediators and Effect of Airway Inflammation in Bronchial Asthma

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Asthma is a disease characterised by **episodic airway obstruction** and **airway hyperresponsiveness (AHR)** that is usually accompanied by **airway inflammation**. In most cases the obstruction is reversible, but in a subset a component becomes irreversible owing to **airway remodeling**. In a large proportion of patients the inflammation is **eosinophilic**, though some have differing inflammatory profiles (neutrophilic, mixed, or pauci-granulocytic) and a minority have no obvious inflammation. Airway inflammation is driven by an orchestrated network of **inflammatory cells** and the **chemical mediators** they release, which together produce the structural and functional changes responsible for symptoms.

Inflammatory cells in the asthmatic airway

Most asthmatics have evidence of **chronic** airway inflammation; while it can be precipitated acutely by inhalant exposure, it usually persists. Both recruited leucocytes and resident structural cells participate.

Cell	Role / products in asthma
Eosinophils	Predominant cell in most asthma; release oxidative radicals and major basic protein (disrupt epithelium, induce AHR), produce cysteinyl-leukotrienes ; aggregates contribute to mucus plugs
Mast cells / basophils	Activated by IgE cross-linking by allergen; release type 2 cytokines, direct smooth-muscle constrictors, PGD₂ , and edema-producing mediators
Neutrophils	Predominate in some severe, non-type 2 / corticosteroid-resistant asthma; source of LTB₄
Type 2 innate lymphoid cells (ILC2)	Activated by epithelial alarmins ; produce IL-5 and IL-13 → link “nonallergic” triggers to eosinophilia
CD4+ T-helper 2 (TH2) cells	Produce IL-4, IL-5, IL-13 — the adaptive arm of type 2 inflammation
Airway epithelium	Disrupted (columnar-to-basal separation); source of alarmins and cytokines that drive the inflammatory cascade
Airway smooth muscle	Hyperresponsive; undergoes hypertrophy/hyperplasia; secretes chemokines/cytokines that promote inflammation and mast-cell survival

Classification of airway inflammation (Type 2 vs Non-Type 2)

The older atopic (extrinsic) vs nonatopic (intrinsic) division has been superseded by an **immunologic nosology** based on whether inflammation is type 2 or non-type 2 — a classification driven by mechanism and by the development of mediator-targeted biologics.

Feature	Type 2 inflammation	Non-type 2 inflammation
Key cells	Eosinophils, mast cells, TH2, ILC2	Neutrophils
Key cytokines	IL-4, IL-5, IL-13; alarmins TSLP, IL-25, IL-33; IL-9	IL-6, IL-17, TNF- α , IL-1 β , IL-8
Triggers	Allergens (adaptive) and irritants/pollutants/fungi/viruses via alarmins→ILC2	Severe disease, atypical infection (<i>Mycoplasma</i>), RADS
Corticosteroid response	Usually suppressed by corticosteroids	Often corticosteroid-resistant; may respond to macrolides

Feature	Type 2 inflammation	Non-type 2 inflammation
Biomarkers	↑ Eosinophils, ↑ FeNO, ↑ IgE	None reliable

Pauci-granulocytic asthma shows the structural changes without inflammatory-cell infiltration (etiology unclear).

Inflammatory mediators

“Many chemical substances or signaling factors contribute to the pathobiology of asthma,” several of which have been successfully drug-targeted.

Cytokines

- ▶ **IL-4** — induces B-cell isotype switching to **IgE** production; IgE then binds mast cells/basophils, conferring environmental sensitivity.
- ▶ **IL-5** — critical regulator of eosinophils: controls their **formation, recruitment and survival**.
- ▶ **IL-13** — induces **airway hyperresponsiveness, mucus hypersecretion and goblet-cell metaplasia**; also drives FeNO.
- ▶ **Alarmins** — TSLP, IL-25, IL-33 are epithelial-derived “proximal” cytokines released after allergic and nonallergic exposures; they activate ILC2 (→ IL-5/IL-13).
- ▶ **Non-type 2 cytokines** — IL-6, IL-17, TNF- α , IL-1 β , IL-8 mediate neutrophilic inflammation.

Fatty-acid (arachidonic-acid-derived) mediators

- ▶ **Cysteinyl-leukotrienes (LTC₄, LTD₄, LTE₄)** — produced by eosinophils and mast cells; **potent smooth-muscle constrictors** that also stimulate mucus secretion, recruit allergic inflammatory cells, cause microvascular leakage, modulate cytokine production and influence neural transmission.
- ▶ **LTB₄ (non-cysteinyl)** — from neutrophils (also macrophages/epithelium); potent **neutrophil chemoattractant**.
- ▶ **Prostaglandins** — largely proinflammatory; PGD₂ from mast cells acts via **CRTH2** receptors on TH2/ILC2/mast cells/eosinophils to **upregulate type 2 inflammation**.
- ▶ **Pro-resolution lipids** — **resolvins and lipoxins** drive resolution of inflammation; their deficiency may underlie persistent inflammation in severe asthma.

Other mediators

- ▶ **Nitric oxide (NO)** — vasodilator; increases mucus production and smooth-muscle proliferation; basis of the FeNO breath test (an indicator of IL-13-induced type 2 inflammation).
- ▶ **Reactive oxygen species (ROS)** — released in respiratory bursts on cell activation; cause **oxidative stress** → ↑ smooth-muscle contraction, ↑ mucus, AHR and epithelial shedding.
- ▶ **Chemokines** — **eotaxin** (eosinophil chemoattractant), **TARC and MDC** (attract TH2 cells), **RANTES** (pluripotent pro-phlogistic).

- ▶ IgE — central to allergen sensitivity through mast-cell/basophil cross-linking.

Effects of airway inflammation (structure–function consequences)

Sustained mediator action produces both acute reversible narrowing and chronic remodeling (Fig. 298-2):

- ▶ **Airway hyperresponsiveness** — the hallmark; exaggerated narrowing to stimuli (e.g., histamine, methacholine, cold/dry air) that do not affect normal subjects.
- ▶ **Bronchoconstriction** — direct smooth-muscle contraction (cysteinyl-leukotrienes, histamine) invaginates the mucosa and narrows the lumen.
- ▶ **Airway (submucosal) edema** — acute and chronic; from microvascular leakage of postcapillary venules.
- ▶ **Mucus hypersecretion & goblet-cell metaplasia** — chronic inflammation proliferates mucus cells; **mucus plugs** (often containing eosinophil aggregates) obstruct medium and small airways and cause persistent obstruction.
- ▶ **Epithelial denudation/shedding** — disruption forms a trophic unit with mesenchyme that elaborates growth factors driving remodeling.
- ▶ **Subepithelial fibrosis / basement-membrane thickening** — deposition of repair collagens, tenascin, periostin, fibronectin, osteopontin from myofibroblasts; **stiffens the airway**, exaggerates responses to wall tension and impairs relaxation → fixed obstruction.
- ▶ **Smooth-muscle hypertrophy and hyperplasia** — thickens the wall and amplifies hyperresponsiveness.
- ▶ **Vascular proliferation (angiogenesis) and neuronal proliferation** (neurotrophin-driven) — add to wall thickening and to abnormal regulation of tone and mucus.

The net result is **airway-wall thickening** (correlating with disease severity and duration) producing a tendency to **narrow disproportionately**, episodic exacerbations and, when remodeling supervenes, partly irreversible obstruction.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Normal vs asthmatic airway cross-section (Fig. 298-2).** Labels: *Smooth muscle (and smooth-muscle hypertrophy and proliferation), invagination of mucosa due to smooth-muscle constriction, airway edema, mucus production / mucus plug, cellular infiltration, collagen deposition and thickening of the basement membrane, epithelial denudation and shedding, vascular proliferation, neuronal proliferation, lumen, submucosa, epithelium, adventitia, thin mucus layer.*
- ▶ **Type 2 / non-type 2 mediator cascade (Fig. 298-3).** Labels: *Allergens / nonallergic stimuli → epithelium → alarmins (TSLP, IL-25, IL-33); ILC2 and TH2 → IL-4, IL-5, IL-13; mast cell (IgE, PGD2/CRT2H2), eosinophil (cysteinyl-leukotrienes, MBP), neutrophil (LTB4, IL-8/IL-*

17, TNF- α); outputs $\rightarrow$ *smooth-muscle hyperresponsiveness & proliferation, fibroblast proliferation & matrix deposition.*

Clinical / Diagnostic significance

- ▶ **Biomarkers of type 2 inflammation guide therapy:** blood eosinophils $\geq 300/\mu\text{L}$ indicate likely response to type 2-targeted drugs; FeNO $>35\text{--}40$ ppb (untreated) reflects IL-13-driven inflammation and falls with inhaled corticosteroids (also a marker of adherence); total IgE >1000 IU/mL prompts consideration of ABPA.
- ▶ **Mediator-targeted controller (biologic) therapy** for severe type 2 asthma: anti-IgE — omalizumab (SC, reduces exacerbations 25–50%); anti-IL-5 / IL-5R — mepolizumab, reslizumab (bind IL-5), benralizumab (binds IL-5 receptor) (rapidly deplete eosinophils, halve exacerbations when eosinophils $\geq 300/\mu\text{L}$); anti-IL-4R α — dupilumab (blocks IL-4 and IL-13 signalling, exacerbations $\downarrow \geq 50\%$); anti-TSLP — tezepelumab (proximal alarmin blockade, broad effect, exacerbations $\downarrow$ 50–70%, works even without elevated FeNO/eosinophils).
- ▶ **Leukotriene modifiers** — CysLT1 antagonists (montelukast, zafirlukast) and 5-lipoxygenase inhibition; moderately effective, particularly useful in aspirin-exacerbated respiratory disease (leukotriene overproduction) and to prevent exercise-induced bronchoconstriction; montelukast favoured in children to avoid corticosteroid growth suppression (note neuropsychiatric warning).
- ▶ **Inhaled corticosteroids** remain the cornerstone anti-inflammatory controller suppressing type 2 inflammation; neutrophilic/non-type 2 disease is relatively steroid-resistant and may respond to macrolides.

High-yield exam pointers

- ▶ Asthma = episodic airway obstruction + AHR + airway inflammation; obstruction usually reversible, partly fixed with remodeling.
- ▶ IL-4 $\rightarrow$ IgE switch; IL-5 $\rightarrow$ eosinophils; IL-13 $\rightarrow$ AHR, mucus, goblet-cell metaplasia, FeNO — memorise this triad.
- ▶ Alarmins = TSLP, IL-25, IL-33 (epithelial, proximal) activate ILC2, linking nonallergic triggers to eosinophilia.
- ▶ Cysteinyl-leukotrienes = LTC₄, LTD₄, LTE₄ (eosinophils/mast cells) — potent bronchoconstrictors; LTB₄ = neutrophil chemoattractant.
- ▶ PGD₂ acts via CRTH2; eotaxin recruits eosinophils; MBP and ROS damage epithelium.
- ▶ FeNO = NO/IL-13-driven marker; eosinophils $\geq 300/\mu\text{L}$ and IgE guide biologic selection.
- ▶ Remodeling = subepithelial fibrosis + smooth-muscle hypertrophy + mucus metaplasia + vascular/neuronal proliferation $\rightarrow$ fixed obstruction.

- ▶ Each major type 2 mediator now has a **biologic** (omalizumab, mepolizumab/reslizumab/benralizumab, dupilumab, tezepelumab).
- ▶ **Resolvins/lipoxins** = pro-resolution lipids; their deficiency perpetuates severe asthma.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 298 "Asthma" (Elliot Israel): sections on *Mechanisms Leading to Acute and Chronic Airway Obstruction, Airway Inflammation (Type 2 and Non-Type 2), Mediators*, biomarkers and biologic therapy; Figs 298-2 and 298-3. Coverage note: Zileuton is named here as the standard 5-lipoxygenase inhibitor and montelukast's neuropsychiatric (suicidality) caution as universally accepted textbook points; the provided text describes "inhibition of 5-lipoxygenase" and "ideation associated with montelukast" without elaboration.



Interstitial lung diseases

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — The interstitial lung diseases (ILDs), or diffuse parenchymal lung diseases, comprise a heterogeneous group of **>200 conditions** that injure the lung parenchyma with varying degrees of **inflammation and fibrosis**. Although the *interstitium* (the space between the alveolar epithelium and the capillary endothelium) is the dominant site of involvement, the alveolar epithelium, airways, and vessels also play a key pathogenic role. Most patients present with **progressive exertional dyspnoea** and/or a **persistent dry cough**, though some are detected incidentally or via non-respiratory features of a multisystem disorder. ILDs carry high morbidity and mortality, so timely, precise diagnosis is essential.

Classification (known vs unknown cause)

A classic, examination-friendly scheme divides ILDs into those of **known** and **unknown** cause (Harrison Fig. 304-1); genetic studies increasingly blur this divide.

Group	Subcategory	Representative disorders
Known cause	Occupational/environmental exposure	Asbestosis, silicosis
	Treatment-related	Radiation; drugs — methotrexate, amiodarone, nitrofurantoin, bleomycin/chemotherapeutics

Group	Subcategory	Representative disorders
	Systemic / connective tissue disease	RA, scleroderma (SSc), polymyositis/dermatomyositis, Sjögren's, SLE
	Granulomatous (with vasculitis)	Granulomatosis with polyangiitis (GPA), eosinophilic GPA (Churg-Strauss)
	Granulomatous lung disease	Hypersensitivity pneumonitis (HP) (bird-fancier's lung)
Unknown cause	Idiopathic interstitial pneumonias (IIPs)	IPF, NSIP, RB-ILD, DIP, COP, AIP, lymphocytic interstitial pneumonia (LIP)
	Granulomatous (unknown)	Sarcoidosis
	Other	Lymphangioleiomyomatosis (LAM), pulmonary alveolar proteinosis, Langerhans cell histiocytosis (PLCH), pleural-parenchymal fibroelastosis

- ▶ The IIPs were precisely defined by the 2002 ATS/ERS consensus statement (Am J Respir Crit Care Med 165:277, 2002).
- ▶ IPF, sarcoidosis, and CTD-associated ILD are collectively the most common forms of ILD.

Diagnostic approach — the multidisciplinary principle

- ▶ **Central tenet:** No single test is diagnostic alone. The **combined weight** of clinical data, laboratory studies, pulmonary function tests (PFTs), imaging, and (when obtained) histopathology is *jointly* required. A UIP biopsy supports IPF but also occurs in RA-associated ILD.
- ▶ Most centres use a **multidisciplinary discussion** — pulmonologist, rheumatologist, radiologist, pathologist — to reach a confident diagnosis.
- ▶ **History — discriminating clues:**
 - **Age:** IPF is most common >60 yr and rare <50 yr; sarcoidosis, CTD-ILD, LAM and PLCH typically present at **20–40 yr**.
 - **Sex:** LAM/tuberous sclerosis — young women; most CTD-ILDs commoner in women **except RA-ILD** (commoner in men); IPF and occupational ILD commoner in men.
 - **Duration:** **Acute (days–weeks)** — eosinophilic pneumonia, AIP, HP, GPA, acute exacerbation of IPF; **chronic indolent (months–years)** — typified by IPF; **subacute (weeks–months)** — sarcoidosis, CTD-ILD, drug-induced ILD, COP.

- *Respiratory symptoms*: dyspnoea and dry cough predominate; **haemoptysis** is rare and suggests diffuse alveolar haemorrhage (**Goodpasture's**, GPA) or LAM.
- *Drugs*: methotrexate, azathioprine, rituximab, TNF- α blockers, nitrofurantoin, amiodarone, bleomycin.
- *Family history*: up to **20%** of pulmonary fibrosis is familial; a relative with an IIP is among the strongest risk factors for IPF.
- *Social/exposure*: smoking is causative in RB-ILD/DIP and present in $\sim 75\%$ of IPF; asbestos and pigeon/bird exposure (pigeon breeder's lung $\rightarrow$ HP).
- ▶ **Physical examination**: end-inspiratory fine “Velcro” basal **crackles/rales** (often the earliest IPF sign); **digital clubbing**; wheeze is uncommon but may occur in sarcoidosis, HP, eosinophilic GPA; advanced disease $\rightarrow$ cyanosis, cor pulmonale.
- ▶ **Laboratory studies**: autoimmune serology for an underlying CTD (e.g. anti-CCP for RA), even when systemic features are absent.
- ▶ **Pulmonary function tests**: classically a **restrictive** pattern — reduced TLC, symmetric reduction of FEV1 and FVC, with a **normal/raised FEV1/FVC ratio** — and a reduced DLCO (may precede volume loss). Airway-involving ILDs (sarcoidosis, HP, LAM) may add obstruction. **Serial FVC decline correlates with increased mortality**.
- ▶ **Imaging**:
 - CXR — hilar adenopathy with upper-zone central nodular opacities suggests sarcoidosis; a basilar reticular pattern suggests IPF.
 - **HRCT** is the **standard of care** in initial evaluation; can be diagnostic for IPF in the right context and may obviate biopsy, and defines disease extent and complications.
- ▶ **Lung biopsy**:
 - *Fibreoptic bronchoscopy with BAL* — supports DAH, **eosinophilia** $>25\%$ (chronic eosinophilic pneumonia), fat globules (lipoid pneumonia); transbronchial biopsy useful for granulomatous disease (sarcoidosis, HP); cryobiopsy role is still being defined.
 - *Surgical (VATS) biopsy* — highest yield (pre-treatment) but carries up to 5% **short-term mortality**, higher in IPF and acute presentations.

Major idiopathic interstitial pneumonias

Entity	Typical patient	HRCT	Histopathology	Treatment / prognosis
IPF	>60 yr, male, smoker	Subpleural reticulation, posterior-basal predominance,	UIP — fibroblast foci, temporal & spatial heterogeneity, honeycombing	Antifibrotics — pirfenidone, nintedanib (slow FVC decline; from 2014 trials); immunosuppression is <i>harmful</i> ; O ₂ , pulmonary rehab; transplant. 50% 3–5 yr survival

Entity	Typical patient	HRCT	Histopathology	Treatment / prognosis
		honeycombing, traction bronchiectasis = UIP pattern		
NSIP	Non-smoking female, ~50 yr; often CTD	Diffuse subpleural symmetric ground-glass + reticular, traction bronchiectasis	Uniform inflammation/fibrosis; honeycombing absent, fibroblast foci rare; cellular vs fibrotic	Steroids ± mycophenolate/azathioprine/cyclophosphamide; rituximab, tocilizumab; antifibrotics if progressive. 5-yr survival >80% (cellular better)
COP	50–60 yr, subacute flu-like illness	Patchy migratory subpleural consolidation; reversed halo / atoll sign	Organizing pneumonia — granulation tissue in small airways/alveoli	Corticosteroids ≥6 months (high relapse); mycophenolate/cyclophosphamide/rituximab
RB-ILD / DIP (smoking-related)	Heavy smoker, 40–50 yr	Centrilobular nodules, ground-glass, bronchial-wall thickening	Pigment-laden macrophages in respiratory bronchioles (RB-ILD) / diffuse (DIP)	Smoking cessation is primary; <10% of IIPs; generally good prognosis
AIP (Hamman-Rich)	Acute respiratory distress + hypoxaemia	Patchy bilateral ground-glass + dependent consolidation	Diffuse alveolar damage (DAD)	Supportive ± ventilation; no proven drug; >50% mortality at 6 months

- ▶ **Acute exacerbation of ILD:** an accelerated phase of injury (onset <30 days) without alternate cause; commonest/most severe in IPF, with **>85% mortality**; histology is DAD; nintedanib may reduce exacerbation frequency in IPF.

ILD associated with connective tissue disease

- ▶ **Systemic sclerosis (SSc):** ILD is the **commonest pulmonary manifestation** — ~50% of diffuse and ~30% of limited SSc; NSIP/UIP patterns; clues = dilated oesophagus, PA enlargement. Treat with **cyclophosphamide or mycophenolate**, ± tocilizumab/nintedanib; **high-dose PPI** for reflux-related injury.

- ▶ **Rheumatoid arthritis:** clinically evident ILD in ~10%, but radiological abnormalities in 40–50%; commoner in men/smokers; UIP pattern predominates (worse survival) > NSIP.
- ▶ **Dermatomyositis/polymyositis: anti-synthetase syndrome** = anti-synthetase (e.g. anti-Jo-1) antibodies, myositis, fever, Raynaud's, **mechanic's hands**, arthritis, progressive ILD; NSIP ± COP, sometimes UIP; treat with steroids + cytotoxics; rapidly progressive DAD carries a poor outcome.

Granulomatous ILDs and genetics

- ▶ **Sarcoidosis** — commonest granulomatous ILD; **noncaseating granulomas** (caseation should prompt search for infection); multisystem (see Ch. 379).
- ▶ **Hypersensitivity pneumonitis** — granulomatous reaction to inhaled organic (bird-fancier's lung) or inorganic dusts (see Ch. 299).
- ▶ **Granulomatous vasculitides** — GPA (Wegener's): lung nodules, ENT and glomerulonephritis, haemoptysis; eosinophilic GPA (Churg-Strauss): asthma, chronic sinusitis, peripheral eosinophilia.
- ▶ **Genetics:** the MUC5B promoter variant is present in ~20% of Caucasians and 35–45% of IPF patients (~sixfold risk); telomere-related genes (TERT, TERC, RTEL1) and surfactant genes (SFTPA2); sarcoidosis — HLA, IL12B, BTNL2; LAM — TSC1/TSC2; Hermansky-Pudlak syndrome (autosomal recessive: pulmonary fibrosis + oculocutaneous albinism + bleeding diathesis + nystagmus).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Classification algorithm of ILD** (Fig. 304-1): a branching tree with the trunk “ILD” splitting into “Known cause” (branches: *Occupational* — asbestosis, silicosis; *Treatment-related* — radiation, methotrexate, amiodarone, nitrofurantoin, chemotherapeutics; *Systemic/CTD* — RA, scleroderma, polymyositis/dermatomyositis; *Granulomatous with vasculitis* — GPA, Churg-Strauss; HP) and “Unknown cause” (branches: *IIPs* — IPF, NSIP, RB-ILD, DIP, COP, AIP, LIP; *Sarcoidosis*; *Other* — LAM, alveolar proteinosis, Langerhans cell histiocytosis, pleural-parenchymal fibroelastosis).
- ▶ **UIP-pattern HRCT chest** (lower-zone slice): label *subpleural reticulation*, *posterior-basal predominance*, *honeycombing*, *traction bronchiectasis*.

Clinical / Diagnostic significance

- ▶ **Pattern-recognition decides therapy and prognosis:** a UIP/IPF diagnosis mandates **antifibrotics** and *avoidance of immunosuppression* (proven harmful), whereas **cellular NSIP** and COP respond well to immunosuppression — misclassification is dangerous.
- ▶ **HRCT + multidisciplinary review** can confidently diagnose IPF and spare a high-risk surgical biopsy.

- ▶ **Serial FVC and DLCO** are the practical tools for monitoring progression and predicting mortality.
- ▶ Always **screen for an occult CTD** (serology, examination) — ILD may be its first manifestation by years.
- ▶ **Lung transplantation** remains the standard of care for advanced/rapidly progressive ILD in eligible patients.

High-yield exam pointers

- ▶ ILD = >200 disorders; hallmark = restrictive PFT (↓TLC, ↓FVC, normal/↑ FEV1/FVC) with reduced DLCO.
- ▶ **UIP pattern** (subpleural, basal, honeycombing, traction bronchiectasis, fibroblast foci, temporal/spatial heterogeneity) = IPF — but also seen in RA.
- ▶ **IPF**: >60 yr, male, smoker; prevalence 50–200/100,000; 50% 3–5-yr survival; treat with **pirfenidone/nintedanib**.
- ▶ **NSIP**: non-smoking woman, CTD-associated, ground-glass dominant, honeycombing absent, 5-yr survival >80%.
- ▶ **COP**: subacute flu-like, **reversed halo (atoll) sign**, steroid-responsive ≥6 months.
- ▶ **AIP** = **Hamman-Rich** = idiopathic DAD, ARDS-like, >50% 6-month mortality.
- ▶ **Acute exacerbation of IPF**: onset <30 days, DAD, mortality >85%.
- ▶ **Anti-synthetase syndrome**: anti-Jo-1, myositis, fever, Raynaud's, **mechanic's hands**, ILD.
- ▶ **MUC5B** promoter variant — strongest common genetic risk factor for IPF (~6-fold).

SOURCE & COVERAGE

Harrison 22e — Ch 304 “Interstitial Lung Disease.” (Cross-references within the chapter: sarcoidosis Ch 379, hypersensitivity pneumonitis Ch 299, systemic sclerosis Ch 372, RA Ch 370, inflammatory myopathies Ch 377.) Coverage note: All classification, patterns, drugs, eponyms and numbers above are drawn from Ch 304; sarcoidosis and HP are only summarised here as Ch 304 defers their detail to Chs 379 and 299 (not provided), so granuloma-staging/specific sarcoid management is intentionally brief. The descriptor “*Velcro crackles*” is standard textbook terminology added for emphasis (Ch 304 states “end-inspiratory fine crackles, or rales”).



Lung Abscess

Asked in: Paper III Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — A **lung abscess** is localised **necrosis and cavitation of lung parenchyma** following **microbial infection**, producing a pus-filled cavity. Abscesses may be single or multiple but

are usually marked by a **single dominant cavity >2 cm in diameter**, classically containing an **air–fluid level**. Most are a consequence of **aspiration of oropharyngeal anaerobes** in a susceptible host, and although their incidence has fallen sharply in the antibiotic era they remain an important cause of morbidity and mortality.

Classification

- ▶ **By origin:**
 - **Primary (~80%)** — arises from **aspiration**, predominantly **anaerobic**, in a host with **no underlying pulmonary/systemic disease**; occurs in immunocompetent individuals.
 - **Secondary** — develops on a background of an **underlying condition**: a **post-obstructive process** (bronchial tumour, foreign body) or a **systemic/immunocompromising state** (HIV, transplant, malignancy). Microbiology is broader and outcomes worse.
- ▶ **By chronicity:** **Acute (<4–6 weeks)** vs **chronic (~40% of cases; symptoms >1 month)**.
- ▶ **By microbiology:** defined by the isolate (e.g., *Pseudomonas* abscess); when **no pathogen is recovered (~40%)** it is termed a **nonspecific lung abscess** (anaerobes presumed). A **putrid lung abscess** = foul-smelling breath/sputum/empyema and is **virtually diagnostic of anaerobic infection**.
- ▶ **Special form: Necrotising pneumonia** = multiple small (<2 cm) cavities within an area of consolidation; lies on the same pathological continuum.

Etiology, Risk Factors and Microbiology

- ▶ **Cardinal risk factor = aspiration.** Predisposing states (CMDT/Harrison):
 - **Impaired consciousness / depressed gag** — alcoholism, drug overdose, sedatives, seizures, general anaesthesia, head trauma, stroke/CNS disease.
 - **Impaired deglutition** — bulbar dysfunction, neuromuscular disease, oesophageal dysmotility, strictures or tumours.
 - **Gastric distension / GERD, the recumbent position, and tracheal or nasogastric tubes** that breach airway defences.
- ▶ **Poor oral hygiene is pivotal:** colonisation of **gingival crevices** by anaerobes and microaerophilic streptococci (gingivitis, periodontal disease) supplies the inoculum. Abscess is considered **rare in the edentulous patient** — if it occurs without teeth, **suspect an obstructing bronchial lesion (malignancy)**.

Clinical setting	Typical pathogens
Primary (aspiration)	Anaerobes — <i>Peptostreptococcus</i> , <i>Prevotella</i> (incl. <i>P. melaninogenica</i>), <i>Bacteroides</i> (usually not <i>B. fragilis</i>), <i>Fusobacterium nucleatum</i> , <i>milleri</i> -group streptococci; microaerophilic streptococci

Clinical setting	Typical pathogens
Secondary / immunocompromised	<i>Staphylococcus aureus</i> , gram-negative rods (<i>Pseudomonas aeruginosa</i> , Enterobacteriaceae, <i>Klebsiella pneumoniae</i>), <i>Nocardia</i> , <i>Aspergillus</i> , Mucorales, <i>Cryptococcus</i> , <i>Legionella</i> , <i>Rhodococcus equi</i> , <i>Pneumocystis jirovecii</i>
Embolic	<i>S. aureus</i> (tricuspid endocarditis); <i>Fusobacterium necrophorum</i> (Lemierre's syndrome)
Endemic	<i>M. tuberculosis</i> , <i>M. avium</i> , <i>M. kansasii</i> ; <i>Coccidioides</i> , <i>Histoplasma</i> , <i>Blastomyces</i> ; parasites (<i>Entamoeba histolytica</i> , <i>Paragonimus westermani</i> , <i>Strongyloides</i>)
Miscellaneous	<i>S. aureus</i> post-influenza/viral infection; <i>Actinomyces</i>

- ▶ Primary abscesses are typically **polymicrobial**; with optimal anaerobic technique, isolate recovery is reported as high as 78%.

Pathogenesis

- ▶ **Primary abscess**: aspirated **anaerobes/microaerophilic streptococci** from the gingival crevices reach the parenchyma in a host with a large aspirated burden or poor clearance → **pneumonitis** (aggravated by gastric-acid injury) → over 7–14 days the bacteria produce **parenchymal necrosis and cavitation**. Anaerobes act **synergistically** in polymicrobial infection to amplify tissue destruction.
- ▶ **Secondary abscess**: a **bronchial obstruction** (tumour, foreign body) blocks clearance of secretions distally; or **impaired host defence** allows opportunists to cavitate.
- ▶ **Septic embolic abscess**: seeding from **right-sided (tricuspid) endocarditis** (*S. aureus*), or **Lemierre's syndrome** — oropharyngeal *F. necrophorum* infection spreads to the **carotid sheath** → **septic thrombophlebitis of the internal jugular vein** with showering of septic pulmonary emboli.
- ▶ **Location reflects gravity**: the dependent segments — **posterior segments of the upper lobes and superior segments of the lower lobes** — are most affected; the **right lung** > left because the **right main bronchus** is wider, shorter and less angulated.

Clinical Features

- ▶ **Anaerobic (typical primary) abscess** — **indolent, subacute**: low-grade fever, cough, sputum over weeks, with **night sweats, fatigue, weight loss and anaemia**; a subset expectorate **foul-tasting / foul-smelling (putrid) sputum**, occasionally pleuritic pain or haemoptysis.
- ▶ ***Non-anaerobic (e.g., S. aureus, Klebsiella) abscess** — **more fulminant*** course with high fever and rapid progression.

- ▶ **Examination:** fever, poor dentition / gingival disease, amphoric or cavernous breath sounds, digital clubbing (chronic), an absent gag reflex; crackles, egophony or dullness if an effusion coexists.

Investigations and Diagnosis

- ▶ **Imaging is the cornerstone.**
 - **Chest radiograph** — thick-walled cavity with an air–fluid level and surrounding consolidation in a dependent segment.
 - **CT chest** — superior definition, detects cavitation early, distinguishes a peripheral abscess from empyema (a treatment-critical distinction), and screens for an underlying obstructing lesion/malignancy.

Feature	Lung abscess	Empyema	Malignant cavity	Septic emboli
Shape	Round (equal in all views)	Oblong/lenticular	Variable, often nodular	Multiple nodules 1–3 cm
Inner wall	Ragged/"shaggy", irregular	Smooth lining	Nodular, thick (≥ 16 mm)	Cavities at differing stages
Effect on lung	Destroys parenchyma; no compression	Compresses adjacent lung	—	Subpleural wedge infarcts
Air–fluid level	Present	May split pleura	Variable	—

- ▶ **Microbiology:** expectorated sputum Gram stain + aerobic, mycobacterial and fungal culture (anaerobic cultures often falsely negative unless rapidly transported/plated). Thoracentesis if effusion present (uncontaminated specimen + excludes empyema). Blood cultures + echocardiography when septic emboli/endocarditis suspected. Molecular methods (e.g., 16S rRNA gene amplification) may improve pathogen identification.
- ▶ **Bronchoscopy** — performed early when bronchial obstruction (tumour/foreign body) is suspected, in non-responders, and in immunocompromised hosts (BAL for opportunists); also therapeutic. Risk: spillage of pus into the contralateral lung.
- ▶ **CT-guided transthoracic needle aspiration** — clean culture specimen, considered early for abscesses >4 cm; risks pneumothorax and bronchopleural fistula.
- ▶ **Endemic/HIV settings:** examine induced sputum for TB early. ANCA if a vasculitis (granulomatosis with polyangiitis) is suspected.

Treatment

- ▶ **Empirical antibiotics must cover anaerobes AND microaerophilic streptococci:**
 - Clindamycin 600 mg IV TID $\rightarrow$ 300 mg PO QID — superior to penicillin in trials (oral anaerobes elaborate β -lactamase); or

- A β -lactam/ β -lactamase inhibitor (ampicillin-sulbactam, piperacillin-tazobactam) IV $\rightarrow$ oral amoxicillin-clavulanate on stabilisation; or a carbapenem.
- Metronidazole alone fails — it misses the microaerophilic streptococci of the mixed flora. Meropenem monotherapy also lacks reliable streptococcal cover. Moxifloxacin 400 mg/day PO is as effective as ampicillin-sulbactam in small trials. CMDT second-line: 3rd-generation cephalosporin + metronidazole, or a fluoroquinolone.
- Targeted cover for monomicrobial isolates: MSSA — cefazolin/nafcillin/oxacillin; MRSA — linezolid (alternative vancomycin; avoid daptomycin — inactivated by surfactant/poor lung penetration).
- ▶ Duration: prolonged — commonly 4–6 weeks, ranging up to 14 weeks; continue until the cavity has cleared or regressed to a small stable scar on imaging (≥ 6 weeks linked to better outcomes).
- ▶ Response: clinical improvement by 3–4 days, defervescence by 7–10 days. 10–20% fail to respond; an abscess >6 –8 cm is less likely to respond to antibiotics alone.
- ▶ Drainage / surgery (~10% of cases): indicated for failure of medical therapy, massive/life-threatening haemoptysis, bronchopleural fistula, empyema, large cavity (>6 cm), or an obstructed bronchus.
 - Percutaneous (CT/US-guided) catheter drainage — for abscess >4 cm, peripheral, or poorly draining lesions, and in poor surgical candidates; place the affected lung dependent to limit spillage. Risks: pneumothorax, haemothorax, pleural seeding/empyema.
 - Endoscopic (bronchoscopic pigtail) drainage — for central lesions or coagulopathy.
 - Surgical resection — lobectomy preferred to segmentectomy (avoids residual necrotic tissue/re-infection); VATS for peripheral lesions; a double-lumen endotracheal tube protects the contralateral lung.
- ▶ Relieve the obstruction and treat the predisposing condition in secondary abscess.

Complications and Prognosis

- ▶ Complications: massive/life-threatening haemoptysis (from hypertrophied bronchial arteries), empyema and bronchopleural fistula, pneumatoceles, bronchiectasis, mediastinitis, recurrence, massive aspiration of cavity contents, and metastatic infection — brain abscess / stroke (clots bypass the pulmonary filter; brain-abscess risk markedly raised, adjusted OR ≈ 8.2).
- ▶ Prognosis: mortality of primary abscess is as low as 2% (overall 15–20% historically); secondary abscess mortality reaches ~75%. Poor prognostic markers: age >60 years, malignancy-related abscess, aerobic organisms, sepsis at presentation, symptom duration >8 weeks, and abscess size >6 cm.
- ▶ Prevention: airway protection, oral hygiene/dental care, minimised sedation with head-of-bed elevation in aspiration-prone patients, and pathogen-specific prophylaxis in selected immunocompromised hosts.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled chest CT / radiograph of a lung abscess:** cavity wall, air–fluid level, surrounding consolidation/ground-glass opacity, ragged inner lining, dependent location (posterior segment right upper lobe). Labels: *Cavity, Air–fluid level, Thick irregular wall, Surrounding consolidation, Right upper lobe (posterior segment)*.
- ▶ **Pathogenesis flow diagram:** *Aspiration of gingival anaerobes → Pneumonitis (7–14 days) → Parenchymal necrosis → Cavitation with air–fluid level → Complications (empyema, haemoptysis, brain abscess).*

Clinical / Diagnostic significance

- ▶ Distinguishing abscess from empyema on CT is treatment-defining — a tube thoracostomy placed inadvertently into an abscess can create a **bronchopleural fistula**; empyema mandates drainage.
- ▶ A lung abscess in an edentulous patient, or one failing therapy, demands bronchoscopy to exclude an obstructing carcinoma or foreign body.
- ▶ Putrid sputum at the bedside is essentially pathognomonic of **anaerobic** infection and guides empirical therapy.
- ▶ Multiple/peripheral cavities at different stages point to **septic emboli** — look for tricuspid endocarditis or Lemierre's syndrome; obtain blood cultures and echocardiography.

High-yield exam pointers

- ▶ Cavity >2 cm with air–fluid level; primary ~80%, chronic ~40%, nonspecific (culture-negative) ~40%.
- ▶ Right lung > left; posterior upper / superior lower segments (dependent).
- ▶ Anaerobes + microaerophilic streptococci → clindamycin (or β -lactam/ β -lactamase inhibitor) preferred; penicillin/metronidazole monotherapy inadequate.
- ▶ Putrid sputum = anaerobic; edentulous abscess = suspect tumour.
- ▶ Lemierre's syndrome = *Fusobacterium necrophorum*, internal-jugular septic thrombophlebitis.
- ▶ Antibiotics 4–6 weeks (up to ~14); treat until radiographic resolution/scar.
- ▶ Surgery/drainage if failure, >6 cm, massive haemoptysis, empyema, BPF, obstruction.
- ▶ Mortality: primary ~2%, secondary up to ~75%; poor signs — age >60, sepsis, aerobes, >8 weeks, >6 cm.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Lung Abscess” (definition, classification, Table 132-1 microbial causes, pathogenesis, Lemierre's syndrome, antibiotic regimens and durations, prognosis, prevention).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Lung Abscess” (radiographic differentiation from empyema/malignancy/septic emboli, microbiology, targeted MSSA/MRSA therapy, percutaneous and endoscopic drainage, surgical indications, brain-abscess association).
- ▶ **CMDT 2026** — “Pulmonary Disorders / Anaerobic Pleuropulmonary Infection” (essentials of diagnosis, predisposing factors, empirical regimens, abscess-vs-empyema drainage caveat).



Management of Acute Respiratory Distress Syndrome

Asked in: Paper III Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Acute respiratory distress syndrome (ARDS) is a clinical syndrome of rapid-onset severe dyspnoea, refractory hypoxaemia and diffuse bilateral pulmonary infiltrates due to diffuse alveolar–capillary injury that is not fully explained by cardiac failure or volume overload. It results from a high-permeability (non-cardiogenic) pulmonary oedema following direct (e.g. pneumonia, aspiration, toxic inhalation) or indirect (e.g. sepsis, pancreatitis, multiple transfusions) lung injury. There is **no specific pharmacotherapy that improves survival**; management is therefore built on aggressive treatment of the precipitating cause plus meticulous, evidence-based supportive care, with **lung-protective mechanical ventilation as the only intervention of proven mortality benefit**.

Diagnostic framework & severity grading (Berlin definition, 2012)

Establishing the diagnosis and severity is the first step because it dictates the ladder of therapy (proning/NMB/ECMO are reserved for the more severe categories).

Berlin criterion	Requirement
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms
Chest imaging	Bilateral opacities (X-ray or CT) not fully explained by effusions, lobar/lung collapse or nodules
Origin of oedema	Respiratory failure not fully explained by cardiac failure/fluid overload; if no risk factor present, exclude hydrostatic oedema objectively (e.g. echocardiography)

Berlin criterion	Requirement
Oxygenation (on PEEP/CPAP ≥ 5 cmH ₂ O)	Mild: $200 < \text{PaO}_2/\text{FiO}_2 \leq 300$; Moderate: $100 < \text{PaO}_2/\text{FiO}_2 \leq 200$; Severe: $\text{PaO}_2/\text{FiO}_2 \leq 100$ mmHg

- ▶ Pulmonary-artery wedge-pressure criterion of the older AECC definition has been **dropped** (PA catheters no longer routine); the term *acute lung injury (ALI)* has been **abolished**.
- ▶ Proposed 2023/2024 updates allow **non-intubated** patients on high-flow nasal oxygen (≥ 30 L/min) or NIV, the **SpO₂/FiO₂ (S/F) ratio** (≤ 315 if SpO₂ $\leq 97\%$) and **lung ultrasound** to be used in resource-limited settings.
- ▶ Natural history runs through three overlapping phases: **exudative** ($\approx$ first 7 days; alveolar oedema, hyaline membranes, diffuse alveolar damage), **proliferative** ($\approx$ day 7–21; type-II pneumocyte proliferation, early organisation) and **fibrotic** (after ≈ 3 –4 weeks; alveolar-duct/interstitial fibrosis, bullae, pulmonary hypertension).

General principles & supportive care

- ▶ **Treat the precipitating cause** — antibiotics and source control for sepsis/pneumonia, surgical débridement/drainage where indicated (both lung and abdomen should be excluded as septic foci).
- ▶ ICU “**bundled care**”: VTE prophylaxis, stress-ulcer prophylaxis, head-of-bed elevation to 30–45° and aspiration precautions, prevention of central-line infection, **daily sedation interruption** and minimisation of unnecessary procedures.
- ▶ **Enteral nutrition** via the enteral route when feasible; trophic and full feeding give equivalent outcomes, and **immunonutrition / omega-3 supplementation is not recommended**.
- ▶ **Transfusion:** maintain haemoglobin ≥ 7 g/dL (restrictive threshold); higher levels confer no benefit.

Lung-protective mechanical ventilation (cornerstone of therapy)

Most patients fatigue and require intubation, though high-flow nasal oxygen / NIV may avert this in milder disease. The aim is adequate gas exchange **while limiting ventilator-induced lung injury (VILI)** — *volutrauma* (alveolar overdistension), *barotrauma* (high pressure), *atelectrauma* (cyclic collapse–reopening) and *biotrauma* (mechano-inflammatory cytokine release).

- ▶ **Low tidal volume (ARMA/ARDSNet trial):** tidal volume **6 mL/kg predicted body weight** with **plateau pressure ≤ 30 cmH₂O** reduced mortality from 39.8% to 31.0% versus 12 mL/kg — the single landmark survival benefit. *Predicted body weight (kg): men = $50 + 0.91 \times (\text{height cm} - 152.4)$; women = $45.5 + 0.91 \times (\text{height cm} - 152.4)$.*
- ▶ **Mode:** volume assist-control is standard; pressure-control is equivalent.
- ▶ **PEEP / “open-lung”:** PEEP prevents atelectrauma and recruits dependent lung, allowing a lower FiO₂ (reduce O₂ toxicity). Higher PEEP is **safe and improves oxygenation but trials show no**

clear mortality benefit; set using the ARDSNet PEEP–FiO₂ table. Favour higher PEEP in severe ARDS (P/F <150) provided haemodynamics tolerate it.

- ▶ **Driving pressure** (plateau – PEEP) may matter more than absolute tidal volume; keeping it low (commonly targeted ≤15 cmH₂O) is associated with better survival.
- ▶ **Permissive hypercapnia**: accept a rising PaCO₂ to protect the lung, keeping pH ≥7.30 (the survival-positive ARDSNet trial treated acidosis aggressively, so avoid marked hypercapnia where possible; caution if raised intracranial pressure).
- ▶ **Oxygenation targets**: SpO₂ 88–95% / PaO₂ 55–80 mmHg using the lowest FiO₂ (aim <0.6).

ARDSNet ventilation protocol	Setting
Mode	Volume assist-control
Tidal volume	≤6 mL/kg predicted body weight
Plateau pressure	≤30 cmH ₂ O
Respiratory rate	6–35/min, titrated to pH 7.30–7.45
Oxygenation goal	PaO ₂ 55–80 mmHg or SpO ₂ 88–95%
PEEP/FiO ₂	Pre-set escalating combinations

Adjuncts for moderate–severe / refractory ARDS

- ▶ **Prone positioning** — for early, severe ARDS (P/F <150 mmHg): improves V/Q matching and lung homogeneity. The **PROSEVA trial** (prone ≥16 h/day) cut 28-day mortality markedly (16% vs 33%). Requires an experienced team; *unstable spinal injury is an absolute contraindication*; watch for tube/line dislodgement and pressure sores.
- ▶ **Neuromuscular blockade** — early **cisatracurium** infusion for 48 h improves patient–ventilator synchrony and abolishes injurious “reverse triggering”. **ACURASYS** showed a 90-day mortality benefit (31.6% vs 40.7%) but **ROSE** (light-sedation control) showed none — hence reserve NMB for severe ARDS with refractory dyssynchrony/high respiratory drive, **not routine use**.
- ▶ **ECMO / extracorporeal life support** — *salvage* for very severe, refractory hypoxaemia, refractory respiratory acidosis or barotrauma. **VV-ECMO** for isolated respiratory failure, **VA-ECMO** when circulatory support is also needed, **ECCO₂R** for CO₂ removal. **CESAR** showed benefit from referral to an ECMO centre; **EOLIA** showed a non-significant mortality reduction (35% vs 46%, with 28% control crossover). Select patients with a **reversible illness, good prior functional/neurological status, no contraindication to anticoagulation**.
- ▶ **Inhaled pulmonary vasodilators** (nitric oxide, epoprostenol/prostacyclin) — transiently improve oxygenation with **no survival benefit** (NO may worsen renal function); rescue use only.
- ▶ **Recruitment manoeuvres** and **high-frequency oscillatory ventilation** are **not recommended** — recruitment + high PEEP and HFOV increased mortality in trials.

Fluid management, pharmacotherapy & evidence summary

- **Conservative fluid strategy (FACTT):** in patients **not in shock**, fluid restriction and diuresis to a low filling pressure (CVP <4 / PAOP <8 mmHg) gave more ventilator-free and ICU-free days without more shock or dialysis. Use **balanced crystalloids**; **pulmonary-artery catheters are not routinely indicated**.
- **Corticosteroids** — historically discouraged, but contemporary evidence (DEXA-ARDS: **dexamethasone 20 mg/day ×5 then 10 mg/day ×5**) showed more ventilator-free days (12.3 vs 7.5) and lower 60-day mortality (21% vs 36%); the **2024 ATS guideline conditionally recommends corticosteroids**, most useful when started <14 days, in severe community-acquired pneumonia or COVID-19. Low-dose **hydrocortisone (200 mg/24 h)** is recommended in septic shock with refractory hypotension and in severe CAP — conditions that frequently coexist with ARDS.
- **Disappointing/ineffective therapies:** exogenous surfactant, β_2 -agonists (salbutamol — harmful), statins, ketoconazole, NSAIDs/ibuprofen, N-acetylcysteine, and partial liquid ventilation.

Therapy	Harrison evidence grade
Low tidal volume ventilation	A (strong RCT evidence)
Minimised left-atrial filling pressure	B
High-PEEP / open-lung	B
Prone positioning (severe ARDS)	B
ECMO (select severe ARDS)	B
Recruitment manoeuvres	C
Routine early neuromuscular blockade	C
High-frequency ventilation	D (against)
Glucocorticoids (routine)	D (against)
Inhaled vasodilators	C
Surfactant / other anti-inflammatory	D (against)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Time-course of ARDS (phase diagram):** an x-axis “Days 0 → 2 → 7 → 14 → 21” with three labelled boxes — *Exudative phase* (alveolar Oedema, Hyaline membranes, neutrophilic/interstitial inflammation, diffuse alveolar damage), *Proliferative phase* (interstitial inflammation, **type-II pneumocyte proliferation**, early fibrosis) and *Fibrotic phase* (Fibrosis, bullae, pulmonary hypertension).

Therapy	Harrison evidence grade
▶ Lung-protective ventilation management algorithm: boxes labelled “Initiate volume/pressure-limited ventilation → Tidal volume ≤ 6 mL/kg PBW, Plateau ≤ 30 cmH₂O, RR ≤ 35” → “Oxygenate: FiO₂ ≤ 0.6, SpO₂ 88–95%” → “Minimise acidosis: pH ≥ 7.30” → “Conservative fluid/diuresis: MAP ≥ 65, avoid hypoperfusion” → severe/refractory branch: “Prone (P/F <150) → NMB → ECMO”.	

Clinical / Diagnostic significance

- ▶ **Differential diagnosis** to exclude: cardiogenic pulmonary oedema (echocardiography; BNP is unreliable for separating the two), diffuse alveolar haemorrhage, bilateral pneumonia, acute interstitial pneumonia and acute eosinophilic pneumonia.
- ▶ **Prognosis:** in-hospital mortality ~30–40% (LUNG SAFE: **34.9% mild, 40.3% moderate, 46.1% severe**); **>80% of deaths are from non-pulmonary causes** (sepsis, multi-organ failure), not refractory hypoxaemia — explaining why supportive ICU care drives survival.
- ▶ Adverse prognostic markers: advanced age, chronic liver disease/alcohol abuse, immunosuppression, direct (vs indirect) lung injury, and a **hyperinflammatory (high IL-6) sub-phenotype**.
- ▶ **Survivor sequelae:** most regain near-normal spirometry by 6–12 months, but **ICU-acquired weakness, reduced 6-minute-walk distance, neurocognitive impairment, depression and PTSD** are common and warrant follow-up.
- ▶ Watch for **ventilation complications:** barotrauma (pneumothorax/pneumomediastinum), **ventilator-associated pneumonia**, post-extubation stridor (do a cuff-leak test), stress ulceration, VTE and delirium.

High-yield exam pointers

- ▶ **Low tidal volume (6 mL/kg PBW) + plateau ≤ 30 cmH₂O is the ONLY ventilator strategy proven to reduce mortality (ARDSNet/ARMA).**
- ▶ Berlin severity = PaO₂/FiO₂ on PEEP ≥ 5 : mild ≤ 300 , moderate ≤ 200 , severe ≤ 100 mmHg.
- ▶ **PROSEVA** — prone positioning >16 h/day in severe ARDS (P/F <150) improves survival.
- ▶ **Cisatracurium $\times 48$ h (ACURASYS)** — selective, not routine (ROSE negative).
- ▶ **Conservative fluid strategy (FACTT)** → more ventilator-free days; **balanced crystalloids**; no routine PA catheter.
- ▶ **ECMO = salvage** (VV for lungs, VA for lungs + circulation, ECCO₂R for CO₂); EOLIA/CESAR.
- ▶ **Dexamethasone/low-dose steroids** beneficial in **early (<14 day) ARDS**; 2024 ATS conditional recommendation.

- ▶ Liberate early via **daily spontaneous breathing trials**, not slow “weaning”; permissive hypercapnia ($\text{pH} \geq 7.30$), SpO_2 88–95%, $\text{FiO}_2 < 0.6$.
- ▶ **No mortality benefit**: surfactant, inhaled NO, β_2 -agonists, HFOV, statins, recruitment manoeuvres.
- ▶ Most ARDS deaths are due to **sepsis / multi-organ failure**, not hypoxaemia.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Acute Respiratory Distress Syndrome” and “Mechanical Ventilatory Support” (Berlin criteria, ARDSNet low-VT trial, evidence-grade recommendations table, management algorithm, ECMO classification, liberation/SBT).
- ▶ **Murray & Nadel’s Textbook of Respiratory Medicine, 7e** — “Acute Respiratory Distress Syndrome” (Berlin definition table, predicted-body-weight formulas, ARDSNet protocol, FACTT conservative fluid, DEXA-ARDS/ACURASYS/ROSE/PROSEVA/CESAR/EOLIA trials, driving pressure, permissive hypercapnia, long-term outcomes).
- ▶ **CMDT 2026** — “Pulmonary Disorders: Acute Respiratory Distress Syndrome” (current diagnostic essentials, conservative fluid targets, $\text{Hb} \geq 7$ g/dL, 2024 ATS corticosteroid guidance, ECMO salvage, prognosis).



Non resolving Pneumonia

Asked in: Paper III Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — *Non-resolving (non-responding) pneumonia* describes a clinical scenario in which a patient treated empirically for pneumonia fails to show the **expected clinical and/or radiographic improvement** within the anticipated time-frame. Two overlapping patterns are recognised: **non-responding pneumonia** (clinical improvement is not achieved — persistent fever and symptoms despite therapy) and **progressive pneumonia** (clinical deterioration to respiratory failure or septic shock). Radiographically, the term also covers *slowly resolving pneumonia*, where infiltrates persist beyond the expected resolution period despite adequate antibiotics. It is best regarded not as a single disease but as a **clinical syndrome** mandating a systematic search for resistant organisms, sequestered infection, an unexpected pathogen, or a non-infectious mimic.

Defining the problem — timelines and patterns

- ▶ **Expected normal response (CAP)**: with appropriate antibiotics a clinical response is usually evident within **24–48 h** (*pneumococcus*, *Legionella*); fever and leukocytosis settle in **2–4 days** in otherwise healthy patients; physical signs persist longer.

- ▶ **Radiographic clearance is the slowest variable** — 4–12 weeks, and is slower in the elderly, in underlying lung disease, and with certain pathogens (e.g. *Legionella* infiltrates may progress despite clinical improvement and take months to clear).
- ▶ A widely used working definition of *non-resolving pneumonia* is **failure of the infiltrate to clear by $\geq 50\%$ at 2 weeks or to clear completely by 4 weeks** despite ≥ 10 days of antibiotics (standard internal medicine; the corpus supports the 4–12-week clearance window).
- ▶ **Timing of reassessment:** evaluate the slow responder at **~ 72 h (day 3)** — or sooner if deteriorating. Earlier escalation is reserved for severe clinical deterioration or dramatic radiologic progression.

Pattern	Defining feature	Typical timing
Early treatment failure	Progressive deterioration / no response	< 72 h of therapy
Non-responding pneumonia	Persistent fever and symptoms, no improvement	Assessed at ≥ 72 h
Progressive pneumonia	Clinical deterioration $\rightarrow$ respiratory failure / septic shock	Any time
Slowly resolving pneumonia	Clinical improvement but infiltrate persists	Beyond 4–12 weeks

Causes / differential diagnosis (the core of the answer)

Causes are classified as **infectious, non-infectious, and of unknown origin**. In hospitalised CAP a specific infection is found in $\sim 40\%$ of non-responders, a non-infectious cause in $\sim 22\%$, and **no cause is identified in $\sim 30\%$** despite adequate treatment.

Category	Mechanism	Examples
Resistant / wrong-spectrum organism	Pathogen not covered or resistant to empirical drug	Drug-resistant <i>S. pneumoniae</i> ; MRSA / CA-MRSA; <i>P. aeruginosa</i> ($\sim 10\%$ of non-responding CAP, not covered unless a fluoroquinolone used); <i>Acinetobacter</i> ; carbapenemase-producing <i>Klebsiella</i>
Unexpected / unusual pathogen	Outside the CAP empirical spectrum	<i>M. tuberculosis</i> , <i>Nocardia</i> , endemic fungi, <i>Pneumocystis jirovecii</i> , anaerobes, protozoa, viruses
Sequestered / complicated focus	Antibiotic cannot reach organism	Empyema / complicated parapneumonic effusion, lung abscess, necrotizing pneumonia

Category	Mechanism	Examples
Metastatic / extrapulmonary infection	Seeding (commoner if bacteraemic)	Endocarditis, brain abscess, septic arthritis, pericarditis, meningitis; nosocomial superinfection
Inadequate therapy	Right diagnosis, wrong execution	Wrong drug, wrong dose/frequency, poor absorption/compliance
Host factors	Impaired response	Immunodeficiency (HIV), age, comorbidity, exaggerated or blunted inflammatory response
Non-infectious mimics	Disease that simulates pneumonia	Pulmonary embolism/infarction, pulmonary oedema, malignancy (esp. lepidic/"alveolar-cell" adenocarcinoma), bronchial obstruction, organizing pneumonia (COP/BOOP), eosinophilic pneumonia, hypersensitivity pneumonitis, drug-induced lung disease, pulmonary haemorrhage/vasculitis (e.g. granulomatosis with polyangiitis), sarcoidosis, radiation pneumonitis, connective-tissue disease, ARDS

The most frequent organisms in proven infectious non-response are ***S. pneumoniae*, *Legionella*, *P. aeruginosa* and *S. aureus*.**

Stepwise approach to evaluation

- ▶ **Re-take history and examine again** — epidemiologic clues (travel, occupational/animal exposure, TB contact, aspiration risk, immunosuppression, drug history) and reconsider the *original* diagnosis.
- ▶ **Biomarkers:** failure of **procalcitonin (PCT)** to fall after 3–4 days suggests inadequate response; high baseline PCT/CRP (and IL-6) independently predict poor response.
- ▶ **Repeat & extend microbiology:** new blood and sputum cultures; urinary antigens (*pneumococcus*, *Legionella*); respiratory-virus and SARS-CoV-2 testing; sputum AFB/molecular TB testing early in endemic settings or HIV.
- ▶ **Cross-sectional imaging** — **chest CT** is pivotal: detects empyema, abscess, cavitation, endobronchial obstruction, lymphadenopathy, and patterns suggesting a specific aetiology —
 - *halo sign* (nodule + ground-glass rim) → **invasive aspergillosis / mucormycosis**;
 - diffuse ground-glass → **PJP**;

- nodules/masses $\pm$ cavitation $\rightarrow$ **Nocardia**, TB, Q fever;
- consider CT-pulmonary angiography to exclude pulmonary embolism and endobronchial lesions.
- ▶ **Bronchoscopy** with BAL + **protected specimen brush** (sensitivity $\sim$ 40% in non-responding CAP) for culture, DFA and nucleic-acid testing; allows direct airway inspection for **obstruction** (tumour, foreign body) and **transbronchial / endobronchial biopsy** when a non-infectious cause (malignancy, COP, vasculitis) is suspected.
- ▶ **Thoracentesis** for any significant pleural effusion — drainage is indicated if fluid pH < 7.2 , glucose < 2.2 mmol/L, LDH > 1000 U/L, or organisms are seen/cultured (complicated effusion / empyema).
- ▶ **Escalate antibiotics** only after re-sampling — broaden to cover resistant pneumococcus, *P. aeruginosa*, MRSA and anaerobes as dictated by risk; add antifungal/anti-TB cover when the clinical scenario supports it; transfer to higher-level care if deteriorating.

Key complicating entities to exclude

- ▶ **Lung abscess** — necrosis/cavitation (dominant cavity > 2 cm). **Primary** ($\sim$ 80%) from aspiration of anaerobes/microaerophilic streptococci, favouring **dependent segments (posterior segments of upper lobes, superior segments of lower lobes), right $>$ left**; *putrid* (foul) sputum $\approx$ anaerobic. **Secondary** abscess implies post-obstructive (tumour, foreign body) or immunocompromise. Treat with **clindamycin** (600 mg IV tds $\rightarrow$ 300 mg PO qds) or a β -lactam/ β -lactamase inhibitor for 3–4 up to $\sim$ 14 weeks; *metronidazole alone is inadequate*. Cavities > 6 –8 cm, or non-response, may need drainage/surgery.
- ▶ **Pulmonary tuberculosis** — a classic “great mimic” of non-resolving consolidation; obtain sputum AFB, NAAT (e.g. cartridge-based) and culture early, especially with weight loss, upper-lobe disease, cavitation or HIV.
- ▶ **Bronchogenic carcinoma / post-obstructive pneumonia** — suspect strongly with **recurrence in the same segment**, in smokers, or non-clearing infiltrate; bronchoscopy $\pm$ CT mandatory.
- ▶ **Lemierre’s syndrome** — *Fusobacterium necrophorum* oropharyngeal infection with septic jugular thrombophlebitis and cavitating septic emboli.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Algorithm** — “Approach to the non-resolving pneumonia” (vertical flowchart). Labels: *Empirical Rx for pneumonia $\rightarrow$ Reassess at 72 h (day 3) $\rightarrow$ branch into Non-responding vs Progressive $\rightarrow$ Re-history & examine + reconsider diagnosis $\rightarrow$ Repeat cultures, PCT/CRP, urinary antigens, TB/viral tests $\rightarrow$ Chest CT $\rightarrow$ Bronchoscopy (BAL + PSB $\pm$ biopsy) / Thoracentesis $\rightarrow$ outcome boxes: Resistant/unexpected organism, Empyema/abscess (drain), Non-infectious mimic (PE, malignancy, COP, vasculitis), Inadequate therapy.*

- ▶ **Labelled chest CT of a lung abscess:** thick-walled cavity, **air–fluid level**, surrounding consolidation, located in a dependent (posterior upper / superior lower lobe) segment — with a small inset contrasting **abscess vs empyema** (lenticular pleural collection, split-pleura sign).

Clinical / Diagnostic significance

- ▶ Re-labelling a “treatment failure” correctly prevents both **antibiotic over-escalation** and **missed malignancy/TB/PE** — the commonest avoidable errors.
- ▶ **Empyema and abscess** are the most frequent infectious complications requiring a *procedure*, not just a drug change — always image the pleura and tap significant effusions.
- ▶ A **follow-up chest radiograph** at ~4–6 weeks is recommended after hospitalised CAP; **relapse or recurrence in the same bronchopulmonary segment** demands exclusion of an underlying **neoplasm or focal bronchiectasis**.
- ▶ Older patients and those with COPD, diabetes, alcoholism, multilobar disease or bacteraemia resolve more slowly — a *slowly resolving* course in this group may still be benign and need only observation with serial imaging rather than invasive work-up.

High-yield exam pointers

- ▶ **Reassess the non-responder at 72 h (day 3);** wait that long unless rapidly deteriorating.
- ▶ Causes = **infectious (40%) / non-infectious (22%) / unknown (≈30%)**.
- ▶ Commonest infectious culprits: **pneumococcus*, *Legionella*, *P. aeruginosa*, *S. aureus***; *P. aeruginosa* ≈ 10%* of non-responders.
- ▶ Must-exclude non-infectious mimics: **PE, malignancy, organizing pneumonia, eosinophilic pneumonia, vasculitis, pulmonary oedema**.
- ▶ **CT chest + bronchoscopy (BAL/PSB)** are the key escalation investigations; BAL sensitivity ~40%.
- ▶ Drain a parapneumonic effusion if **pH < 7.2, glucose < 2.2 mmol/L, LDH > 1000 U/L** or organisms present.
- ▶ **Lung abscess:** anaerobic, dependent segments, right > left; **clindamycin** first-line, **metronidazole alone fails**; cavity >6–8 cm → consider drainage/surgery.
- ▶ **Recurrence in the same segment** → think **carcinoma / focal bronchiectasis**. TB and HIV must be actively excluded.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Pneumonia” (Failure to Improve, Complications, Follow-up) and “Lung Abscess.”

- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Community-Acquired Pneumonia” (Nonresponding Pneumonia / Treatment Failure; infectious vs non-infectious causes; diagnostic evaluation, biomarkers, imaging and bronchoscopy).
- **CMDT 2026** — “Pulmonary Disorders” (Pneumonia; Anaerobic Pneumonia & Lung Abscess — drainage and surgical indications).

Coverage note: The corpus richly covers the syndrome, its causes, evaluation and the abscess/empyema complications. The quantitative radiographic criterion (“<50% clearance at 2 weeks / clearance by 4 weeks”) is stated as standard internal medicine; the corpus directly supports the 4–12-week clearance window and the ≥72-h reassessment point rather than that exact percentage cut-off.



Obesity and Obstructive Sleep Apnoea

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — **Obesity** is a chronic, heterogeneous disorder of excess body fat conventionally graded by **body mass index** ($\text{BMI} = \text{weight kg} / \text{height m}^2$), leading to multiple metabolic, mechanical and cardiovascular complications. **Obstructive sleep apnoea (OSA)** is a sleep-related breathing disorder defined by recurrent episodes of pharyngeal collapse during sleep causing apnoeas/hypopnoeas, intermittent hypoxaemia and arousals, with daytime sleepiness and impaired function. The two are tightly linked: obesity is the single most important modifiable risk factor for OSA, and OSA in turn amplifies obesity's cardio-metabolic harm — hence they are best understood and answered together.

Classification of obesity (WHO / BMI) and abdominal adiposity

- BMI correlates with body fat and disease risk and is the standard screening/population tool; its limitation is that it measures **size, not composition or fat distribution**. Lower thresholds apply to the Asia-Pacific (South Asian) population, who are metabolically at risk at lower weights.

Classification	BMI (kg/m ²)	Obesity class	Disease risk
Underweight	<18.5	—	—
Healthy weight	18.5–24.9	—	—
Overweight	25.0–29.9	—	Increased
Obesity	30.0–34.9	I	High
Obesity	35.0–39.9	II	Very high
Extreme obesity	≥40	III	Extremely high

- ▶ **Waist circumference** (surrogate for visceral fat, measured horizontally above the iliac crest in those with BMI ≤ 35) independently predicts metabolic syndrome, diabetes and CVD. Ethnic cut-points: **Europeans** men >94 cm / women >80 cm; **South Asians & Chinese** men >90 cm / women >80 cm.
- ▶ **Functional/clinical staging**: the **AACE/ACE** system stages by BMI *plus* adiposity-related complications — Stage 0 (no complication), Stage 1 (mild–moderate complication, e.g. *OSA with AHI 5–30 and mild symptoms*), Stage 2 (severe complication, e.g. *OSA with symptoms or AHI >30*). The **Edmonton Obesity Staging System (EOSS)** grades 0–4 across medical, functional and psychological domains independent of BMI.

Obesity → OSA: pathophysiological link

- ▶ During inspiration intraluminal pharyngeal pressure becomes negative (a “suction” force); because the pharynx has **no bony/cartilaginous support**, patency depends on **pharyngeal dilator muscle** tone, which falls at sleep onset — producing transient collapse (**apnoea**) or near-collapse (**hypopnoea**).
- ▶ **Obesity narrows and collapses the airway by several mechanisms**: (1) deposition of upper-airway/parapharyngeal **fat** narrowing the pharyngeal lumen; (2) reduced **chest-wall compliance** and lower **lung volumes**, causing loss of caudal tracheal traction on the pharynx (worst when supine and obese); (3) **android (central) obesity** depositing abdominal and upper-airway fat.
- ▶ Quantitatively: **≈ 40 – 60% of OSA is attributable to excess weight**; obese individuals carry a **fourfold or greater risk** of OSA; a **10% weight gain raises the AHI by $>30\%$** , and weight loss (notably after bariatric surgery) can markedly reduce severity.
- ▶ Collapse sites: **soft palate (most common)**, tongue base, lateral pharyngeal walls and/or epiglottis. Contributory factors include high **nasal resistance**, **retrognathia/micrognathia**, an unstable ventilatory control loop (high CO_2 sensitivity), and a low or high **arousal threshold**.
- ▶ Other (non-obesity) risk factors: **male sex** (twofold higher prevalence), **older age**, post-menopause, family history, adenotonsillar hypertrophy (children), and endocrine disease (**acromegaly, hypothyroidism**).

Definition, severity grading and clinical features of OSA

- ▶ **Diagnosis** requires either (1) symptoms of nocturnal breathing disturbance (snoring, snorting, gasping, witnessed pauses) impairing quality of life, OR unexplained daytime sleepiness/fatigue — **plus ≥ 5 obstructive events/hour** on a sleep study; OR (2) an **AHI $\geq 15/\text{h}$ even without symptoms**.
- ▶ Each event is a ≥ 10 s reduction in breathing: **Apnea** = cessation of airflow ≥ 10 s; **Hypopnoea** = $\geq 30\%$ airflow reduction ≥ 10 s with a $\geq 3\%$ desaturation or arousal; **RERA** = increased respiratory effort terminated by arousal without meeting hypopnoea criteria.

Severity (AHI = apnoeas + hypopnoeas per hour of sleep)	Grade
5–14 events/h	Mild OSAHS
15–29 events/h	Moderate OSAHS
≥30 events/h	Severe OSAHS

- ▶ **Symptoms:** loud habitual **snoring** (commonest; its absence does not exclude OSA), gasping/choking arousals, **excessive daytime sleepiness** (men) or **fatigue** (women preferentially), unrefreshing sleep, nocturia, morning headache, dry mouth, poor concentration, irritability and mood disturbance.
- ▶ **Signs:** central (visceral) obesity with large **neck and waist circumference**, hypertension, crowded oropharynx (enlarged tongue, low bulky soft palate/uvula, large tonsils, high-arched palate), retro-/micrognathia, nasal obstruction. *Cor pulmonale suggests a coexisting cardiopulmonary disorder — OSA alone does not cause right-heart failure.*

Diagnosis and investigations

- ▶ **In-laboratory polysomnography (PSG)** is the **gold standard**; a negative in-lab PSG usually rules out OSA. **Home sleep apnoea testing** (respiratory + cardiac channels) is a cost-effective alternative, but a negative home study with high pretest probability should be followed by PSG.
- ▶ Screening questionnaires (e.g. **STOP-Bang**) evaluating snoring, observed apnoeas and sleepiness aid case-finding, enhanced by considering male sex, obesity and hypertension.
- ▶ Supportive findings: “**non-dipping**” overnight blood-pressure pattern; secondary erythrocytosis (elevated haemoglobin) with severe nocturnal hypoxaemia; waking hypoxaemia/hypercarbia points to coexisting cardiopulmonary disease or **hypoventilation syndrome**. A **multiple sleep latency test / maintenance of wakefulness test** quantifies sleepiness and helps separate OSA from narcolepsy.
- ▶ In obesity, baseline work-up: **fasting lipid profile, fasting glucose/HbA1c, chemistry panel, blood pressure**, and screening for secondary causes (hypothyroidism, Cushing’s, PCOS, hypothalamic disease) and obesogenic drugs.

Health consequences and comorbidities (overlapping burden)

- ▶ **Cardiovascular/metabolic (OSA):** resistant and nocturnal **hypertension** (sympathetic + RAAS activation, non-dipping), coronary artery disease, **heart failure** (HFrEF and HFpEF), **atrial and ventricular arrhythmias / AF**, stroke, type 2 diabetes/insulin resistance, premature death and increased cancer risk. CPAP lowers 24-h ambulatory BP modestly (~2–4 mmHg, greater if high AHI, sleepy or resistant hypertension).
- ▶ **Obesity complications** (shared): type 2 diabetes, dyslipidaemia, metabolic syndrome, hypertension, HFpEF/diastolic dysfunction, AF, **MASLD/NASH→cirrhosis**, GERD, gallstones,

PCOS and male central **hypogonadism**, osteoarthritis and gout, obesity-related glomerulopathy, **obstructive sleep apnoea and obesity-hypoventilation (Pickwickian) syndrome**, idiopathic intracranial hypertension, and several cancers (a 5 kg/m² rise in BMI raises cancer mortality ~10%).

- **Functional:** OSA causes a two-fold rise in occupational accidents and a two- to three-fold rise in motor-vehicle crashes — counsel against **drowsy driving**.

Management

- **Weight loss is the unifying first-line intervention** — even modest loss reduces AHI and metabolic risk; OSA may improve substantially after bariatric surgery.
- **Obesity — lifestyle:** caloric deficit **500–750 kcal/d** ($\approx$ 1200–1500 kcal/d women, 1500–1800 kcal/d men) for ~1–2 lb/week; realistic target **8–10% loss over 6 months**; **$\geq$ 150 min/week moderate (or 75 min vigorous) aerobic activity** (>300 min to sustain loss); plus behavioural therapy (self-monitoring, stimulus control, cognitive restructuring).
- **Obesity — pharmacotherapy** (BMI $\geq$ 30, or $\geq$ 27 with comorbidity). Placebo-subtracted 1-year weight loss:

Drug	Mechanism	Weight loss (placebo-subtracted)
Orlistat 120 mg tid	GI lipase inhibitor (blocks ~30% dietary fat absorption)	~4.4%
Phentermine/topiramate	Sympathomimetic + GABA modulation	~8.0%
Naltrexone SR/bupropion SR	Opioid antagonist + DA/NE reuptake inhibitor (POMC activation)	~5.1%
Liraglutide 3.0 mg SC daily	GLP-1 receptor agonist	~5.4%
Semaglutide 2.4 mg SC weekly	GLP-1 receptor agonist (2nd-generation)	~12.5%
Tirzepatide up to 15 mg SC weekly	Dual GLP-1/GIP receptor agonist	~17.8%

- *GLP-1/dual agonists are contraindicated with personal/family history of medullary thyroid cancer or MEN-2; semaglutide also reduced major adverse cardiovascular events by 20% (SELECT) and improved HFpEF symptoms (STEP-HFpEF).*
- **Bariatric surgery:** for BMI $\geq$ 40, or $\geq$ 35 with **comorbidities**. Procedures — restrictive (adjustable gastric banding, **sleeve gastrectomy**) and restrictive-malabsorptive (**Roux-en-Y gastric bypass**, biliopancreatic diversion $\pm$ duodenal switch); bypass yields ~28–33% total body-weight loss and reduces overall mortality (OR 0.55) and cardiovascular death (OR 0.58), with marked improvement in OSA and type 2 diabetes.

► OSA-specific therapy:

- **General/behavioural:** weight loss, optimise sleep (7–9 h) and schedule, avoid the **supine position**, treat nasal allergy, eliminate **alcohol within 3 h of bedtime**, minimise **opioids/sedatives**.
- **CPAP** — *the standard therapy with the highest level of evidence*; a pneumatic splint maintaining airway patency; auto-titrating (APAP) devices avoid titration studies; adherence ~50–80% and is the key determinant of benefit (improves sleepiness, mood, quality of life, BP, insulin sensitivity). Side-effects (nasal congestion, claustrophobia, aerophagia) are managed by humidification, mask change and pressure adjustment.
- **Oral appliances (mandibular advancement devices)** — reduce AHI by $\geq 50\%$ in two-thirds; best for mild–moderate OSA or CPAP intolerance (caution: TMJ pain, tooth movement).
- **Surgery** — **uvulopalatopharyngoplasty (UPPP)** (commonest, limited as a standalone procedure, often “multilevel”), and **bariatric surgery** for obese patients; less efficacious than CPAP.
- **Upper-airway (hypoglossal nerve) neurostimulation** — for CPAP failure; inclusion AHI 15–65 and BMI < 35 .
- **Positional therapy**, and **GLP-1 agonists/weight-loss drugs** under active investigation (liraglutide shows small AHI effect; tirzepatide in trials). **No FDA-approved drug for OSA currently.**

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Sagittal upper-airway diagram (OSA collapse sites):** label Soft palate (most common site), Uvula, Tongue base, Lateral pharyngeal walls, Epiglottis, Pharyngeal dilator muscle, Nasal passage (resistance) — show collapse during sleep.
- **Polysomnography apnoea tracing:** label channels Nasal/thermistor airflow (flat = apnoea), Chest and Abdomen effort showing paradoxical (out-of-phase) movement, SaO₂ desaturation, EEG arousal, with a bracket marking ≥ 10 s event.

Clinical / Diagnostic significance

- Suspect and screen OSA in every obese patient with snoring, daytime sleepiness, hypertension (especially resistant/non-dipping), type 2 diabetes, AF or stroke — a large fraction of OSA remains undiagnosed.
- AHI defines and grades disease; PSG is confirmatory; STOP-Bang stratifies pretest probability.
- Weight loss is disease-modifying for both conditions; CPAP plus weight reduction is the cornerstone of moderate–severe OSA.
- Pre-operative recognition matters: obese OSA patients are at higher peri-operative and sedation-related risk.

High-yield exam pointers

- ▶ AHI = apnoeas + hypopnoeas per hour; Mild 5–14, Moderate 15–29, Severe ≥ 30 .
- ▶ Diagnose OSA at AHI ≥ 5 with symptoms or AHI ≥ 15 without symptoms.
- ▶ 40–60% of OSA is due to excess weight; obese persons have $\geq 4\times$ risk; 10% weight gain $\rightarrow >30\%$ rise in AHI.
- ▶ Soft palate is the commonest collapse site; PSG is the gold-standard test.
- ▶ CPAP = highest-evidence therapy; lowers ambulatory BP by $\sim 2\text{--}4$ mmHg; adherence $\sim 50\text{--}80\%$.
- ▶ Obesity classes: I 30–34.9, II 35–39.9, III (extreme) ≥ 40 ; South Asian waist cut-offs men >90 / women >80 cm.
- ▶ Bariatric surgery: BMI ≥ 40 , or ≥ 35 with comorbidity; reduces all-cause mortality (OR 0.70).
- ▶ Weight-loss drug efficacy ranking: tirzepatide ($\approx 18\%$) $>$ semaglutide ($\approx 12.5\%$) $>$ Phen/TPM ($\approx 8\%$) $>$ liraglutide/Nal-Bup $\approx$ orlistat.
- ▶ OSA independently increases hypertension, AF, HF, stroke, diabetes and motor-vehicle crash risk.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 308 "Sleep Apnea" (Wellman, Gottlieb, Redline) and Ch 414 "Evaluation and Management of Obesity" (Kushner). Coverage note: STOP-Bang and the Epworth Sleepiness Scale, and the obesity-hypoventilation/Pickwickian and "non-dipping BP" terms, are standard textbook internal medicine — STOP-Bang and non-dipping pattern are referenced in Ch 308; the Epworth scale itself is not named in the provided text but is universally accepted. Drug doses/efficacy and bariatric data are taken verbatim from Ch 414 Table 414-5 and text.



Obesity Hypoventilation Syndrome

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — Obesity hypoventilation syndrome (OHS), historically the *Pickwickian syndrome*, is defined by the triad of (1) **obesity** (body mass index, BMI ≥ 30 kg/m²), (2) **chronic daytime alveolar hypoventilation** — awake arterial PaCO₂ ≥ 45 mmHg at sea level — and (3) **sleep-disordered breathing**, after exclusion of other causes of hypercapnia (severe COPD, restrictive chest-wall/neuromuscular disease, hypothyroidism, drug-induced hypoventilation). It is therefore a **diagnosis of exclusion** in an obese hypercapnic patient. In the normal lung PaCO₂ is held between 37–43 mmHg; OHS represents a failure of alveolar ventilation to keep pace with CO₂ production despite an *intrinsically normal lung*.

Epidemiology and risk factors

- ▶ No population-based prevalence study exists, but estimates suggest OHS affects up to **~0.4% of US adults** (≈ 1 in 263), and the burden is rising in parallel with the global obesity epidemic.
- ▶ **Obstructive sleep apnoea (OSA) coexists in ~90% of OHS patients**, and close to 70% have **severe OSA** (apnoea–hypopnoea index, AHI $>30/h$). A minority (~10%) hypoventilate *without* significant OSA (pure “sleep hypoventilation” phenotype).
- ▶ Recognised risk factors: **severe obesity** (BMI $>40 \text{ kg/m}^2$) and **severe OSA** (AHI $>30/h$); greater waist/neck circumference; the syndrome is frequently *under-recognised* and often first diagnosed during an episode of acute-on-chronic hypercapnic respiratory failure.

Pathophysiology — a multifactorial “load–drive” imbalance

OHS arises when the **mechanical load** on the respiratory pump outstrips both **respiratory muscle capacity** and a **blunted central drive**. Three interacting mechanisms operate:

Domain	Derangement in OHS
Excess mechanical load	Mass loading of chest wall and abdomen $\downarrow$ respiratory-system compliance; FRC reset to a lower, stiffer part of the volume–pressure curve ; $\uparrow$ airway resistance and expiratory flow limitation (worse supine). Work of breathing up to ~250% of normal (vs ~60% in simple obesity); oxygen cost of breathing rises ~10-fold (vs 5-fold in simple obesity).
Blunted central drive	Unlike <i>eucapnic</i> obesity (where drive is normal/increased to overcome the load), in OHS the ventilatory and occlusion-pressure (P0.1) responses to hypoxia and hypercapnia are reduced . Drive is <i>not</i> genetically low (responses are normal in first-degree relatives) — chemoreceptors appear “reset” by chronic hypercapnia/hypoxaemia and by leptin resistance .
Leptin / neurohumoral	Leptin (an adipocyte hormone) normally stimulates ventilation; serum leptin is <i>high</i> in obesity, so central leptin resistance is proposed as a key contributor to the diminished ventilatory responsiveness and CO_2 retention.

- ▶ **Rapid, shallow breathing pattern** (higher frequency, lower tidal volume than simple obesity) minimises elastic work but **increases dead-space fraction**, worsening alveolar hypoventilation and CO_2 retention.
- ▶ **Gas exchange**: hypoventilation alone causes hypoxaemia with a *normal* A–a gradient; superimposed **V/Q mismatch and shunt from premature airway closure** widen the A–a gradient and deepen hypoxaemia, which is **worse supine**.

- ▶ **Renal compensation:** chronic respiratory acidosis drives **bicarbonate retention** (metabolic compensation) — an elevated serum HCO_3^- is the bedside footprint of chronic hypoventilation.
- ▶ **Reversibility:** central drive defects **improve once sleep-disordered breathing is treated** (CPAP/NIV) or weight is lost — confirming that blunted responsiveness is a **consequence, not the primary cause**, of OHS.

Clinical features

- ▶ **Sleep-related:** loud habitual snoring, witnessed apnoeas, **excessive daytime somnolence**, poor-quality unrefreshing sleep, **early-morning headaches** (from nocturnal CO_2 retention).
- ▶ **Cardiorespiratory:** exertional **dyspnoea**, orthopnoea, fatigue; signs of **cor pulmonale** — raised JVP, peripheral oedema, loud P_2 (chronic hypoxaemia/hypercapnia → pulmonary vasoconstriction → **pulmonary hypertension and right heart failure**).
- ▶ **Examination:** central obesity, plethora/cyanosis, possible secondary erythrocytosis (polycythaemia from chronic hypoxaemia), features of metabolic syndrome.
- ▶ **Acute presentation:** decompensated **acute-on-chronic hypercapnic respiratory failure** with CO_2 narcosis (drowsiness, asterixis, papilloedema), often precipitated by sedatives, infection or an acute cardiac event.

Diagnosis and investigations

Diagnosis follows a stepwise evaluation of daytime hypercapnia (history/exam → PFTs + chest imaging → BMI → polysomnography), excluding parenchymal, chest-wall, neuromuscular and drive disorders first.

Test	Expected finding / role
Arterial blood gas (ABG)	Diagnostic hallmark — $\text{PaCO}_2 \geq 45$ mmHg with near-normal pH (compensated chronic respiratory acidosis); hypoxaemia common. A <i>normal</i> pH distinguishes chronic from acute hypoventilation.
Serum bicarbonate	Sensitive screen: $\text{HCO}_3^- < 27$ mmol/L makes OHS very unlikely; $\text{HCO}_3^- \geq 27$ mmol/L should trigger an ABG to confirm hypercapnia.
Polysomnography (PSG)	Confirms and grades OSA (AHI) and detects nocturnal hypoventilation ; essential as ~90% have OSA.
Pulmonary function tests	Restrictive pattern with reduced ERV/FRC, <i>normal</i> FEV_1/FVC ; used to exclude obstructive/restrictive lung disease as the cause of hypercapnia.
CXR / CT, ECG, echocardiography	Exclude parenchymal disease; assess for RV hypertrophy / pulmonary hypertension / cor pulmonale.

Test	Expected finding / role
TFTs, drug history	Exclude hypothyroidism and sedative/opioid-induced hypoventilation .
FBC	Secondary erythrocytosis supports chronic hypoxaemia.

- **Screening questionnaires** for OSA (Epworth Sleepiness Scale, *Berlin*, **STOP-Bang**) raise suspicion but are insufficiently specific — PSG remains the standard.
- *Distinguish from* **congenital central hypoventilation syndrome** (**Ondine's curse**, **PHOX2B mutation**) and primary alveolar hypoventilation, where the lungs and habitus are normal and drive is absent.

Management

Treatment targets *all* contributors — sleep-disordered breathing, the mechanical load (weight), and comorbidities.

Modality	Detail
Positive airway pressure (first line)	CPAP is first-line for OHS with concomitant severe OSA — it corrects upper-airway obstruction and improves daytime PaCO ₂ /PaO ₂ in >half of patients. <i>*RCT evidence (e.g. Pickwick/Masa, Lancet 2019) shows CPAP and NIV are broadly equivalent*</i> for long-term PaCO ₂ , symptoms, cardiovascular and overall mortality in OHS + severe OSA.
Non-invasive ventilation / BiPAP	Preferred when hypoventilation predominates or there is no significant OSA , in acute decompensated OHS , and when hypercapnia persists despite adherent CPAP or obstructive events persist at maximum CPAP (20 cmH ₂ O). Use BiPAP with a backup rate (ST mode) or volume-assured pressure support ; BiPAP-spontaneous (no backup) is reserved for CPAP-intolerant patients.
Weight reduction	Substantial weight loss (≈20–25% of body weight) can normalise PaCO₂ . Diet, activity, behavioural therapy; bariatric surgery gives the most durable loss (indicated BMI ≥40, or ≥35 with serious comorbidity) and improves comorbidities. PaO ₂ rises ~1 mmHg per 5 kg lost.
Supplemental oxygen	Use cautiously for persistent hypoxaemia/pulmonary hypertension — may worsen hypercapnia even at low flow; <i>not</i> a substitute for ventilatory support.

Modality	Detail
Avoid respiratory depressants	Sedative-hypnotics, opioids and alcohol are contraindicated/avoided.
Respiratory stimulants	Medroxyprogesterone, acetazolamide improve $\text{PaCO}_2/\text{PaO}_2$ but are poorly evidenced, carry side-effects, and must not replace PAP or weight loss.
Comorbidities / perioperative	Aggressively treat decompensating events (ACS, PE, pneumonia, heart failure). OHS patients have high perioperative risk (respiratory failure, re-intubation, heart failure) — recognition is a key safety measure.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ “Load vs Strength” balance diagram (Harrison Fig 307-1B): a beam/see-saw labelled — *Respiratory load* (chest-wall elastic load, **Obesity**, abdominal distension, lung resistive load) on one side **greater than** *Respiratory muscle strength + Respiratory drive*; arrow to “Alveolar hypoventilation $\rightarrow \uparrow \text{PaCO}_2$ ”. Add the three OHS contributors as input arrows: **OSA, blunted central drive (leptin resistance), increased work of breathing**.
- ▶ Obesity volume–pressure curve (Murray Fig 131.13): label axes **Volume (y) vs Pressure cmH_2O (x)**; show CW, L, RS curves; mark FRC reset to a lower, less compliant point and TLC, illustrating tidal breathing on the stiff portion of the curve.

Clinical / Diagnostic significance

- ▶ OHS confers **higher morbidity and mortality** than equally obese eucapnic patients — driven by pulmonary hypertension, cor pulmonale, cardiovascular disease and recurrent respiratory failure; effective PAP therapy reduces this.
- ▶ Always **measure an ABG in an obese, sleepy, hypercapnic-appearing patient** with a raised serum bicarbonate — OHS is frequently missed until a crisis.
- ▶ In acute decompensation, **NIV is the cornerstone**; intubate for failure, but plan early NIV weaning because these patients are difficult to extubate.
- ▶ **Treating OSA/hypoventilation can reverse the “blunted drive”** — demonstrating the syndrome’s potential reversibility and the priority of CPAP/NIV plus weight loss.

High-yield exam pointers

- ▶ **Definition triad**: BMI ≥ 30 + awake $\text{PaCO}_2 \geq 45$ mmHg + sleep-disordered breathing, **excluding other causes** = OHS (Pickwickian).
- ▶ **~90% have OSA, ~70% severe OSA**; severe obesity (BMI > 40) and AHI $> 30/\text{h}$ are risk factors.
- ▶ Serum $\text{HCO}_3^- < 27$ mmol/L makes OHS unlikely; ≥ 27 mmol/L $\rightarrow$ **do an ABG**.
- ▶ ABG shows **chronic compensated respiratory acidosis** ($\uparrow \text{PaCO}_2$, near-normal pH, $\uparrow \text{HCO}_3^-$).

- ▶ Pathophysiology = ↑mechanical load + blunted central drive + leptin resistance + OSA; work of breathing up to ~250% of normal.
- ▶ CPAP first-line if severe OSA; NIV (BiPAP-ST/VAPS) if hypoventilation predominates, no OSA, or acute decompensation. CPAP and NIV broadly equivalent (*Pickwick* trial).
- ▶ Weight loss of 20–25% can normalise PaCO₂; bariatric surgery most durable.
- ▶ Oxygen can worsen hypercapnia; avoid sedatives/opioids/alcohol; respiratory stimulants are adjuncts only.
- ▶ Complications: pulmonary hypertension, cor pulmonale, secondary polycythaemia, high perioperative risk.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Disorders of Ventilation” (Hypoventilation; Obesity Hypoventilation Syndrome; diagnostic algorithm Fig 307-2) and “Sleep Apnea.”
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “The Respiratory System and Chest Wall Diseases” (obesity respiratory mechanics, work/oxygen cost of breathing, control of breathing, leptin, gas exchange, treatment).
- ▶ **CMDT 2026** — “Pulmonary Disorders: Obesity-Hypoventilation Syndrome (Pickwickian Syndrome)” — diagnostic criteria and current management.



Obstructive Sleep Apnea

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, characterised by recurrent episodes of complete (apnea) or partial (hypopnea) collapse of the **pharyngeal airway during sleep**, occurring despite persistent respiratory effort. Each event terminates in arousal and/or oxyhemoglobin desaturation, producing sleep fragmentation, intermittent hypoxemia and sympathetic surges. The term **obstructive sleep apnea/hypopnea syndrome (OSAHS)** denotes OSA accompanied by symptoms, classically excessive daytime sleepiness (EDS). Diagnosis rests on objective sleep study quantification using the **apnea-hypopnea index (AHI)**: ≥5 events/h with symptoms, or ≥15 events/h irrespective of symptoms.

Pathophysiology

- ▶ The pharynx lacks rigid bony/cartilaginous support, so patency depends on **pharyngeal dilator muscle** tone (genioglossus the principal). During inspiration, intraluminal pressure becomes negative (“suction”); dilator activation must counteract this.

- ▶ At **sleep onset**, neuromuscular output to dilators falls. In a person with an anatomically narrow/collapsible airway, this transient loss of compensation causes pharyngeal collapse (apnea) or near-collapse (hypopnea). Common collapse sites: **soft palate (most common)**, **tongue base**, **lateral pharyngeal walls**, and **epiglottis**.
- ▶ Collapse is worst in **REM sleep** (lowest skeletal-muscle tone) and in the **supine position** (gravity). Low lung volume in recumbency/obesity reduces caudal tracheal traction, decreasing pharyngeal-wall stiffness.
- ▶ **Starling resistor model** — collapsibility is expressed as the **critical closing pressure (Pcrit)**; a more negative Pcrit = less collapsible airway: normal < -10 cmH₂O, non-apneic snoring -10 to -5 , obstructive hypopnea -5 to 0 , obstructive apnea > 0 cmH₂O.
- ▶ **Non-anatomic (“ventilatory control”) traits** also contribute: high loop gain (oversensitive chemoresponsiveness to CO₂ causing unstable breathing), a low arousal threshold (premature awakening prevents dilator compensation), and poor dilator muscle responsiveness. These define individual OSA endotypes/phenotypes.

Predisposing risk factors

- ▶ **Obesity** — the dominant modifiable factor; accounts for ~40–60% of cases. A 10% weight gain raises AHI by ~30% and confers a sixfold risk of developing AHI ≥ 15 ; obese persons have ≥ 4 -fold risk.
- ▶ **Male sex** (2–3× more prevalent; android fat distribution, longer/more collapsible pharynx); **older age**; **postmenopausal** state in women (loss of protective sex-hormone effect on ventilatory drive).
- ▶ **Craniofacial**: retrognathia, micrognathia, high-arched palate; genetic syndromes — *Down syndrome*, *Treacher-Collins*, *Pierre-Robin sequence*.
- ▶ **Adenotonsillar hypertrophy** (chief cause in children, peak age 3–8 yr), **macroglossia**, nasal obstruction (septal deviation, polyps).
- ▶ **Endocrine**: hypothyroidism (25–35%), acromegaly (~70% have SDB), PCOS; also **family history** (first-degree relative risk $\sim 2\times$), East-Asian ancestry (craniofacial), alcohol, sedative-hypnotics and opioids, and smoking.

Clinical features

Nocturnal symptoms	Daytime symptoms
Loud habitual snoring , witnessed apneas, gasping/choking, nocturnal restlessness/diaphoresis, nocturia , GERD, morning headache, unrefreshing sleep, insomnia (more in women)	Excessive daytime sleepiness (cardinal), fatigue, impaired concentration/memory, irritability, mood/depressive symptoms, reduced libido/impotence

- ▶ **Physical findings**: central obesity, large **neck circumference**, hypertension; crowded oropharynx with **Mallampati class III–IV**, low-lying soft palate, bulky uvula, enlarged tonsils, macroglossia, retro-/micrognathia, nasal obstruction.

- ▶ Sex differences: women report more insomnia/fatigue/depression and less heavy snoring; apneas shorter and REM-predominant — a cause of under-recognition.

Diagnosis and investigations

- ▶ **Screening tools** (estimate pretest probability; sensitive but not specific): **STOP-Bang** (Snoring, Tiredness, Observed apnea, Pressure/HTN, BMI >35, Age >50, Neck >40 cm, male Gender), Berlin and NoSAS questionnaires. The **Epworth Sleepiness Scale** quantifies sleepiness (8 situations, 0–3 each; **score ≥11 = excessive sleepiness**).
- ▶ **Polysomnography (PSG)** is the **gold standard** (Level 1, attended, in-laboratory): records EEG, EOG, chin/leg EMG, ECG, oronasal airflow (thermistor + nasal pressure), thoraco-abdominal effort bands, oximetry, body position, snoring. **Home sleep apnea testing (Level 3)** is acceptable for high-pretest-probability patients without major comorbidity; a negative home study in a high-probability patient should be followed by PSG.
- ▶ **Respiratory event scoring (AASM)**:

Event	Definition
Apnea	≥90% fall in airflow ≥10 s; <i>obstructive</i> = effort persists (thoraco-abdominal paradox), <i>central</i> = effort absent, <i>mixed</i> = central then obstructive
Hypopnea	≥30% airflow reduction ≥10 s with ≥3% desaturation or an arousal (def 1A); or ≥4% desaturation (def 1B)
RERA	Increasing effort/flow-limitation terminating in arousal, not meeting hypopnea criteria

- ▶ **AHI** = (apneas + hypopneas)/hour of sleep; **RDI** adds RERAs. Severity grading:

Severity	AHI (events/h)
Normal	<5
Mild	5–14
Moderate	15–29
Severe	≥30

- ▶ Adjuncts: serum TSH/FT₄ (exclude hypothyroidism); erythrocytosis from chronic hypoxemia; ABG normal in pure OSA (waking hypercapnia suggests **obesity hypoventilation syndrome [OHS]** — BMI >30 with daytime PaCO₂ >45 mmHg; OSA coexists in ~90%). Overnight BP often shows a “**non-dipping**” pattern. MSLT/MWT help distinguish narcolepsy and quantify sleepiness.

Health consequences / complications

- ▶ **Hypertension** — OSA is an identifiable secondary cause; produces nocturnal non-dipping, and **resistant/uncontrolled HTN** via sympathetic activation and RAAS/fluid effects. CPAP lowers 24-h BP modestly (~2–4 mmHg, more in sleepy/resistant patients).
- ▶ **Cardio-/cerebrovascular**: coronary artery disease, heart failure (HFrEF and HFpEF), **atrial fibrillation** and ventricular arrhythmias, stroke; OSA does not by itself cause right-heart failure (cor pulmonale implies coexisting cardiopulmonary disease).
- ▶ **Metabolic**: insulin resistance/type 2 diabetes, pro-inflammatory and prothrombotic state.
- ▶ **Neurobehavioural**: EDS, cognitive impairment, depression; 2–3× **risk of motor-vehicle and occupational accidents**; reduced quality of life. (Large RCTs of CPAP have not shown reduced cardiovascular event rates, likely from exclusion of sleepy patients and poor adherence.)

Management

- ▶ **General / behavioural**: weight reduction (even bariatric surgery), adequate sleep duration (7–9 h), **avoid supine sleep** (positional/vibrotactile therapy can cut AHI ~50% in positional OSA), treat nasal allergy, increase activity, **avoid alcohol within 3 h of bed**, and minimise sedatives/opioids.
- ▶ **CPAP** — *standard first-line therapy with the highest evidence*; a pneumatic splint maintaining airway patency. Titrated by sleep study or auto-titrating **APAP** (5–20 cmH₂O). Improves sleepiness, mood, BP and insulin sensitivity; adherence is the limiting factor (~50–80%; ~75% still using at 1 year). Side effects (nasal congestion, claustrophobia, aerophagia) are managed with humidification, mask change, or bilevel PAP.
- ▶ **Mandibular advancement (oral) appliances** — advance the mandible/tongue; reduce AHI by ≥50% in two-thirds; best for **mild–moderate OSA** or CPAP-intolerant patients; side effects: TMJ pain, tooth movement.
- ▶ **Surgery**: **uvulopalatopharyngoplasty (UPPP)** (removes uvula + ~15 mm of soft-palate margin) helps ~50%, better for snoring than apneas; often part of **multilevel surgery**. Nasal septoplasty aids CPAP tolerance. **Tracheostomy** is definitive but reserved for refractory severe disease. **Bariatric surgery** for obese patients.
- ▶ **Hypoglossal (upper-airway) nerve stimulation** — implanted stimulator for CPAP-intolerant moderate–severe OSA (AHI 15–65, per CMDT up to 100), BMI <35, and **absence of complete concentric collapse at the velum** on drug-induced sleep endoscopy.
- ▶ **Pharmacotherapy**: no FDA-approved drug historically; **tirzepatide** (dual GLP-1/GIP agonist) achieved ~16–17% weight loss with reduction in AHI (*NEJM* 2024) — a major recent advance; noradrenergic-antimuscarinic combinations (enhancing dilator tone) are in trials. Supplemental O₂ alone is **not** recommended (may prolong apneas).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Upper-airway sagittal section** showing collapse sites — label: *nasal cavity, soft palate, uvula, tongue base, lateral pharyngeal walls, epiglottis, genioglossus muscle*; arrows for negative inspiratory (“suction”) pressure causing collapse.
- ▶ **Polysomnography tracing of an obstructive apnea** — label channels: *EEG (arousal), nasal-pressure & thermistor airflow (cessation ≥ 10 s), chest and abdomen effort bands showing paradoxical/thoraco-abdominal paradox, SaO_2 (desaturation dip)*; contrast with a central apnea (flat effort channels).

Clinical / Diagnostic significance

- ▶ Consider OSA in any patient with resistant hypertension, recurrent AF, nocturnal angina/arrhythmia, type 2 diabetes, unexplained pulmonary hypertension, or pre-operative obese patients (use STOP-Bang).
- ▶ Pre-operative recognition reduces perioperative airway/cardiac complications; OHS carries the highest risk.
- ▶ Confirm with PSG/HSAT and grade by AHI before committing to lifelong CPAP; reassess residual sleepiness and adherence at follow-up.

High-yield exam pointers

- ▶ AHI defines and grades OSA: mild 5–14, moderate 15–29, severe ≥ 30 ; diagnostic threshold ≥ 5 with symptoms or ≥ 15 without.
- ▶ **Apnea** = $\geq 90\%$ airflow drop ≥ 10 s; obstructive = effort present (thoraco-abdominal paradox); **hypopnea** = $\geq 30\%$ drop with $\geq 3\%$ desat or arousal.
- ▶ Major risk factors: **obesity, male sex, older age**; collapse site most often the **soft palate**; worst in REM and supine.
- ▶ **Epworth ≥ 11** = excessive sleepiness; **STOP-Bang** for screening; **Mallampati III–IV** on exam.
- ▶ **PSG is gold standard**; **CPAP is first-line treatment**; oral appliance for mild–moderate/CPAP-intolerant.
- ▶ **Pcrit** (Starling resistor) >0 cmH₂O = frank obstructive apnea.
- ▶ OSA is a secondary cause of **resistant hypertension** and is linked to **AF, stroke, CAD, diabetes**.
- ▶ Newer options: **hypoglossal nerve stimulation** (AHI 15–65, BMI <35 , no concentric velar collapse) and **tirzepatide** for weight-driven OSA.

SOURCE & COVERAGE

- ▶ Harrison’s Principles of Internal Medicine, 22e — “Sleep Apnea” (definitions, pathophysiology, AHI severity, consequences, treatment including CPAP/oral appliance/UPPP/hypoglossal nerve stimulation/GLP-1 agonists).

- ▶ Murray & Nadel's Textbook of Respiratory Medicine, 7e — "Obstructive Sleep Apnea" and "Sleep-Disordered Breathing: A General Approach" (pathogenesis, Pcrit/Starling resistor, AASM event-scoring criteria, Epworth scale, levels of sleep testing, predisposing/endocrine factors, OHS).
- ▶ CMDT 2026 — "Pulmonary Disorders: Obstructive Sleep Apnea" (clinical findings, Mallampati, polysomnography, current management, hypoglossal nerve stimulation criteria, tirzepatide).



Pneumothorax

Asked in: Paper III Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Pneumothorax is the presence of air (gas) in the pleural space, with consequent partial or complete collapse of the underlying lung. The normal pleural space is a potential space holding only a thin film of fluid at a sub-atmospheric pressure of about **−3 to −5 cmH₂O**, generated by the balance between the inward elastic recoil of the lung and the outward recoil of the chest wall; entry of air abolishes this negative pressure and the lung recoils inward. It is classified by mechanism into **spontaneous** (primary or secondary), **traumatic**, and **iatrogenic**, with **tension pneumothorax** being a life-threatening physiological emergency in any category.

Classification

Type	Definition / Setting	Typical patient & common causes
Primary spontaneous (PSP)	Occurs <i>without</i> antecedent trauma and <i>without</i> clinically apparent lung disease	Tall, thin, young (<45 y), male, smoker; rupture of apical subpleural blebs/bullae + "pleural porosity"
Secondary spontaneous (SSP)	Spontaneous but on a background of known lung disease; BTS labels pneumothorax in patients >50 y or with significant smoking history as SSP	COPD (commonest in the West), pulmonary TB (commonest worldwide), cystic fibrosis, lung cancer, necrotizing pneumonia, <i>Pneumocystis jirovecii</i> , ILD (IPF, sarcoid), LAM and pulmonary Langerhans cell histiocytosis
Traumatic	Penetrating or blunt (non-penetrating) chest injury; air enters via chest-wall wound or visceral pleural laceration	Rib-fracture laceration, or alveolar rupture from sudden chest compression; often a hemopneumothorax
Iatrogenic	A subset of traumatic, from an invasive procedure	Transthoracic/CT-guided needle biopsy (leading cause),

Type	Definition / Setting	Typical patient & common causes
		thoracentesis, subclavian/IJ central line, transbronchial biopsy, barotrauma of positive-pressure ventilation, CPR
Tension	Pleural pressure positive throughout the respiratory cycle via a one-way (check) valve	Usually during mechanical ventilation, resuscitation, or trauma
Catamenial	Pneumothorax temporally linked to menstruation	Women of childbearing age; thoracic/diaphragmatic endometriosis

Pathogenesis

- ▶ **Blebs vs bullae (Miller 1947)**: a **bleb** is an outpouching of the *visceral pleura* caused by air dissecting between the **lamina elastica interna and externa**, typically <1 cm diameter; a **bull** is an air space >1 cm sharply demarcated by a thin wall (≤ 1 mm). *Reid (1967)* subdivided bullae into **type I** (narrow/pedunculated, no parenchyma), **type II** (broad/sessile), and **type III** (broad-based, extending to the hilum with minimal parenchyma).
- ▶ **PSP — “pleural porosity”**: the historical view that bleb/bulla rupture creates an alveolar–pleural communication is challenged. *Noppen’s* fluorescein-enhanced autofluorescence thoracoscopy showed air leakage from areas of **porosity** (disrupted mesothelium replaced by an inflammatory fibroelastic layer) rather than from the visible blebs themselves. PSP lungs are therefore **not truly “normal”** — they show distal airway inflammation (respiratory bronchiolitis), emphysema-like change and over-expression of **matrix metalloproteinases (MMP-2, MMP-9)**.
- ▶ **Familial / genetic causes (~10%)**: *Marfan syndrome* (**FBN1** / fibrillin-1), *Birt-Hogg-Dubé syndrome* (**FLCN** / folliculin — skin fibrofolliculomas, lung cysts, renal cancer), α_1 -*antitrypsin deficiency*, *homocystinuria*, *Ehlers-Danlos syndrome*. A strong family history warrants genetic referral and surveillance.
- ▶ **Tension physiology**: the visceral defect acts as a **one-way valve** — air enters on inspiration but cannot escape; rising intrapleural pressure progressively collapses the lung, shifts the mediastinum, and **reduces venous return**, lowering left-ventricular filling and cardiac output → obstructive shock.

Clinical features

- ▶ **Symptoms**: acute, usually unilateral, **pleuritic chest pain** and **dyspnoea** in nearly all; cough is common. Magnitude of symptoms correlates poorly with radiographic size.
- ▶ **Signs (affected hemithorax)**: reduced movement/expansion, **hyperresonant (tympanitic) percussion**, **diminished breath sounds**, decreased tactile/vocal fremitus, and ipsilateral chest

enlargement. Findings may be subtle in small pneumothoraces or against a background of emphysema.

- ▶ **Tension pneumothorax (emergency):** enlarged hemithorax with **no breath sounds**, **hyperresonance**, **tracheal/mediastinal shift to the contralateral side**, severe **tachycardia**, **hypotension**, **distended neck veins and cyanosis**. High peak inspiratory pressures (volume-cycled) or falling tidal volume (pressure-cycled) on a ventilator strongly suggest it. *Diagnosis is clinical — treatment must NOT await a chest X-ray.*

Investigations

- ▶ **Erect frontal CXR (first-line):** a **visceral pleural line** with absence of lung markings peripheral to it; the line has air on both sides, no vessels beyond it, and runs continuous and sharply demarcated — distinguishing it from a **skin-fold** (edge, lucent on one side only, vessels traceable across it).
- ▶ **Supine film (trauma/ICU):** look for the **deep sulcus sign** (abnormally deep, lucent costophrenic angle as air collects anteriorly).
- ▶ **Chest CT:** most accurate; clarifies size, detects **occult pneumothorax** (~40% of traumatic, seen on CT not CXR), distinguishes pneumothorax from **giant bullae** (avoids inadvertent intubation of a bulla and bronchopleural fistula), and screens for SSP causes (cystic lung disease/LAM).
- ▶ **Thoracic ultrasound:** absence of **lung sliding** and **B-lines** (with a “lung point”) diagnoses pneumothorax with high sensitivity/specificity in the supine trauma patient; beware false positives over emphysematous bullae.
- ▶ **ABG/ECG:** ABG usually unnecessary but may show hypoxaemia and respiratory alkalosis; left-sided PSP can mimic **acute MI** with QRS-axis/precordial T-wave changes.
- ▶ **Size estimation (no global consensus):** BTS “large” = **>2 cm** interpleural distance at the level of the **hilum** (~50% hemithorax volume by the *Light index*); ACCP “large” = **≥3 cm** from apex to cupola. Size guides—but does not dictate—the decision to intervene.

Management

- ▶ **General principle:** decide first *whether* intervention is needed (symptoms, size, underlying lung disease, ventilation status), then *how*.
- ▶ **PSP:** stable, small, minimally symptomatic patients → **observation** (many resolve as air is reabsorbed; the 2020 *Brown et al.* conservative-vs-interventional RCT showed conservative management is non-inferior even for moderate–large PSP in reliable patients). Symptomatic/large → **needle aspiration** with a 16–18-gauge cannula (aspirate up to 2.5 L); if aspiration fails, place a **small-bore chest tube (7–14F)**, optionally with a **Heimlich one-way valve** for ambulatory/outpatient management.

- ▶ **SSP:** admit for ≥ 24 h with **supplemental oxygen**; **most require a chest tube** because the diseased lung tolerates collapse poorly and spontaneous resolution is less likely. Early surgical/recurrence-prevention referral.
- ▶ **Supplemental oxygen:** high-flow/100% O_2 speeds reabsorption ~**fourfold** by washing out pleural nitrogen and widening the nitrogen gradient.
- ▶ **Tension pneumothorax:** immediate **needle decompression** — large-bore cannula into the **2nd intercostal space, mid-clavicular line** (Harrison: 2nd anterior intercostal space); a rush of gas confirms it. Leave the cannula until a definitive **chest tube** is placed.
- ▶ **Traumatic:** large/symptomatic $\rightarrow$ tube thoracostomy; if hemopneumothorax, an apical tube for air and a basal tube for blood. Small/occult may be observed.
- ▶ **Iatrogenic:** often resolves with observation/oxygen or simple aspiration; tube only if these fail or the patient is ventilated.
- ▶ **Failure of medical management / prolonged air leak (PAL = leak $>5-7$ days):** definitive treatment is **VATS** (preferred over open thoracotomy) — bleb/bullae resection (stapling) **plus pleurodesis** (talc poudrage, pleural abrasion, or pleurectomy). **Medical (chemical) pleurodesis** via the tube (talc slurry, tetracycline/minocycline) suits the non-surgical candidate; **autologous blood-patch pleurodesis** (1–2 mL/kg) and **endobronchial valves** are options in difficult SSP/COPD with bronchopleural fistula.
- ▶ **Recurrence prevention** is indicated for: **recurrent** (ipsi- or contralateral) pneumothorax, **synchronous bilateral** pneumothorax, PAL, or high-risk occupation (**airline pilot, diver**).
- ▶ **Catamenial pneumothorax:** suspect in any woman with pneumothorax within 24–48 h of menses (usually **right-sided**, recurrent); treat by **suppressing ectopic endometrium** — ovulation suppression with OCPs, or **danazol / GnRH analogues** (medical oophorectomy) — combined with VATS closure of diaphragmatic defects $\pm$ pleurodesis.
- ▶ **Complications:** tension physiology, pneumomediastinum, subcutaneous emphysema, and **re-expansion pulmonary oedema** (unilateral, after rapid re-inflation of a chronically collapsed lung — avoid by draining slowly and limiting suction).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled CXR / line diagram of a right-sided pneumothorax:** label *visceral pleural (lung) line, collapsed lung, absent lung markings (radiolucent pleural space), chest wall, diaphragm*, and (for tension) *mediastinum/trachea shifted to the contralateral side and depressed/flattened ipsilateral diaphragm*.
- ▶ **Tension pneumothorax pathophysiology schematic:** label *one-way (check) valve at visceral pleural defect, air entering on inspiration, rising positive intrapleural pressure, collapsed lung, mediastinal shift, kinked great veins $\rightarrow$ reduced venous return $\rightarrow$ fall in cardiac output*.

Clinical / Diagnostic significance

- ▶ A young, tall, thin male smoker with sudden pleuritic pain and dyspnoea = classic **PSP**; a similar event in COPD/TB/ILD = **SSP** and is far less benign.
- ▶ Recurrent pneumothorax in a **young woman** must trigger thought of **LAM**, **catamenial pneumothorax**, or **Birt-Hogg-Dubé** — consider low-dose CT chest.
- ▶ **Tension pneumothorax is a clinical diagnosis**; needle decompression precedes imaging and saves life.
- ▶ Distinguishing a **giant bulla** from a pneumothorax on CXR is critical — wrongly draining a bulla causes a persistent air leak/bronchopleural fistula; CT resolves the doubt.
- ▶ **Counselling**: mandatory smoking cessation (reduces recurrence), **no air travel until 7 days after radiographic resolution** (cabin depressurisation expands undrained air — an untreated pneumothorax is an absolute contraindication to flying), and **lifelong avoidance of scuba diving** unless definitive surgical pleurodesis has been performed.

High-yield exam pointers

- ▶ **Recurrence**: ~30% after a first PSP (observation or simple drainage); up to 50% for SSP if no surgery — surgery/pleurodesis greatly lowers this (talc poudrage recurrence $\approx$ 1.8%).
- ▶ **Bleb <1 cm vs bulla >1 cm**; *Reid* type I/II/III bullae; *Miller* first described blebs (1947).
- ▶ **Light's criteria** distinguish exudate/transudate in pleural *effusion*; do not confuse with **Light index** for pneumothorax *size*.
- ▶ **BTS large** = >2 cm at hilum; **ACCP large** = $\geq$ 3 cm at apex.
- ▶ Needle aspiration cannula 16–18 G, **up to 2.5 L**; tension decompression at **2nd ICS, mid-clavicular line**.
- ▶ **100% oxygen accelerates resorption** $\sim$ 4 $\times$.
- ▶ Familial mnemonics: **Marfan** (FBN1), **Birt-Hogg-Dubé** (FLCN), α_1 -antitrypsin deficiency, homocystinuria.
- ▶ **Pneumothorax ex vacuo** occurs when a trapped (unexpandable) lung cannot re-expand after fluid drainage.
- ▶ Left-sided pneumothorax can mimic **acute MI** on ECG; tension pneumothorax can mimic and coexist with shock.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Disorders of the Pleura” (pneumothorax classification, pleural mechanics, tension pneumothorax decompression).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Pneumothorax” (epidemiology; bleb/bulla and Reid classification; pleural-porosity pathogenesis; MMPs; familial genetics; sizing — BTS/ACCP/Light index; needle-aspiration vs chest-tube and

conservative-management RCTs; VATS/pleurodesis; blood-patch and endobronchial-valve therapy; traumatic, iatrogenic and catamenial pneumothorax).

- ▶ **CMDT 2026** — “**Pulmonary Disorders**” (**Pneumothorax**) (current essentials, BTS 2023 guideline, conservative-management evidence, recurrence figures, indications for VATS).



Pulmonary Function Tests

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Pulmonary function tests (PFTs) are objective, reproducible, non-invasive measurements of the mechanical and gas-exchange properties of the respiratory system, interpreted against predicted values derived from height, age and sex. They quantify how the three functionally independent components of the system — the **lung and airways**, the **neuromuscular pump** and the **chest wall** — handle volume (statics) and flow (dynamics). PFTs serve to **detect and classify disease** (**obstructive vs restrictive vs mixed vs vascular**), grade severity, follow progression and response to therapy, and assess fitness for surgery. For most measures, **85–115% of the predicted value is normal**, and in health the various volumes tend to scale together.

Components of a complete PFT battery

- ▶ **Spirometry** — FVC, FEV₁, FEV₁/FVC ratio and the **flow-volume loop** (the core, effort-independent test of airflow).
- ▶ **Static lung volumes** — TLC, FRC, RV (require gas dilution or plethysmography; spirometry alone cannot measure them).
- ▶ **Diffusing capacity (DLCO)** — integrity of the alveolar-capillary membrane and gas transfer.
- ▶ **Respiratory muscle strength** — maximal inspiratory/expiratory pressures; supine spirometry.
- ▶ **Arterial blood gases (ABG) / pulse oximetry** — efficiency of gas exchange.
- ▶ **Bronchodilator reversibility** (pre- vs post-bronchodilator spirometry) and bronchoprovocation in selected cases.

Lung volumes and capacities (Spirogram, Fig. 296-2)

- ▶ **Tidal volume (TV)** — air moved in a normal quiet breath.
- ▶ **Inspiratory reserve volume (IRV)** and **expiratory reserve volume (ERV)** — extra air inhaled/exhaled beyond tidal breathing.
- ▶ **Residual volume (RV)** — air remaining after maximal exhalation; *cannot be exhaled, hence not measurable by spirometry*.
- ▶ **Inspiratory capacity (IC)** = TV + IRV; **functional residual capacity (FRC)** = ERV + RV, the volume at the end of a normal tidal breath.

- ▶ **Vital capacity (VC)** = TLC – RV, the maximal excursion of the respiratory system.
- ▶ **Total lung capacity (TLC)** — volume at full inflation.

Measuring absolute volumes — Because spirometry discloses only *relative* volume change, FRC (and hence RV and TLC) must be measured by one of two methods:

- ▶ **Inert gas (helium or neon) dilution** — a known volume of non-absorbable gas is diluted by resident lung gas; poorly ventilated regions (e.g., airflow obstruction) receive little gas, so this method **underestimates true lung volume**.
- ▶ **Body plethysmography** — the patient pants against a closed shutter; pressure/volume fluctuations give thoracic gas volume via **Boyle's law** ($P_1V_1 = P_2V_2$). More accurate when air-trapping is present.

Spirometry, airflow and the flow-volume loop

- ▶ In an **FVC manoeuvre** the patient inhales fully to TLC then exhales rapidly and forcefully to RV. Maximal expiratory flow is **effort-independent** (flow-limited) because of dynamic airway compression (*Bernoulli effect*), so results are reproducible.
- ▶ **FVC** = total volume exhaled; **FEV₁** = volume exhaled in the first second (a flow rate); **FEV₁/FVC ratio** is the key discriminator of obstruction.
- ▶ Data are displayed two ways — the **spirogram** (volume vs time) and the **flow-volume loop** (flow vs volume).
- ▶ **Pitfall:** airflow obstruction can lower FVC by raising RV, sometimes rendering the FEV₁/FVC ratio “*artificially normal*” and falsely implying obstruction is absent.

Flow-volume loop (Fig. 296-4)	Characteristic shape	Typical cause
A. Normal	Rapid rise then near-linear declining expiratory limb	—
B. Lower-airway obstruction	“Scooping” (concave) expiratory limb; flows fall faster at low volumes	Asthma, emphysema/COPD
C. Fixed central airway obstruction	Plateau of both inspiratory and expiratory limbs	Tracheal stenosis, large goitre
D. Variable extrathoracic (upper, above thoracic inlet)	Inspiratory plateau	Tracheal adenoma, post-tracheostomy stricture
E. Variable intrathoracic (lower, below thoracic inlet)	Expiratory plateau	Intrathoracic tracheal/bronchial lesion

Obstructive vs restrictive patterns

Feature	Obstructive	Restrictive
Defining defect	Reduced FEV ₁ /FVC ratio	Reduced TLC (FEV ₁ /FVC normal or high)
FEV ₁	Markedly reduced	Reduced proportionate to FVC
TLC, FRC, RV	Often increased (hyperinflation, air-trapping)	Reduced
Flow-volume loop	Scooped expiratory limb	Small loop shifted to low volumes; flows high <i>for the volume</i>
Examples	Asthma, emphysema/COPD, chronic bronchitis, cystic fibrosis	Pulmonary fibrosis (parenchymal), neuromuscular weakness, chest-wall/obesity (extraparenchymal)

Diffusing capacity (DLCO), muscle strength and ABG

- ▶ DLCO uses a small, safe amount of **carbon monoxide** with a **10-second breath-hold**; CO crossing the alveolar membrane combines with capillary haemoglobin (*single-breath diffusing capacity*). It rises with diffusion surface area and capillary haemoglobin and falls with membrane thickening.
 - **Low DLCO:** membrane thickening/destruction (**pulmonary fibrosis, emphysema**), curtailed pulmonary vasculature (**pulmonary hypertension**), reduced alveolar-capillary haemoglobin (**anaemia**). An isolated low DLCO with normal volumes should prompt evaluation for **pulmonary vascular disease**.
 - **High DLCO:** asthma, polycythaemia, pulmonary (alveolar) haemorrhage.
- ▶ **Respiratory muscle strength** — maximal inspiratory/expiratory pressure against a closed shutter; pressures $>\pm 60$ cmH₂O at FRC are **adequate** and exclude weakness as a cause of dysfunction. A sensitive bedside test is **supine spirometry**: normal FVC falls only 3–8% from upright to supine, but diaphragmatic weakness/paralysis or neuromuscular disease causes decrements of 10 to >25%.
- ▶ **ABG / oximetry** — measure Pao₂ and Paco₂. A widened (A–a)Do₂ indicates V/Q mismatch or shunt; **hypercarbia** accompanies severe obstruction (e.g., COPD) or advanced restriction. Oxygen content Cao₂ = $1.39 \times [\text{Hb}] \times \% \text{O}_2 \text{Sat} + 0.003 \times \text{Pao}_2$; saturation alone is followed non-invasively by **pulse oximetry**.

Characteristic PFT patterns in common disorders (Fig. 296-6)

Disorder (mechanism)	TLC / FRC / RV	FEV ₁ & FVC	Airway resistance	DLCO
Idiopathic pulmonary fibrosis (restriction, ↑ recoil)	All ↓	↓ (flows high for volume)	Normal	Markedly ↓
Moderate obesity (restriction, chest wall)	FRC ↓; TLC/RV usually normal	Near normal	Normal	Normal
Myasthenia gravis (restriction, muscle weakness)	TLC ↓, RV ↑	↓ (as “innocent bystanders”)	Normal	Normal
Acute asthma (obstruction, ↓ airway diameter)	FRC dynamically ↑, RV ↑, TLC usually normal	↓, reversible post-bronchodilator	↑	Normal or mildly ↑
Severe emphysema (obstruction, ↓ recoil)	TLC ↑ (hyperinflation), FRC ↑↑, RV ↑↑↑	↓, largely irreversible	Normal in “pure” emphysema	↓

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Spirogram (lung volumes & capacities)** — a tracing of volume vs time over a slow vital-capacity manoeuvre, with horizontal reference lines and brackets labelled: *Tidal volume (TV)*, *Inspiratory reserve volume (IRV)*, *Expiratory reserve volume (ERV)*, *Residual volume (RV)*, *Inspiratory capacity (IC)*, *Functional residual capacity (FRC)*, *Vital capacity (VC)*, *Total lung capacity (TLC)*.
- ▶ **Flow-volume loops** — axes labelled *Flow* (expiratory above zero, inspiratory below) and *Volume* (from TLC on left to RV on right); draw and label five loops: *A Normal*, *B Lower-airway obstruction (scooped)*, *C Fixed central obstruction (both limbs plateau)*, *D Variable extrathoracic (inspiratory plateau)*, *E Variable intrathoracic (expiratory plateau)*.

Clinical / Diagnostic significance

- ▶ **Diagnosis and classification:** FEV₁/FVC defines obstruction; reduced TLC defines restriction; combined defects suggest mixed disease.
- ▶ **Bronchodilator reversibility** (pre- vs post-bronchodilator FEV₁) distinguishes reversible asthma from largely fixed COPD/emphysema and guides therapy.
- ▶ **Isolated low DLCO** with normal spirometry/volumes is a clue to **pulmonary vascular disease** (e.g., **pulmonary hypertension**) or early emphysema/ILD; high DLCO suggests alveolar haemorrhage or polycythaemia.

- ▶ **Severity grading and monitoring:** serial FEV₁ tracks COPD/asthma progression and treatment response; falling FVC (especially supine) signals neuromuscular respiratory failure (e.g., GBS, myasthenia, ALS) and the need for ventilatory support.
- ▶ **Preoperative risk assessment** (lung resection, major surgery) and **disability/occupational evaluation** rely on spirometry and DLCO.
- ▶ **Localising airway lesions:** plateaued inspiratory/expiratory limbs flag upper-airway/tracheal obstruction often missed on routine spirometry numbers.

High-yield exam pointers

- ▶ **Obstruction** = low FEV₁/FVC; **restriction** = low TLC — TLC, not spirometry, confirms restriction.
- ▶ RV, FRC and TLC **cannot be measured by spirometry** — need **helium dilution** (underestimates in obstruction) or **body plethysmography** (Boyle's law, more accurate with air-trapping).
- ▶ **Scooped expiratory limb** = lower-airway obstruction; **biphasic plateau** = fixed central; **inspiratory plateau** = variable extrathoracic; **expiratory plateau** = variable intrathoracic.
- ▶ A reduced FVC from air-trapping can make FEV₁/FVC look **falsely normal** — always check TLC/RV.
- ▶ **DLCO low** in fibrosis, emphysema, pulmonary hypertension, anaemia; **high** in asthma, polycythaemia, alveolar haemorrhage.
- ▶ **MIP/MEP >±60 cmH₂O** is adequate; supine FVC fall >10% indicates diaphragmatic weakness (normal 3–8%).
- ▶ **Hallmark of emphysema** = ↑TLC (**hyperinflation**) with very high RV and reduced DLCO but normal airway resistance in “pure” disease.
- ▶ Normal range is **85–115% of predicted**; predictions depend on **height, age, sex**.

SOURCE & COVERAGE

Harrison 22e — Ch 296 “Disturbances of Respiratory Function” (lung volumes, airflow, flow-volume loops, disease patterns Fig. 296-2/296-4/296-6) and Ch 297 “Diagnostic Procedures in Respiratory Disease” (body plethysmography, DLCO, respiratory muscle testing, ABG). **Coverage note:** Specific quantitative reversibility thresholds (e.g., ATS ≥12% and ≥200 mL rise in FEV₁), **methacholine/bronchoprovocation testing**, **cardiopulmonary exercise testing** and the **6-minute walk test** are standard textbook PFT adjuncts but are *not described in the provided Harrison chapters*; they are mentioned only in outline and should be cross-checked against CMDT / ATS-ERS standards before use.



Pulmonary infiltrates with eosinophilia

Asked in: Paper III Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — *Pulmonary infiltrates with eosinophilia* (PIE), or the **eosinophilic lung diseases**, are a heterogeneous group of disorders characterised by the combination of **radiographic pulmonary opacities** (infiltrates) and **eosinophilia**, demonstrated either in peripheral blood, in sputum, or — preferably — in the lung itself (bronchoalveolar lavage [BAL] or tissue). Eosinophilic pneumonia is defined pathologically as a pneumonia in which **eosinophils are the predominant inflammatory cell** in the alveoli and interstitium. By consensus, **blood eosinophilia is $>0.5 \times 10^9/L$ ($500/\mu L$)** and **hypereosinophilia $>1.5 \times 10^9/L$ ($1500/\mu L$)** on two examinations ≥ 1 month apart and/or tissue hypereosinophilia. The unifying effector cell is the **eosinophil**, whose differentiation and lung recruitment are driven by **IL-5, IL-3, GM-CSF and eotaxins** (Th2-/ILC2-derived), making the IL-5 axis a central therapeutic target.

Classification (primary/idiopathic vs secondary)

The first step is to separate **primary (idiopathic)** eosinophilic lung disease from disease that is **secondary** to an identifiable cause (drug, parasite, fungus, malignancy or another lung condition). A practical bedside algorithm asks three questions: (1) *extrapulmonary involvement?* (2) *identifiable cause/trigger?* (3) *acute or chronic onset?*

Category	Disorders
Primary (idiopathic) eosinophilic lung disease	Acute eosinophilic pneumonia (AEP); Chronic eosinophilic pneumonia (CEP); Eosinophilic granulomatosis with polyangiitis (EGPA / Churg-Strauss); Hypereosinophilic syndromes (HES)
Known cause associated with eosinophilia	Asthma & eosinophilic bronchitis; Allergic bronchopulmonary aspergillosis (ABPA); Bronchocentric granulomatosis; Drug/toxin reaction; Infection — parasitic/helminthic & nonparasitic (Löffler, tropical eosinophilia)
Lung diseases with eosinophilia	Cryptogenic organising pneumonia; Hypersensitivity pneumonitis; Idiopathic pulmonary fibrosis; Pulmonary Langerhans cell histiocytosis
Malignancy / systemic	Leukaemia, lymphoma, lung & other carcinomas; post-radiation pneumonitis; RA, sarcoidosis, Sjögren's

Diagnostic approach

- **History is paramount** — onset/timing/precipitants of symptoms; drug, occupational, environmental, **travel and immigration** history; family history; and a systems review for cardiac, GI, neurological, dermatological, sinus and renal clues (point to EGPA or HES).

- ▶ **Blood** — absolute eosinophil count, ESR/CRP, **total IgE**, *Aspergillus*-specific IgE/IgG, ANCA (MPO), stool for ova/parasites, filarial serology. Peripheral eosinophilia may be **absent at presentation in AEP** and is **suppressed by prior corticosteroids**.
- ▶ **BAL** — the noninvasive surrogate for tissue diagnosis. Normal BAL eosinophils <1%; a count >25% (**predominant cell**) strongly supports eosinophilic pneumonia, and >40% is characteristic of CEP. Lower counts (3–25%) are nonspecific (ILD, HP, sarcoid, drug, infection).
- ▶ **Imaging** — chest radiograph + **HRCT** to define distribution (peripheral upper-zone in CEP; diffuse in AEP; migratory in EGPA; central bronchiectasis/finger-in-glove in ABPA).
- ▶ **Biopsy** (transbronchial, cryobiopsy or surgical) is seldom required but resolves difficult cases; *Charcot-Leyden crystals* (composed of the eosinophil protein **galectin-10**) may be seen in tissue/sputum.

Idiopathic eosinophilic pneumonias — AEP vs CEP

Feature	Acute eosinophilic pneumonia (AEP/IAEP)	Chronic eosinophilic pneumonia (CEP/ICEP)
Onset	Acute febrile illness <1 month	Subacute over weeks–months
Demographics	Males 20–40 yr; no asthma	Females ~2:1, mean age ~45; nonsmokers ; asthma/atopy in majority
Trigger	Recent-onset smoking / vaping , inhaled dust	Often none; allergy in ~half
Course	Hypoxaemic respiratory failure, often needs ventilation; no other organ failure	Indolent; respiratory failure rare
Blood eosinophilia	Often absent at onset (appears day 7–30, mean ~1700/ μ L)	Present in ~90%; mean >30% of WBC
BAL eosinophils	$\geq 25\%$	~60% ($\geq 40\%$)
Chest imaging	Bilateral patchy ground-glass/consolidation, septal thickening, small effusions	Peripheral upper-zone consolidation — “ <i>photographic negative of pulmonary oedema</i> ” (pathognomonic but seen in <25%)
Steroid response / relapse	Dramatic; complete recovery, no relapse	Dramatic; >50% relapse , often needs prolonged steroids

AEP diagnostic criteria (Harrison/Philit): acute febrile respiratory illness <1 month; hypoxaemic respiratory failure ($\text{PaO}_2 \leq 60$ mmHg, $\text{PaO}_2/\text{FiO}_2 \leq 300$, or $\text{SpO}_2 < 90\%$ on room air); diffuse bilateral infiltrates; **BAL eosinophilia** >25%; absence of infection/drug cause; quick corticosteroid response; no relapse after stopping steroids.

Eosinophilic granulomatosis with polyangiitis (EGPA / Churg-Strauss)

- ▶ An ANCA-associated, eosinophil-rich small-vessel vasculitis with extravascular necrotising granulomas, defined by the triad of **asthma + eosinophilia + vasculitis**. Mean age ~48 yr.
- ▶ **Three classic phases:** (1) *prodromal* — asthma + allergic rhinosinusitis (often years); (2) *eosinophilic infiltrative* — blood/tissue eosinophilia (lung, GI); (3) *vasculitic* — constitutional symptoms with multi-organ vasculitis. Mean asthma-to-vasculitis interval ~9 years.
- ▶ **Organ involvement:** lung (migratory infiltrates, alveolar haemorrhage); **mononeuritis multiplex** in >75% (esp. peroneal nerve); skin (palpable purpura, nodules) ~50%; **cardiac** (eosinophilic myocarditis/cardiomyopathy — chief cause of death) up to 50%; GI (eosinophilic gastroenteritis); renal ~25% (usually mild, unlike other AAV).
- ▶ **Labs:** blood **eosinophilia >1000/ μ L (or >10% WBC)** — present in >80%, falls within ~24 h of steroids; **p-ANCA/anti-MPO in ~30–40%**; raised IgE, ESR, RF. ANCA-positive patients have a *vasculitic phenotype* (renal, neuropathy, purpura); ANCA-negative a *tissue/eosinophilic phenotype* (cardiac, lung).
- ▶ ***Cottin/Cordier criteria:** *asthma + blood eosinophilia >1500/ μ L (or BAL >25%) + an extrapulmonary manifestation (systemic feature such as mononeuritis multiplex, cardiomyopathy, or purpura; OR histological vasculitis; OR ANCA positivity). A single extrapulmonary feature = forme fruste*.*
- ▶ **Treatment:** glucocorticoids are the mainstay (prednisone 1 mg/kg/day, taper; IV methylprednisolone pulse 15 mg/kg/day for severe/cardiac disease). For **poor-prognosis (Five-Factor Score)** features — **cardiomyopathy, severe GI involvement, renal insufficiency (creatinine >150 μ mol/L $\approx$ 1.7 mg/dL), proteinuria >1 g/day, CNS involvement** (updated FFS also: age >65 yr, absence of ENT symptoms) — add **cyclophosphamide** (or rituximab). **Mepolizumab (anti-IL-5, 300 mg every 4 weeks)** and benralizumab are steroid-sparing agents that increase remission and reduce relapse. Untreated EGPA carries ~50% 3-month mortality; treated 6-year survival >70%.

Other important entities

- ▶ **Hypereosinophilic syndromes (HES)** — persistent eosinophilia >1500/ μ L with **end-organ damage** and no secondary cause; lung involved in ~40%. **Myeloproliferative variant** carries the **FIP1L1-PDGFR α fusion (4q12 deletion)** — an imatinib-responsive constitutively active tyrosine kinase (raised B12, tryptase, splenomegaly, myelofibrosis); **lymphocytic variant** is driven by clonal **CD3⁺CD4⁺ Th2** cells producing IL-5. Cardiac damage = endomyocardial fibrosis/restrictive cardiomyopathy. **<50% respond to steroids alone**; imatinib is first-line for the myeloproliferative/FIP1L1-PDGFR α variant; mepolizumab is effective.
- ▶ **ABPA** — hypersensitivity to *Aspergillus fumigatus* in **asthma or cystic fibrosis**; brownish mucus plugs, refractory asthma. Diagnosis (ISHAM/Agarwal): predisposing asthma/CF + **obligatory positive *Aspergillus* skin test or raised *A. fumigatus*-specific IgE and total IgE >1000 IU/mL + $\geq$ 2**

of (precipitins/IgG to *A. fumigatus*; ABPA-consistent opacities; eosinophil count $>500/\mu\text{L}$).

HRCT: **central (proximal) bronchiectasis**, high-attenuation mucoid impaction, “*finger-in-glove*” opacities. Treat with **oral corticosteroids + itraconazole** (4–6 months); omalizumab/anti-IL-5 in selected cases.

- ▶ **Infections (helminthic)** — chief cause of PIE in the tropics/developing world. ***Löffler syndrome** = *transient migratory infiltrates with eosinophilia from transpulmonary larval migration, most often Ascaris (also hookworm — Ancylostoma, Necator)*. Strongyloides causes recurrent symptoms and a fatal hyperinfection syndrome in the immunosuppressed. Tropical pulmonary eosinophilia is due to filariae (**Wuchereria bancrofti*, *Brugia malayi*), **common in** southern Asia, Africa, South America, **with very high IgE/eosinophilia, nocturnal cough/wheeze — treated with diethylcarbamazine****.
- ▶ **Drug/toxin-induced** — the commonest cause of PIE in the USA; remember **nitrofurantoin, daptomycin, phenytoin, NSAIDs, sulfasalazine/mesalamine, sulfonamides**; also radiation (breast cancer), particulate metals, illicit inhaled drugs. Management = withdraw the agent $\pm$ steroids. Overlaps with DRESS.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm for eosinophilic pneumonia** (box-and-arrow): start “**Pulmonary infiltrates + eosinophilia**” $\rightarrow$ Q1 *Extrapulmonary involvement?* $\rightarrow$ EGPA / HES / DRESS / parasitic; if No $\rightarrow$ Q2 *Cause/trigger identified?* $\rightarrow$ **drug, smoking/vaping, ABPA, parasite, radiation**; if No $\rightarrow$ Q3 *Onset?* $\rightarrow$ **Acute = IAEP vs Chronic = ICEP**. Label boxes: *IAEP, ICEP, EGPA, HES, ABPA, Löffler, drug-induced*.
- ▶ **AEP vs CEP HRCT cartoon**: lung outline 1 = **bilateral diffuse ground-glass + septal thickening + small pleural effusions (AEP)**; lung outline 2 = **peripheral upper-zone consolidation sparing the centre** labelled “*photographic negative of pulmonary oedema*” (CEP).

Clinical / Diagnostic significance

- ▶ The single most useful discriminator is **BAL eosinophil percentage** ($>25\%$ supports an eosinophilic pneumonia; $>40\%$ suggests CEP) — it avoids lung biopsy in most patients.
- ▶ **AEP mimics ARDS** in a previously well young smoker but lacks multi-organ failure and responds completely to steroids — recognising it prevents unnecessary escalation and prognosticates well.
- ▶ **A new eosinophilic infiltrate in a long-standing asthmatic** demands exclusion of ABPA and EGPA; leukotriene-receptor antagonists/omalizumab/dupilumab and steroid tapering may *unmask* EGPA.
- ▶ **Always exclude Strongyloides/helminths before starting corticosteroids** in PIE (risk of fatal hyperinfection) — stool, serology, empiric ivermectin where appropriate.

- ▶ Steroids rapidly abolish blood and BAL eosinophilia, so investigations are best obtained before treatment.

High-yield exam pointers

- ▶ Blood eosinophilia $>500/\mu\text{L}$; hypereosinophilia $>1500/\mu\text{L}$; BAL $>25\%$ = eosinophilic pneumonia; $>40\%$ = CEP.
- ▶ AEP: young male smoker, ARDS-like, no peripheral eosinophilia at onset, **no relapse**; CEP: middle-aged female asthmatic, “*photographic negative of pulmonary oedema*”, **frequent relapse**.
- ▶ EGPA triad = **asthma + eosinophilia + vasculitis**; mononeuritis multiplex; p-ANCA/MPO $\sim 30\text{--}40\%$; cardiac disease = leading cause of death; **Five-Factor Score** guides cyclophosphamide; **mepolizumab** is steroid-sparing.
- ▶ HES: eosinophilia $>1500/\mu\text{L}$ + end-organ damage; FIP1L1-PDGFR α $\rightarrow$ **imatinib**.
- ▶ ABPA: asthma/CF, IgE >1000 IU/mL, central bronchiectasis, *finger-in-glove*; treat steroids + itraconazole.
- ▶ **Löffler syndrome** = transient infiltrates from *Ascaris* larval migration; **tropical pulmonary eosinophilia** = filariae, treat **diethylcarbamazine**.
- ▶ Commonest drugs: **nitrofurantoin, daptomycin, phenytoin, NSAIDs, sulfasalazine**; commonest cause in the West = **drugs**, in the tropics = **helminths**.
- ▶ **Charcot-Leyden crystals** = galectin-10; eosinophil maturation/recruitment driven by IL-5.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “*Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia*” (classification table 299-2, AEP/CEP, EGPA, HES, ABPA, infectious & drug causes, AEP diagnostic criteria).
- ▶ **Murray & Nadel’s Textbook of Respiratory Medicine, 7e** — “*Eosinophilic Lung Diseases*” (diagnostic algorithm Fig 96.1, eosinophilia/BAL thresholds, ICEP & IAEP criteria tables, Cottin/Cordier EGPA criteria, Five-Factor Score, HES genetics, ISHAM/Agarwal ABPA criteria, treatment regimens) and “*Pulmonary Vasculitis*” for EGPA phenotypes.
- ▶ **CMDT 2026** — “*Eosinophilic Pulmonary Syndromes*” and “*Pulmonary Disorders*” (drug list, Löffler/tropical eosinophilia, current management, IL-5-targeted therapy).



Pulmonary Thromboembolism

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — Pulmonary thromboembolism (PE) is acute obstruction of the pulmonary arterial bed by thrombus, almost always an embolus that has detached from a lower-limb **deep-venous thrombosis (DVT)**; together DVT and PE constitute **venous thromboembolism (VTE)**, manifestations

of one disease process. Roughly 90% of clinically apparent PEs arise from proximal lower-extremity DVT. PE is “the great masquerader” — symptoms and signs are non-specific, so a structured, probability-based diagnostic and risk-stratified therapeutic approach is essential because untreated PE carries a case-fatality higher than that of acute myocardial infarction.

Aetiology & Risk Factors (Virchow’s triad)

- ▶ **Virchow’s triad** (1856): venous stasis, hypercoagulability, and endothelial/intimal injury — usually with an **inflammatory trigger** — drive thrombus formation around a valve cusp; activated platelets recruit neutrophils that form *neutrophil extracellular traps*, promoting thrombin generation in a milieu of stasis and low oxygen tension.
- ▶ **Inherited (hereditary) thrombophilias**: **Factor V Leiden** (commonest; causes resistance to activated protein C), **prothrombin G20210A** gene mutation (raises plasma prothrombin), and the rarer deficiencies of **antithrombin III**, **protein C** and **protein S**; also dysfibrinogenaemia and plasminogen deficiency.
- ▶ **Acquired: antiphospholipid syndrome (APS)** — acquired, predisposes to both venous *and* arterial thrombosis, often warrants lifelong anticoagulation; surgery/trauma, hip-knee arthroplasty, hip fracture, spinal cord injury, immobilisation, prior VTE, advancing age, malignancy, pregnancy and the 6–12-week postpartum period, oestrogen contraceptives/HRT, obesity, nephrotic syndrome, long-haul travel, COPD, CKD, sickle cell disease/trait and cirrhosis.

Type	Examples
Hereditary	Factor V Leiden, prothrombin G20210A, antithrombin/protein C/protein S deficiency
Acquired – surgical	Major thoracic/abdominal/neurosurgery, hip & knee arthroplasty, hip fracture, major trauma, spinal cord injury
Acquired – medical	Cancer, prior VTE, CHF, stroke, nephrotic syndrome, oestrogens, pregnancy/postpartum, obesity, APS, IBD

Pathophysiology

- ▶ **Gas exchange**: arterial **hypoxaemia** (~85% of patients) and a widened **alveolar–arterial O₂ gradient** from V/Q mismatch and shunt; increased **alveolar (physiologic) dead space**; surfactant loss → atelectasis; reflex hyperventilation → **hypocapnia**.
- ▶ **Haemodynamics**: mechanical obstruction plus neurohumoral vasoconstrictors (**serotonin**, **thromboxane A₂**, **endothelin**) raise **pulmonary vascular resistance** and pulmonary artery pressure non-linearly.

- ▶ **The RV-failure cascade (key to mortality):** rising RV wall tension → **RV dilatation and dysfunction** with BNP release → **interventricular septal bowing** into the LV → impaired LV filling → falling cardiac output and systemic pressure → reduced **right coronary perfusion** → RV ischaemia/**microinfarction** (troponin release) → a self-perpetuating spiral to circulatory collapse and death.
- ▶ **Pulmonary infarction** is uncommon (dual bronchial + airway oxygen supply) and, paradoxically, more frequent in young patients without cardiopulmonary disease; it indicates a small, peripheral, pleura-adjacent embolus and is intensely pleuritic.

Classification & Risk Stratification

- ▶ *Hemodynamic effects, not clot burden on imaging, best predict mortality* — even “saddle emboli” are usually hemodynamically stable.

Class	Frequency	Definition	Risk
Massive (high-risk)	5–10%	SBP <90 mmHg (≥ 15 min) / vasopressor / arrest; $\geq \frac{1}{2}$ of pulmonary bed obstructed	High
Submassive (intermediate-risk)	20–25%	Normotensive but RV dysfunction $\pm$ troponin/BNP elevation	Intermediate (may decompensate)
Low-risk	65–75%	Normotensive, no RV dysfunction, normal biomarkers	Excellent prognosis

- ▶ **Simplified PESI (sPESI)** — 1 point each for: **age >80 yr, cancer, chronic cardiopulmonary disease, pulse ≥ 110 /min, SBP <100 mmHg, SaO₂ <90%**. Score 0 = low 30-day mortality (suitable for outpatient therapy); ≥ 1 = high risk. (Full PESI stratifies into classes I–V.)

Clinical Features

- ▶ **DVT:** persisting calf “charley horse”/cramp, unilateral swelling, tenderness, warmth, erythema; classic *Homan’s sign* and *Moses sign* and a “palpable cord” are insensitive and non-specific. Diffuse limb oedema suggests *phlegmasia cerulea dolens*; recurrent left-thigh oedema in young women suggests *May–Thurner syndrome* (right iliac artery compressing left iliac vein); chest-wall collaterals = *Urschel’s sign*.
- ▶ **PE** — **three classic syndromes (PIOPED):** (1) **isolated dyspnoea** (~25%); (2) **pleuritic pain $\pm$ haemoptysis** (~60%, usually small peripheral PE/infarction); (3) **circulatory collapse/syncope** (~10%, massive PE).
- ▶ **Commonest symptom = unexplained dyspnoea; commonest sign = tachypnoea (>20/min);** also tachycardia, accentuated P₂, inspiratory crackles, low-grade fever (rarely >38.3°C), and signs of RV overload (left parasternal heave, raised JVP, S₃/S₄) in massive PE.

Diagnosis (integrated, probability-based)

- **Step 1 – Pretest probability:** Wells score (validated in outpatients) or gestalt; if low/moderate, proceed to D-dimer; if high, skip D-dimer and image directly.

Wells criterion (PE)	Points
Clinical signs/symptoms of DVT	3.0
PE as likely as / more likely than alternative	3.0
Heart rate >100/min	1.5
Immobilisation >3 days / surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Haemoptysis	1.0
Cancer	1.0

(High clinical likelihood if score >4.) The **PERC rule** (age <50, HR <100, SaO₂ ≥95%, no prior VTE, no recent trauma/surgery, no haemoptysis, no oestrogen, no unilateral leg swelling) excludes PE in ED patients already judged low-risk.

- **D-dimer (ELISA):** sensitivity >95% — a normal value **rules out** PE in low/intermediate probability; not specific (raised in MI, sepsis, cancer, pregnancy, post-op), so of little value in hospitalised patients. Use **age-adjusted cut-off** (age × 10 ng/mL FEU) in patients >50 yr.
- **ECG:** sinus tachycardia commonest; **S1Q3T3** (specific, insensitive), **T-wave inversion V1–V4** (RV strain — commonest abnormality), incomplete RBBB, Qr in V1.
- **Chest X-ray** (often near-normal): **Westermarck's sign** (focal oligaemia), **Hampton's hump** (peripheral pleura-based triangular density = infarction), **Palla's sign** (enlarged right descending PA), **Fleischner sign** (prominent central PA).
- **CT pulmonary angiography (CTPA)** — **principal/first-line imaging:** directly visualises emboli to ≤1 mm, gives a four-chamber view (**RV:LV diameter ratio >1** predicts 30-day death) and alternative diagnoses; limited for subsegmental clots and needs iodinated contrast.
- **V/Q scan** — second-line (contrast allergy/renal failure/pregnancy): **normal scan excludes PE;** high-probability scan (≥2 segmental mismatched defects) ~87–90% predictive. **SPECT-V/Q** gives fewer non-diagnostic results.
- **Venous compression ultrasound** — loss of vein compressibility is the key DVT criterion; a positive leg study in suspected PE carries equivalent therapeutic implication.
- **Echocardiography** — not for diagnosis but for **risk stratification:** RV dilatation/hypokinesis, **McConnell's sign** (RV free-wall hypokinesis with apical sparing), reduced TAPSE; also excludes mimics (tamponade, MI, aortic dissection).

Management / Treatment

- ▶ **Anticoagulation is the cornerstone** for all PE; start empirically when suspicion is high and bleeding risk low. **DOACs are first-line** for most patients.

Agent	Regimen
UFH	Bolus 80 U/kg, then 18 U/kg/h; target aPTT 60–80 s (anti-Xa 0.3–0.7 U/mL)
Enoxaparin (LMWH)	1 mg/kg SC 12-hourly (no monitoring unless obese/CKD)
Fondaparinux	Weight-based SC OD; does not cause HIT
Rivaroxaban	15 mg BID × 3 weeks → 20 mg OD (monotherapy)
Apixaban	10 mg BID × 1 week → 5 mg BID (monotherapy)
Dabigatran / Edoxaban	After 5 days parenteral: dabigatran 150 mg BID / edoxaban 60 mg OD
Warfarin	Bridge with parenteral ≥5 days until INR 2.0–3.0 ×2 readings

- ▶ **HIT**: use **argatroban** (hepatic) or **bivalirudin** (renal); fondaparinux is an alternative. **APS and pregnancy** → **not** DOACs (warfarin/LMWH respectively).
- ▶ **Massive (high-risk) PE**: cautious volume (≈500 mL normal saline — over-filling worsens RV strain), **norepinephrine** (pressor of choice) + **dobutamine** (inotrope), and **systemic thrombolysis** — FDA-approved **alteplase 100 mg IV over 2 h** (off-label 50 mg). Major bleeding ~10%, intracranial haemorrhage 2–3%; contraindicated with intracranial disease, recent surgery/trauma, stroke <3 months. **VA-ECMO** for refractory shock.
- ▶ **Submassive (intermediate-risk) PE**: anticoagulate + **monitor closely**; routine thrombolysis is controversial (PEITHO: reduced decompensation but excess major bleeding/ICH, no mortality benefit) — reserve thrombolysis/catheter therapy for clinical deterioration.
- ▶ **Catheter-directed therapy** (pharmacologic, mechanical/suction, or pharmacomechanical/ultrasound-facilitated low-dose lysis) and **surgical embolectomy** — for high-risk PE when thrombolysis fails or is contraindicated.
- ▶ **IVC filter** — only for **active bleeding precluding anticoagulation** or **recurrent VTE despite adequate anticoagulation**; prefer a **retrievable** filter.
- ▶ **Duration (ESC 2019)**: “provoked/unprovoked” terminology de-emphasised; ≥3 months for major transient risk factor; **extended/indefinite** anticoagulation for no identifiable/persistent risk factor, recurrent VTE, active cancer (LMWH or apixaban/edoxaban) or APS, with periodic risk–benefit review.
- ▶ **Long-term sequelae**: post-PE syndrome (persistent dyspnoea/RV dysfunction), postthrombotic syndrome, and **chronic thromboembolic pulmonary hypertension (CTEPH)** in ~2% — treat

with **pulmonary thromboendarterectomy** (mortality 1–5% at expert centres), or balloon pulmonary angioplasty + pulmonary vasodilators if inoperable.

- ▶ **Prevention:** low-dose UFH/LMWH/fondaparinux prophylaxis in at-risk hospitalised and surgical patients; mechanical (IPC/graduated stockings) when anticoagulation is contraindicated.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Integrated diagnostic algorithm** — boxes/arrows: *Suspect PE* → *assess clinical probability (Wells)* → *Low/Moderate: D-dimer (normal = stop; raised = CTPA)* → *High: straight to CTPA* → *CTPA positive = treat; negative = consider V/Q / leg ultrasound*. Labels: **Clinical probability, D-dimer, CTPA, V/Q scan, Venous ultrasound, Risk-stratify (PESI/sPESI, RV function, troponin)**.
- ▶ **Pathophysiology flow-chart of massive PE:** PE → ↑RV afterload → ↑RV wall tension → RV dilatation/dysfunction → septal shift → ↓LV filling → ↓cardiac output/↓systemic BP → ↓RV coronary perfusion → RV ischaemia/microinfarction → circulatory collapse.

Clinical / Diagnostic significance

- ▶ Risk stratification (haemodynamics + sPESI + RV function + troponin) directly determines therapy: low-risk → outpatient anticoagulation; intermediate → admit and monitor; high-risk → reperfusion.
- ▶ A **negative D-dimer** in a low-probability patient safely avoids imaging and radiation; CTPA simultaneously diagnoses PE, assesses RV size, and offers alternative diagnoses.
- ▶ Persisting/initial pulmonary hypertension after PE mandates echocardiographic follow-up at ~6 weeks and 6 months to detect CTEPH, a potentially curable cause of PH.

High-yield exam pointers

- ▶ 90% of PE arise from proximal lower-limb DVT; commonest symptom = dyspnoea, commonest sign = tachypnoea.
- ▶ **Wells score** >4 = high probability → image directly; **age-adjusted D-dimer** = age × 10 ng/mL in >50 yr.
- ▶ CTPA is first-line imaging; **normal V/Q or normal perfusion scan** excludes PE.
- ▶ **S1Q3T3** and **T-inversion V1–V4** on ECG; **McConnell's sign** on echo; **Westermarck/Hampton's hump/Palla's sign** on CXR.
- ▶ **sPESI** = age >80, cancer, cardiopulmonary disease, pulse ≥110, SBP <100, SaO₂ <90% (1 each).
- ▶ **Alteplase 100 mg over 2 h** for massive PE; **norepinephrine + dobutamine** for PE shock; cautious fluids only.
- ▶ **DOACs first-line; warfarin/LMWH (not DOACs)** in APS and pregnancy; HIT → argatroban/bivalirudin.

- ▶ **IVC filter** only if anticoagulation contraindicated or VTE recurs despite it; CTEPH in ~2% → thromboendarterectomy.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Deep-Venous Thrombosis and Pulmonary Thromboembolism” (epidemiology, pathophysiology, classification, diagnostic algorithm, anticoagulation table, massive-PE management, ESC 2019 duration guidance).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Pulmonary Thromboembolism: Presentation and Diagnosis” and “Prophylaxis and Treatment” (Wells/PERC/YEARS, PESI/sPESI, risk stratification, PEITHO, reperfusion strategies).
- ▶ **CMDT 2026** — “Pulmonary Disorders” (current risk-stratified treatment, thrombolysis indications, IVC filter, outpatient management).



Refractory Bronchial Asthma

Asked in: Paper III Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Refractory* (severe/difficult-to-treat) asthma is asthma that **remains uncontrolled despite, or requires, the highest-intensity guideline therapy** (GINA Step 4–5: high-dose ICS/LABA ± LAMA) once adherence, inhaler technique, triggers, comorbidities and alternative diagnoses have been optimised. It constitutes only ~5–10% of all asthmatics yet consumes nearly 50% of asthma-related costs and carries the bulk of asthma morbidity and mortality. The modern approach is to first distinguish *true* severe asthma from “difficult-to-treat” asthma, then **phenotype/endotype** the patient (type-2 high vs type-2 low) to target add-on biologic therapy.

Terminology — difficult-to-treat vs severe vs uncontrolled

Term	Definition (ERS/ATS, GINA)
Difficult-to-treat asthma	Uncontrolled despite high-dose ICS + second controller (LABA/LAMA), OR needing this therapy to stay controlled — <i>before</i> modifiable factors are addressed. Chronic OCS dependence is included.
Severe (refractory) asthma	Asthma that remains difficult to treat after correcting adherence, inhaler technique, triggers and comorbidities — i.e. requires GINA Step 4/5 to prevent it becoming uncontrolled, or stays uncontrolled despite this.
Uncontrolled asthma (ERS/ATS — any one of 4)	1. Poor symptom control : ACQ ≥1.5 or ACT ≤19; 2. Frequent severe exacerbations : ≥2 systemic-steroid bursts (≥3 days each) in past year; 3. Serious exacerbation : ≥1 hospitalisation, ICU stay or

Term	Definition (ERS/ATS, GINA)
	mechanical ventilation in past year; 4. Airflow limitation: FEV ₁ <80% predicted (with FEV ₁ /FVC below the lower limit of normal) after withholding bronchodilators.

- ▶ Up to 50% of “poorly controlled” referrals are due to poor adherence or wrong inhaler technique, not truly refractory disease — these must be excluded first.

Step 1 — Confirm the diagnosis and unmask the “fakers”

- ▶ **Re-confirm asthma objectively** — reversible obstruction ($\geq 12\%$ and 200 mL, or the newer $\geq 10\%$ rise in FEV₁ % predicted), peak-flow variability $>20\%$, or airway hyperresponsiveness (methacholine PD₂₀ ≤ 400 μg). $>1/3$ of physician-labelled “asthma” does not meet diagnostic criteria.
- ▶ **Exclude mimics** (overlapping obstructive picture): heart failure, COPD / asthma-COPD overlap, α_1 -antitrypsin deficiency, inducible laryngeal obstruction (vocal-cord dysfunction) — present in up to 75% of asthmatics, diagnosed by truncated/flattened inspiratory flow-volume loop and laryngoscopy showing paradoxical adduction with posterior “chinking”, endobronchial mass/foreign body, bronchiectasis, bronchiolitis obliterans, tracheobronchomalacia.
- ▶ **Identify aggravating comorbidities:** chronic rhinosinusitis $\pm$ nasal polyps, GERD, obesity (blunts steroid response), OSA, anxiety/depression, ongoing smoking and occupational/allergen exposure.
- ▶ **Screen for specific refractory phenotypes:** ABPA (IgE >1000 IU/mL, eosinophils $>500/\mu\text{L}$, positive *Aspergillus* skin test, specific IgE & IgG, central bronchiectasis — treat with itraconazole/voriconazole + OCS) and aspirin-exacerbated respiratory disease (AERD) (asthma + eosinophilia + sinusitis + nasal polyps + COX-1-inhibitor-triggered attacks from leukotriene overproduction).

Step 2 — Phenotype and endotype (the key to refractory asthma)

Type-2 HIGH (eosinophilic/allergic)	Type-2 LOW (non-eosinophilic)
Early-onset allergic asthma; late-onset eosinophilic asthma; AERD; exercise-induced; exacerbation-prone	Obesity-related late-onset; paucigranulocytic (fixed obstruction, little inflammation); neutrophilic; smoking-related
Biomarkers $\uparrow$: blood eos $\geq 300/\mu\text{L}$, sputum eos $>2-3\%$, FeNO $>25-50$ ppb, $\uparrow$ IgE / specific IgE	Biomarkers low/absent; poor steroid response
Responds to ICS and to type-2 biologics	Often steroid-resistant; $\sim 30-50\%$ of asthmatics; consider tiotropium, macrolide (azithromycin 500 mg thrice weekly)

- ▶ FeNO is IL-13-driven: >20–25 ppb on moderate–high ICS in severe asthma indicates persistent type-2 inflammation OR non-adherence (FeNO is steroid-suppressible, so it doubles as an adherence check).
- ▶ Extreme eosinophilia should prompt search for eosinophilic granulomatosis with polyangiitis (EGPA) or hypereosinophilic syndromes.

Step 3 — Pharmacologic escalation (GINA Step 5)

- ▶ **Optimise inhaled therapy: high-dose ICS/LABA** (formoterol-based as both maintenance & reliever — “MART/AIR” strategy), then **add-on LAMA** (tiotropium).
- ▶ **Adjuncts:** leukotriene modifiers (especially in AERD — leukotriene overproduction; and exercise-induced symptoms), **azithromycin** in selected eosinophilic and non-eosinophilic patients.
- ▶ **Chronic OCS** only as a last resort at lowest effective dose (alternate-day if possible) given cumulative toxicity — diabetes, osteoporosis, cataract/glaucoma, hypertension, adrenal suppression; add bone-protection and *Pneumocystis* prophylaxis if ≥ 20 mg prednisone/day chronically.
- ▶ **Bronchial thermoplasty** (radiofrequency ablation of airway smooth muscle over 3 bronchoscopies) — only in trials/registries; sham effect prominent and device now largely withdrawn.

Step 4 — Add-on biologic (“targeted”) therapy for severe type-2 asthma

Biologic	Target / MOA	Selection biomarker	Dose
Omalizumab	Anti-IgE (binds free IgE Cε3 domain)	IgE 30–700 IU/mL + perennial allergen sensitisation	75–375 mg SC every 2–4 wk (by weight & IgE)
Mepolizumab	Anti-IL-5	Blood eos $\geq 150/\mu\text{L}$ (or $\geq 300/\mu\text{L}$ prior yr)	100 mg SC every 4 wk (300 mg for EGPA)
Reslizumab	Anti-IL-5	Blood eos $\geq 400/\mu\text{L}$; age ≥ 18	3 mg/kg IV every 4 wk
Benralizumab	Anti-IL-5Rα (depletes eosinophils)	Blood eos $\geq 300/\mu\text{L}$	30 mg SC $\times 3$ every 4 wk, then every 8 wk
Dupilumab	Anti-IL-4Rα (blocks IL-4 and IL-13)	Blood eos $\geq 300/\mu\text{L}$ or FeNO >25 ppb	200/300 mg SC every 2 wk (caution eos >1500/ μL)
Tezepelumab	Anti-TSLP (upstream epithelial <i>alarmin</i>)	Works even without raised type-2 biomarkers	SC (cuts exacerbations 50–70%)

- ▶ Biologics **reduce exacerbations** by ~50% (tezepelumab up to 70%) and are OCS-sparing (mepolizumab, benralizumab, dupilumab proven; not reslizumab). Mepolizumab, dupilumab and benralizumab also treat coexisting **nasal polyposis**; mepolizumab is the only one approved for EGPA.
- ▶ Assess response at ~4 months: most have a partial response, **10–15% are non-responders** (switch biologic), a few achieve complete response (then wean OCS/ICS, watch for adrenal insufficiency).

Step 5 — Acute severe asthma / status asthmaticus

- ▶ **Recognise impending failure**: silent chest, exhaustion, altered sensorium, and a **normal or rising PaCO₂ in a distressed, tachypnoeic patient** (most present with hypocapnia — normocapnia = danger).
- ▶ **Oxygen** to keep SpO₂ >90%; **high-dose nebulised SABA** (≥3 in first hour, then frequent/continuous) + **ipratropium**; **systemic corticosteroid early** (prednisone 40–60 mg/day or methylprednisolone 1.5–2 mg/kg IV).
- ▶ **IV magnesium sulfate 2 g over 20 min** (40 mg/kg in children, max 2 g) for severe exacerbation (FEV₁ <25% predicted or non-responders).
- ▶ **NIV** in alert, cooperative patients; **heliox** and inhaled volatile anaesthetics (isoflurane/halothane) for refractory bronchospasm.
- ▶ **Mechanical ventilation** if respiratory arrest/impending arrest: **low minute ventilation** (RR 12–14, V_t 6–8 mL/kg), **high inspiratory flow**, **minimal/no PEEP**, **permissive hypercapnia** to avoid dynamic hyperinflation/barotrauma; deep sedation ± short-term paralysis. Avoid sedatives/mucolytics outside ventilation; antibiotics only for proven infection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Asthmatic vs normal airway cross-section** — label: *epithelial denudation/shedding, basement-membrane (subepithelial collagen) thickening, smooth-muscle hypertrophy & hyperplasia, submucosal oedema, mucus plug/goblet-cell metaplasia, eosinophil/cellular infiltrate, vascular & neuronal proliferation, narrowed lumen.*
- ▶ **Type-2 inflammatory cascade with biologic targets** — label: *allergen/alarmins (TSLP, IL-33, IL-25) → epithelium → ILC2 / Th2 → IL-4, IL-5, IL-13 → IgE, eosinophils, mucus/AHR, with arrows naming omalizumab (IgE), mepolizumab/reslizumab/benralizumab (IL-5/IL-5R), dupilumab (IL-4Ra), tezepelumab (TSLP).*

Clinical / Diagnostic significance

- ▶ A structured “**confirm–exclude–phenotype–target**” pathway converts unselected “difficult” asthma into treatable subgroups and is the single highest-yield concept.

- ▶ **Biomarkers (eos, FeNO, IgE) are predictive, not merely diagnostic** — they select biologic responders and monitor type-2 activity and adherence.
- ▶ **Recognising AERD and ABPA changes management** (leukotriene modifiers/aspirin desensitisation; antifungal + steroid respectively).
- ▶ **In acute care, response to the first hour of therapy predicts need for admission better than presentation severity.**

High-yield exam pointers

- ▶ Severe asthma = GINA Step 4–5; ~5–10% of asthmatics, ~50% of cost.
- ▶ **ERS/ATS uncontrolled = any of:** ACT ≤ 19 /ACQ ≥ 1.5 ; ≥ 2 OCS bursts/yr; ≥ 1 hospitalisation-ICU-ventilation/yr; FEV₁ $< 80\%$ predicted.
- ▶ **First step is always adherence + inhaler technique** (cause in up to 50%).
- ▶ **Type-2 high** (eos ≥ 300 , FeNO ≥ 25 , $\uparrow$ IgE) responds to ICS + biologics; **type-2 low** is steroid-resistant.
- ▶ **6 biologics:** anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL-4R α (dupilumab), anti-TSLP (tezepelumab); **tezepelumab works in biomarker-low disease.**
- ▶ **ABPA:** IgE > 1000 IU/mL + eos > 500 + central bronchiectasis $\rightarrow$ itraconazole + steroid.
- ▶ **AERD:** asthma + nasal polyps + aspirin sensitivity $\rightarrow$ leukotriene modifier / aspirin desensitisation / anti-IL-5 / dupilumab.
- ▶ **Status asthmaticus:** normalising PaCO₂ = impending failure; ventilate with permissive hypercapnia, low rate/V_T, minimal PEEP.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Asthma” (definitions of severe/difficult-to-treat asthma, pathophysiology, type-2/non-type-2 inflammation, biologics incl. tezepelumab, AERD, ABPA, acute attack/status asthmaticus management, high-risk-death features).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Asthma: Diagnosis and Management” (ERS/ATS severe-asthma and uncontrolled-asthma criteria, phenotype/endotype & biomarker tables, FDA-approved biologics table with doses, difficult-to-treat vs severe definitions, acute asthma & mechanical-ventilation strategy, vocal-cord dysfunction).
- ▶ **CMDT 2026** — “Pulmonary Disorders” (Asthma) (current stepwise/add-on management, IV magnesium indication, acute-exacerbation severity & antibiotic guidance).



Role of Glucocorticoids in Management of Chronic Obstructive Pulmonary Disease

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — Chronic obstructive pulmonary disease (COPD) is a common, preventable, treatable disorder characterised by persistent, incompletely reversible airflow limitation arising from chronic airway and systemic inflammation driven by noxious particles/gases (chiefly cigarette smoke and biomass fuel). Because inflammation is central to its pathogenesis, **glucocorticoids** — with their broad anti-inflammatory action — are an attractive intervention. However, the inflammation of COPD is relatively *steroid-resistant*, so glucocorticoids occupy a **selective, eosinophil- and exacerbation-guided** role rather than being universal therapy. Their utility differs sharply by route (inhaled vs systemic) and by setting (stable disease vs acute exacerbation).

Rationale and why COPD is relatively steroid-resistant

- ▶ Airway and systemic inflammation are critical to COPD pathogenesis; glucocorticoids suppress transcription of pro-inflammatory cytokine genes, and **inhaled corticosteroids (ICS)** offer this benefit while minimising systemic exposure.
- ▶ Unlike asthma, COPD inflammation responds **poorly** to steroids. The molecular basis is *oxidative/nitrosative inactivation of histone deacetylase-2 (HDAC-2)* — cigarette-smoke-derived reactive oxygen species and peroxynitrite nitrate and inactivate HDAC-2, the enzyme normally recruited by the glucocorticoid receptor to switch off activated inflammatory genes.
- ▶ Consequently steroid efficacy is blunted; *low-dose theophylline* can partially **restore HDAC-2 activity and steroid responsiveness** (basis for theophylline as an add-on, though limited by its narrow therapeutic window).
- ▶ This explains the cardinal clinical rule: **ICS are never used as monotherapy in COPD** and the response is best in patients with an *eosinophilic/asthma-like* inflammatory signature.

Inhaled corticosteroids (ICS) in stable COPD

- ▶ **Main role = reduction of exacerbations**, especially in those with $FEV_1 \leq 60\%$ predicted and a frequent-exacerbator phenotype; exacerbation reduction (~20–25%) is comparable to that of a LABA or LAMA.
- ▶ Effect on lung function is **modest** — improvement in FEV_1 of only ~50–100 mL, less than achieved with bronchodilators; four large 3–5-year trials failed to show that ICS slow the long-term decline in lung function.
- ▶ **Little symptomatic benefit alone**, so ICS are always combined with a long-acting bronchodilator: ICS + LABA, or as **triple therapy** ICS + LABA + LAMA (single-inhaler triple therapy improves adherence).
- ▶ Landmark trials shaping practice:

- *TORCH* (6112 patients, 3 years; placebo vs fluticasone vs salmeterol vs combination) — fluticasone–salmeterol improved lung function, health status and exacerbations more than either agent alone; a post-hoc analysis suggested a reduced rate of FEV₁ decline.
 - *IMPACT* — triple therapy (ICS/LABA/LAMA) and ICS/LABA reduced **all-cause mortality** versus LABA/LAMA in an on-treatment analysis (strongest signal for an ICS mortality benefit, in fairly severe disease: mean FEV₁ ≈45%, CAT ≈20).
 - *FLAME* — in exacerbators, LABA/LAMA (indacaterol–glycopyrronium) was **superior** to ICS/LABA (fluticasone–salmeterol) for exacerbation reduction (0.98 vs 1.19/year), reinforcing that ICS are not first-line for all exacerbators.
- Common ICS molecules: **fluticasone (propionate/furoate)**, **budesonide**, **mometasone**, **beclomethasone**, combined with LABAs (salmeterol, formoterol, vilanterol).

Eosinophil-guided ICS use and GOLD placement

The blood eosinophil count is the key biomarker predicting ICS benefit and is built into GOLD recommendations.

Blood eosinophil count	Likelihood of ICS benefit	Practical implication
< 100 cells/μL	Low — little/no exacerbation reduction	ICS generally not favoured; consider withdrawal
100–300 cells/μL	Intermediate zone	ICS may be tried and response assessed (add if exacerbations persist on dual bronchodilators)
≥ 300 cells/μL	Greatest likelihood of benefit	ICS supported as part of initial/escalation therapy; ICS withdrawal risks more exacerbations

GOLD (2024) initial pharmacological therapy — ICS placement:

Group	Definition	Recommended start	Role of ICS
A	≤1 exacerbation (no admission); low symptoms (mMRC 0–1 / CAT <10)	A bronchodilator	No
B	≤1 exacerbation; more symptoms (mMRC ≥2 / CAT ≥10)	LABA + LAMA	No
E	≥2 moderate exacerbations or ≥1 leading to hospitalisation	LABA + LAMA	Consider adding ICS if blood eos ≥300

- ▶ On **follow-up**, ICS is **added** to dual bronchodilator therapy if exacerbations persist and eos ≥ 100 ; in stable patients without exacerbations, **ICS withdrawal** may be considered (withdrawal does not increase exacerbations overall but may cause a small fall in FEV₁; de-escalation is riskier if eos ≥ 300).
- ▶ Other favourable factors for ICS: **concomitant asthma/ACO, history of hospitalised exacerbations**.

Systemic (oral) glucocorticoids in stable COPD

- ▶ **Chronic oral glucocorticoids are NOT recommended** for stable COPD because of an unfavourable benefit/risk ratio — and chronic systemic steroid use is associated with **increased mortality**.
- ▶ Tapering patients off chronic low-dose prednisone (~10 mg/day) does **not** worsen exacerbation frequency, quality of life or lung function — supporting withdrawal.
- ▶ A rare exception: in exacerbation-prone patients requiring repeated high-dose courses, the *lowest possible* maintenance dose may occasionally reduce total annual steroid exposure, but this is discouraged.

Glucocorticoids in acute exacerbations of COPD (AECOPD)

This is the **strongest, evidence-based indication** for glucocorticoids in COPD.

- ▶ **Benefits in hospitalised exacerbations:** shorten length of stay, **hasten recovery** (faster improvement in FEV₁ and oxygenation), and **reduce the chance of relapse / subsequent exacerbation**.
- ▶ **Regimen:**
 - *Harrison 22e / GOLD:* **prednisone 40 mg orally (or equivalent) once daily for 5 days** — a short course is as effective as longer courses (REDUCE-trial principle).
 - *CMDT 2026:* **prednisone ~0.5 mg/kg/day orally for 7–10 days** in hospitalised patients, with even 5 days often adequate.
 - Oral and IV routes are equivalent in most patients; IV methylprednisolone is reserved for those unable to take oral or critically ill.
- ▶ **Key acute complication: hyperglycaemia**, most frequent in patients with pre-existing diabetes — requires glucose monitoring.
- ▶ Combined with the rest of AECOPD therapy: short-acting bronchodilators (SABA $\pm$ SAMA), **antibiotics** (for increased sputum purulence/volume + dyspnoea, typically 5–7 days), controlled **oxygen** (target SpO₂ 88–92%) and NIV for respiratory acidosis (PaCO₂ >45 mmHg, pH ≤ 7.35).

Adverse effects of glucocorticoids in COPD

Inhaled corticosteroids (ICS)	Systemic / oral glucocorticoids
Oral/oropharyngeal candidiasis (thrush)	Hyperglycaemia / glucose intolerance (commonest acute AE)
Dysphonia (hoarseness)	Osteoporosis and fractures
Pneumonia (increased incidence, esp. severe COPD)	Weight gain, fluid retention, cushingoid features
Easy bruising / skin capillary fragility	Cataracts, glaucoma
Reduced bone density, cataracts (with prolonged use)	Increased risk of infection ; myopathy; HPA-axis suppression; increased mortality with chronic use

Mitigation: spacer use, mouth rinsing/gargling after ICS, lowest effective dose, ICS withdrawal when stable, and short steroid courses for exacerbations.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **GOLD 2024 ABE initial-therapy + eosinophil decision tree (showing where glucocorticoids fit).** Labels: *Groups A / B / E; Group A → a bronchodilator; Group B → LABA + LAMA; Group E → LABA + LAMA, consider + ICS if eos ≥ 300 ; eosinophil ladder boxes — <100 (no ICS), $100-300$ (intermediate, trial ICS), ≥ 300 (ICS favoured); arrows for escalation (add ICS) and de-escalation (withdraw ICS).*
- ▶ **HDAC-2 mechanism of steroid resistance.** Labels: *cigarette smoke → oxidative/nitrosative stress (ROS, peroxynitrite) → inactivation/nitration of HDAC-2 → failure to switch off pro-inflammatory genes → relative steroid resistance; side-arrow theophylline → restores HDAC-2 activity.*

Clinical / Diagnostic significance

- ▶ **Phenotype-directed therapy:** measure the **blood eosinophil count** before committing a patient to long-term ICS — it predicts who benefits and limits unnecessary pneumonia/steroid risk.
- ▶ ICS reduce exacerbations but do **not** alter the relentless FEV₁ decline or (mostly) mortality — set patient expectations accordingly.
- ▶ **Pneumonia vigilance:** in a patient on ICS who develops recurrent pneumonia, consider ICS de-escalation, especially if eos <100 .
- ▶ For an **acute exacerbation**, give a short systemic steroid course early — it is one of the few interventions that shortens admission and prevents relapse; monitor capillary glucose.
- ▶ Avoid **chronic oral steroids** for stable COPD; if a patient is steroid-dependent, attempt a structured taper.

High-yield exam pointers

- ▶ Glucocorticoid role in COPD is **selective**, NOT universal — driven by **exacerbation risk + blood eosinophils**.
- ▶ **ICS are never used as monotherapy** — always with LABA ($\pm$ LAMA = triple therapy).
- ▶ ICS **reduce exacerbations** (~20–25%) but give only ~50–100 mL FEV₁ gain and do not slow lung-function decline.
- ▶ **Eosinophil thresholds**: <100 = **no benefit**; ≥ 300 = **favour ICS**; 100–300 = trial and assess.
- ▶ Key ICS adverse effects: **oral candidiasis, dysphonia, pneumonia**, reduced bone density, cataracts.
- ▶ **Chronic oral glucocorticoids are NOT recommended** (unfavourable risk/benefit; increased mortality).
- ▶ **AECOPD**: prednisone **40 mg/day $\times$ 5 days** (GOLD/Harrison) or **0.5 mg/kg/day $\times$ 7–10 days** (CMDT) — shortens stay, hastens recovery, cuts relapse; **hyperglycaemia** is the commonest acute complication.
- ▶ Trials to quote: **TORCH** (fluticasone–salmeterol), **IMPACT** (triple therapy $\rightarrow$ lower all-cause mortality), **FLAME** (LABA/LAMA > ICS/LABA in exacerbators).
- ▶ Mechanism of steroid resistance = **oxidative inactivation of HDAC-2**; theophylline restores it.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Chronic Obstructive Pulmonary Disease” (inhaled and oral glucocorticoids in stable disease, eosinophil-guided ICS, GOLD ABE initial therapy, systemic glucocorticoids in exacerbations — prednisone 40 mg $\times$ 5 days).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “COPD: Diagnosis and Management” (ICS efficacy/FEV₁ 50–100 mL, ~20–25% exacerbation reduction, TORCH/IMPACT/FLAME, eosinophil thresholds, adverse effects, chronic systemic steroids and mortality) and “COPD: Pathogenesis and Natural History” (HDAC-2 inactivation and steroid resistance; theophylline restoring HDAC-2).
- ▶ **CMDT 2026** — “Pulmonary Disorders / COPD” (judicious ICS in severe COPD with frequent exacerbations / eos ≥ 300 / concomitant asthma; ICS withdrawal after 2 years stable; oral corticosteroids not for long-term use; hospitalised exacerbation prednisone 0.5 mg/kg/day for 7–10 days).



Sarcoidosis

Asked in: Paper III Jun 2024 · Paper III Nov 2022 (2 $\times$) — RGUHS MD General Medicine

Definition / Introduction — Sarcoidosis is a multisystem inflammatory disease of unknown aetiology characterised by the formation of **nonnecrotizing (noncaseating) epithelioid-cell granulomas** in affected organs. It involves the **lung and intrathoracic lymph nodes in >90%** of cases but can afflict almost any organ. It is presumed to result from an **exaggerated TH1 immune response to an undetermined antigen in a genetically susceptible host**. The skin lesions were first described by *Jonathan Hutchinson* (lupus pernio, Mortimer's malady) and termed "*sarkoid*" by *Caesar Boeck* (1899) because they resembled sarcoma yet were benign. Course is highly variable — spontaneous remission in just over half, chronic organ-threatening disease in the rest.

Epidemiology & Etiopathogenesis

- ▶ **Incidence/prevalence:** highest in **African Americans (~35.5/100,000)** and **Northern Europeans/Swedes (~24/100,000)**; US Black Women's Health Study noted prevalence ~2%. Female preponderance (ratio usually <2:1). **Peak age 35–45 years**, though a significant proportion present after 55.
- ▶ **Risk factors:** familial clustering, certain occupational/environmental exposures (firefighters; post-9/11 World Trade Center responders had markedly raised "sarcoid-like" disease), mould/musty environments, raised BMI. *Smoking is consistently associated with reduced odds (negative predictor)*.
- ▶ **Putative antigens:** mycobacterial proteins (*mKatG*, *ESAT-6*, *superoxide dismutase A*, *antigen 85A*, *heat-shock proteins*) and *Cutibacterium (Propionibacterium) acnes*; transmissibility supported by the historical **Kveim–Siltzbach reagent** (splenic homogenate inducing granulomas) and donor-derived sarcoid-like disease in transplant recipients.
- ▶ **Genetics:** HLA class II haplotypes determine acute vs chronic phenotype; risk/prognosis variants include **BTNL2 (butyrophilin-like 2)**, **TNF- α** and **ANXA11 (annexin A11)**.
- ▶ **Pathogenesis:** poorly degradable antigen presented by macrophages/dendritic cells via **MHC** to **CD4⁺ T cells** → **highly polarized TH1 response** (IFN- γ , IL-2, IL-12/15/18, CXCR3) → activated macrophages aggregate into tightly formed granulomas. Dysregulated **T-regulatory and TH17** responses underlie failure of resolution and progression to fibrosis.

Clinical Features & Organ Involvement

- ▶ **Constitutional:** fever, malaise, night sweats, weight loss, multifactorial fatigue (up to 80%).
- ▶ **Acute syndromes (excellent prognosis, often spontaneous remission ~80%):**
 - **Löfgren syndrome** — *fever + erythema nodosum + bilateral hilar lymphadenopathy + ankle arthritis/peri-arthralgia*; common in Northern Europeans (20–30% of Caucasians), rare in Asians/African Americans.
 - **Heerfordt (uveoparotid fever) syndrome** — *anterior uveitis + parotid enlargement + fever + facial (VII) nerve palsy*. Both are clinically diagnostic and may obviate biopsy.

Organ	Approx. frequency	Key features
Lungs/thoracic nodes	~95%	Upper-lobe predominant; perilymphatic nodules, BHL; restriction ± obstruction
Skin	~16%	Erythema nodosum (non-granulomatous); lupus pernio (chronic, poor prognosis)
Peripheral lymph nodes	~15%	Discrete, mobile, nontender
Eyes	~12%	Uveitis (commonest), optic neuropathy (vision-threatening)
Liver	~12%	Granulomas common; ↑alkaline phosphatase; usually subclinical
Spleen	~7%	Splenomegaly, usually silent
Nervous system	~5%	Cranial neuropathy (VII, optic), basal meningitis, hypothalamic-pituitary dysfunction, small-fibre neuropathy
Salivary/parotid	~4%	Heerfordt; Sjögren-like
Heart	~2% clinical	AV block, VT, cardiomyopathy, sudden death
Kidney	~1%	Interstitial nephritis; nephrocalcinosis from hypercalciuria

- ▶ **Hypercalcaemia (10–20%) / hypercalciuria (up to 50%)**: unregulated **1- α -hydroxylase** (CYP27B1) activity in macrophages converts vitamin D to **calcitriol (1,25-(OH) $_2$ D $_3$)** *despite suppressed PTH* → ↑gut absorption + bone resorption → nephrocalcinosis.
- ▶ **Cardiac sarcoidosis**: ventricular tachycardia is the commonest arrhythmia; **sudden cardiac death is the commonest cause of death** in cardiac involvement and may be the presenting event.
- ▶ **Pulmonary hypertension**: a **WHO Group 5** cause; consider when symptoms/desaturation are disproportionate to parenchymal disease or DLCO is low.

Diagnosis & Investigations

- ▶ **Three diagnostic criteria** (the diagnosis is never absolutely secure): (1) **compatible clinical/radiological picture**, (2) **histological nonnecrotizing granuloma** in ≥1 tissue, and (3) **exclusion of alternative causes** (TB/atypical mycobacteria, fungi, berylliosis, hypersensitivity pneumonitis, lymphoma, IgG4-RD, vasculitis, drug/checkpoint-inhibitor reactions).
- ▶ **Biopsy**: least-invasive accessible site (skin, conjunctiva, peripheral node). For mediastinal/hilar disease, **EBUS-guided TBNA** has high yield with low risk; **transbronchial lung biopsy** yield

~75–90%. Airway granulomas give a *cobblestone* mucosa. Surgical biopsy/mediastinoscopy reserved for nondiagnostic cases.

- ▶ **Histology:** tightly formed granuloma of epithelioid cells + **multinucleated giant cells**, rimmed by lymphocytes/fibroblasts; CD4⁺ cells central, CD8⁺/B cells peripheral. Inclusions: **asteroid bodies**, **Schaumann bodies**, **Hamazaki-Wesenberg bodies**, birefringent calcium oxalate/carbonate crystals (all non-specific).
- ▶ **BAL:** lymphocytosis with **CD4:CD8 ratio** >3.5 supports the diagnosis (specificity ~95% in some series); a normal ratio does not exclude it. Also excludes infection.
- ▶ **Baseline workup (all patients):** history/examination, PFTs, **chest imaging**, **ophthalmologic exam** (silent uveitis), ECG, serum creatinine, alkaline phosphatase, **calcium**, CBC, and 25-/1,25-vitamin D.
- ▶ **Chest radiograph — Scadding stages** (predict resolution, *not* activity):

Stage	Radiographic finding	Spontaneous resolution
0	Normal chest X-ray	—
I	Bilateral hilar lymphadenopathy alone	55–90%
II	BHL + parenchymal infiltrates	40–70%
III	Parenchymal infiltrates without BHL	10–20%
IV	Pulmonary fibrosis, volume loss, architectural distortion	~0%

- ▶ **HRCT:** perilymphatic micronodules along bronchovascular bundles and subpleural surfaces, beaded interlobular septa, mediastinal/hilar nodes; advanced → honeycombing, traction bronchiectasis, cavitation.
- ▶ **Cardiac:** ECG screening in all; **cardiac MRI with late gadolinium enhancement is the preferred test** (FDG-PET if MRI unavailable/contraindicated), largely replacing endomyocardial biopsy (low sensitivity owing to patchy involvement); perfusion shows *reverse redistribution*.
- ▶ **Serum markers:** **ACE** (from epithelioid cells) is *neither sensitive nor specific* — roughly tracks granuloma burden, not diagnostic; soluble IL-2 receptor correlates with activity/relapse. Hypercalcaemia, ↑ESR and ↑alkaline phosphatase are supportive.

Treatment

- ▶ **Principle:** there is **no cure**; aim is to suppress granulomatous inflammation, prevent irreversible fibrosis and relieve symptoms. **Treat only when indicated** — asymptomatic Stage I and mild disease are observed (high spontaneous remission). Treat for significant/progressive pulmonary impairment or dangerous extrapulmonary disease (cardiac, neuro, ocular/vision-threatening, symptomatic hypercalcaemia, disfiguring skin).

Line	Agent(s)	Dose / note
First-line	Oral corticosteroids (prednisone/prednisolone)	0.5 mg/kg/day or ~20–40 mg/day × 4 wk, taper to maintenance <10 mg/day; SARCORT (India) — 20 mg ≈ 40 mg starting dose
Second-line (steroid-sparing)	Methotrexate (most recommended)	7.5–20 mg/week + folic acid; monitor LFT/CBC; avoid in alcohol use
	Azathioprine / Leflunomide / Mycophenolate	alternatives; azathioprine has higher infection/malignancy risk
	Hydroxychloroquine	200–400 mg/day — useful for skin & hypercalcaemia, not pulmonary
Refractory / steroid-dependent	Infliximab (TNF- α mAb, best evidence) / Adalimumab	screen for TB first; avoid in heart failure
Ineffective	Etanercept	TNF-receptor antagonist — <i>not effective, do not use</i>
Topical/local	Inhaled or injected/topical steroids	mild airway cough, skin lesions

- **Refractory** = failure to respond to the equivalent of **prednisone 40 mg/day**. **Duration ~1 year** (shorter courses → higher relapse). Bisphosphonates to prevent steroid-induced osteoporosis; periodic eye exams on steroids/hydroxychloroquine. **Organ transplantation** (lung/heart/liver/kidney) for end-stage disease; granulomas may recur in the graft but rarely cause graft failure.
- **Supportive / parasarcoidosis syndromes**: fatigue, small-fibre neuropathy, pain, depression and cognitive impairment often respond poorly to immunosuppression — manage with exercise training, sleep/pain/neuropsychiatric care.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Immunopathogenesis schematic**: Unknown antigen → APC/macrophage with MHC → TCR on CD4⁺ T cell (activated) → TH1 response (IFN- γ , IL-2) with TH17 → noncaseating granuloma → branch to Resolution vs Fibrosis (modulated by Treg). Labels: *Unknown antigen, MHC, TCR, CD4⁺ T cell, TH1, TH17, Treg, Granuloma, Resolution, Fibrosis*.
- **Sarcoid granuloma vs comparators**: (A) Sarcoidosis — tightly formed, nonnecrotizing; (B) Tuberculosis/fungal — tight with caseous necrotic centre; (C) Hypersensitivity pneumonitis — loosely formed, non-necrotizing. Label central **epithelioid** +

multinucleated giant cells, peripheral lymphocyte rim, and inclusions (asteroid / Schaumann bodies).

Clinical / Diagnostic significance

- ▶ A diagnosis of **exclusion** — always rule out TB (critical in India) and lymphoma before labelling; necrosis on biopsy argues strongly against sarcoidosis.
- ▶ Every patient needs **baseline ophthalmology, ECG, calcium and PFTs** because silent uveitis, conduction disease and hypercalcaemia are organ/sight/life-threatening.
- ▶ **Scadding stage predicts resolution rate, not disease activity** — do not use it alone to decide treatment.
- ▶ **Pulmonary fibrosis is the leading cause of sarcoid death** (Western populations); **cardiac involvement predominates as cause of death in Japanese patients**.
- ▶ Steroid-sparing agents should be introduced early when prolonged (>1 year) therapy is anticipated to limit cumulative steroid toxicity.

High-yield exam pointers

- ▶ **Noncaseating granuloma + lung/intrathoracic nodes in >90%**; histology of **exclusion**.
- ▶ **Löfgren** = EN + BHL + ankle arthritis + fever (good prognosis); **Heerfordt** = uveoparotid fever + VII palsy.
- ▶ BAL CD4:CD8 > 3.5; EBUS-TBNA preferred for mediastinal nodes; TBLB yield 75–90%.
- ▶ **Scadding stages I–IV**: I 55–90%, II 40–70%, III 10–20%, IV ~0% resolution.
- ▶ **Hypercalcaemia** from macrophage 1- α -hydroxylase → **calcitriol with low PTH**.
- ▶ **ACE is neither sensitive nor specific** — for activity monitoring, not diagnosis.
- ▶ **Cardiac MRI (LGE)** preferred for cardiac sarcoid; VT commonest arrhythmia, **sudden death** commonest cardiac death.
- ▶ **First-line steroids**; methotrexate second-line; **infliximab** refractory; **etanercept** ineffective.
- ▶ Poor-prognosis markers: **lupus pernio, chronic uveitis, neuro/cardiac involvement, chronic hypercalcaemia/nephrocalcinosis, pulmonary hypertension, fibrotic (Stage IV) disease, African origin**.
- ▶ **Smoking is protective**; PH in sarcoidosis is **WHO Group 5**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Sarcoidosis” (Gerke; immunopathogenesis, organ involvement frequencies, Scadding staging with resolution rates, hypercalcaemia mechanism, treatment table including doses, prognosis).

- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Sarcoidosis” (Scadding patterns, HRCT perilymphatic distribution, serum ACE from epithelioid cells, BAL CD4:CD8 specificity, Löfgren/Heerfordt definitions, refractory = failure of prednisone 40 mg/day, corticosteroid-sparing rationale, parasarcoidosis syndromes).
- **CMDT 2026** — “Sarcoidosis” (**Pulmonary Disorders**) (essentials, staging, transbronchial-biopsy yield, prednisone 0.5–1.0 mg/kg/day, SARCORT 20 vs 40 mg trial, cardiac MRI over PET, prognosis figures).



Screening Tools, Etiology and Treatment of Obstructive Sleep Apnea

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterised by recurrent episodes of complete (apnea) or partial (hypopnea) collapse of the pharyngeal airway during sleep, producing intermittent hypoxemia, hypercapnia, large intrathoracic pressure swings and cortical arousals. Diagnosis requires either symptoms of disturbed nocturnal breathing (snoring, gasping, witnessed pauses) or unexplained daytime sleepiness **plus** ≥ 5 obstructive apneas/hypopneas per hour of sleep (the **apnea–hypopnea index, AHI**) on a sleep study; OSA may also be diagnosed *asymptotically* if $\text{AHI} \geq 15$. It is the commonest medical cause of daytime sleepiness, affects 5–15% of middle-aged and $>20\%$ of elderly adults (largely undiagnosed), and is a major driver of hypertension and cardiovascular disease.

Screening tools for OSA

Because symptoms and signs poorly predict disease severity, validated questionnaires are used to *risk-stratify* patients and decide who needs objective sleep testing (they screen, they do not diagnose).

- **STOP-BANG questionnaire** — the most widely used screen in both medical and surgical (pre-operative) populations. It combines **three symptoms** (Snoring, Tiredness, Observed apnea) with **five clinical characteristics** (high blood Pressure, BMI, Age, Neck circumference, male Gender). Each “yes” scores 1 (range 0–8). A higher score escalates probability of moderate–severe OSA (conventionally: 0–2 low risk; 3–4 intermediate; 5–8 high risk). Specificity can be improved by adding pulse oximetry, **serum bicarbonate**, or body shape (apple vs pear).

Letter	Item	Threshold
S	Snoring (loud)	Louder than talking / heard through door
T	Tiredness / daytime sleepiness	Most days

Letter	Item	Threshold
O	Observed apnea	Witnessed pauses
P	Pressure (hypertension)	Treated or untreated
B	BMI	>35 kg/m ²
A	Age	>50 years
N	Neck circumference	>40 cm
G	Gender	Male

- ▶ **Epworth Sleepiness Scale (ESS)** — quantifies *subjective daytime sleepiness* across 8 everyday situations, each rated 0–3 (total 0–24); a score >10 indicates excessive daytime sleepiness. Useful to track symptom response to therapy but does not correlate tightly with AHI.
- ▶ **Berlin Questionnaire** — three categories (snoring/witnessed apnea, daytime sleepiness/fatigue, and hypertension or obesity); patients positive in ≥2 categories are “high risk.”
- ▶ **Other instruments** — *Sleep Apnea Clinical Questionnaire*, *Pittsburgh Sleep Quality Index (PSQI)* for overall sleep quality, *Insomnia Severity Index (ISI)*, and the *Functional Outcomes of Sleep Questionnaire*. Validation in patients with coexisting pulmonary disease (e.g., COPD) is limited.
- ▶ **Confirmatory testing follows a positive screen** — overnight in-laboratory polysomnography (PSG) is the gold standard; **home sleep apnea testing (HSAT)** is a cost-effective alternative when pre-test probability is moderate–high and there is no significant cardiorespiratory comorbidity. A negative home study with high prior probability should be followed by PSG. Overnight oximetry alone is insufficient to diagnose OSA.

Etiology and risk factors

OSA arises when an **anatomically collapsible pharynx** (no bony/cartilaginous support) loses the stabilising tone of the pharyngeal dilator muscles at sleep onset; non-anatomic (“endotypic”) traits modulate this. The major risk factors are **obesity, male sex and older age**.

Category	Specific factors
Obesity (40–60% attributable)	Upper-airway fat narrowing the lumen; reduced lung volume → loss of caudal tracheal traction; reduced chest-wall compliance. <i>10% weight gain → >30% rise in AHI; ≥4-fold OSA risk vs lean</i>
Soft-tissue crowding	Macroglossia, enlarged tonsils/adenoids (chief cause in children 3–8 yr), bulky uvula, low-lying/long soft palate, increased lymphoid tissue
Craniofacial / skeletal	Mandibular retrognathia, micrognathia, mandibular retroposition, small posterior airway space, high-arched palate (most evident in non-obese patients)

Category	Specific factors
Nasal obstruction	Septal deviation, polyps, turbinate hypertrophy, allergic rhinitis ($\uparrow$ nasal resistance $\rightarrow$ mouth opening, tongue falls back)
Ventilatory-control instability (non-anatomic endotypes)	High loop gain (oversensitive CO ₂ response), low arousal threshold, poor pharyngeal muscle responsiveness
Demographic / genetic	Male sex (2 $\times$; android obesity, longer pharynx), older age, post-menopausal women, strong heritability (1st-degree relative $\rightarrow$ $\sim$ 2 $\times$ risk), East-Asian craniofacial predisposition, higher risk in African Americans
Genetic syndromes	Down syndrome, Treacher-Collins syndrome
Endocrine / metabolic	Acromegaly, hypothyroidism; associations with diabetes, PCOS
Comorbid / provocative	Hypertension, heart failure, atrial fibrillation; alcohol within 3 h of sleep, sedative-hypnotics and opiates ($\downarrow$ pharyngeal tone); supine posture and REM sleep worsen events

Diagnosis and severity grading

- ▶ **Respiratory events** — *Apnea*: ≥ 10 s cessation of airflow with persistent effort (obstructive). *Hypopnea*: $\geq 30\%$ airflow reduction for ≥ 10 s with $\geq 3\%$ desaturation **or** an arousal. *RERA*: increased inspiratory effort terminating in arousal without meeting hypopnea criteria.
- ▶ **Indices** — AHI = apneas + hypopneas per hour of sleep; RDI additionally includes RERAs.
- ▶ **Severity (AHI)** — **Mild** 5–14/h; **Moderate** 15–29/h; **Severe** ≥ 30 /h. Hypoxemic burden, event duration, sleep fragmentation and degree of sleepiness further characterise severity.
- ▶ A “non-dipping” nocturnal blood-pressure pattern, secondary erythrocytosis and a screening TSH (to exclude hypothyroidism) are typical supportive findings.

Treatment options

Management is comprehensive and individualised; therapies are *not mutually exclusive* and combination/switching is common. Objective sleep testing should precede treatment.

- ▶ **Behavioural / risk-factor modification** (foundation in all patients) — weight loss (markedly effective, including after bariatric surgery); optimise sleep duration (7–9 h) and regular schedule; **avoid supine sleep**; treat nasal allergy; increase physical activity; **eliminate alcohol within 3 h of bedtime**; minimise opiates; avoid sedative-hypnotics in moderate–severe OSA; counsel against drowsy driving.

- ▶ **Positive airway pressure (PAP)** — CPAP is the standard first-line therapy with the highest level of evidence; it acts as a pneumatic splint maintaining pharyngeal patency. **Auto-titrating CPAP (APAP, 5–20 cmH₂O)** removes the need for an in-lab titration in many patients; **BPAP** helps those who cannot exhale against pressure. Adherence is variable (~50–80%; only ~75% continue at 1 year) and is improved by a skilled team managing side effects (nasal congestion → heated humidification/saline; claustrophobia → mask change; aerophagia → antacids).
- ▶ **Oral appliances (mandibular advancement devices)** — advance the mandible and pull the tongue forward; reduce AHI by ≥50% in two-thirds of patients; best for **mild–moderate OSA or CPAP intolerance**; side effects: temporomandibular joint pain, tooth movement (need adequate dentition).
- ▶ **Positional therapy** — vibrotactile devices for **supine-predominant OSA** can cut AHI by up to 50%.
- ▶ **Upper-airway surgery** — less effective than CPAP, reserved for snorers, mild OSA, or CPAP failure. **Uvulopalatopharyngoplasty (UPPP)** is the commonest (helps ~50%, better for snoring than apnea); often combined as **multilevel surgery**; **maxillomandibular advancement** for skeletal deficiency; nasal septoplasty for anatomical deformity. **Bariatric surgery** benefits the obese. **Tracheostomy** is the definitive bypass but has major morbidity.
- ▶ **Hypoglossal nerve (upper-airway) stimulation** — implanted device for **moderate–severe OSA** (AHI 15–65, up to 100), BMI <35 (FDA <40), absence of complete concentric collapse at the velum on drug-induced sleep endoscopy, and <25% central events; for CPAP-intolerant/failed patients; durable benefit ≥5 years; also approved for children ≥13 yr and Down syndrome (AHI 10–50).
- ▶ **Pharmacotherapy** — *no agent is yet FDA-approved as primary therapy*. **GLP-1 / dual GLP-1–GIP receptor agonists** (tirzepatide ~16–17% weight loss with AHI reduction; liraglutide smaller effect) and **SGLT-2 inhibitors** are under investigation; noradrenergic–antimuscarinic combinations are in phase-3 trials. **Wake-promoting agents** (e.g., **modafinil, solriamfetol**) treat *residual* sleepiness despite adequate CPAP. **Supplemental oxygen is not routine** (may prolong apneas).
- ▶ **Treat secondary/contributory disease** — hypothyroidism, acromegaly, heart failure; optimise comorbid hypertension and atrial fibrillation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Sagittal upper-airway diagram** (Fig 308-1): mid-sagittal pharynx showing the sites of collapse — label **Palate** (soft palate, most common), **Tongue base**, **Lateral pharyngeal walls**, **Epiglottis**, with the **nasopharynx**, **oropharynx**, **hypopharynx** and CPAP/mandibular-advancement effect arrows.

- ▶ **Polysomnography tracing of an obstructive event (Fig 308-2):** stacked channels labelled EEG, EOG, chin EMG, ECG, snore, nasal-pressure airflow, thermistor flow, chest, abdomen, SaO₂ — show **flat airflow with persistent chest–abdomen paradox** (effort against an occluded airway) terminating in an **arousal + SaO₂ desaturation**.

Clinical / Diagnostic significance

- ▶ **Cardiometabolic burden:** OSA causes/aggravates **resistant and nocturnal (non-dipping) hypertension**, coronary artery disease, heart failure (HFrEF and HFpEF), atrial and ventricular arrhythmias, stroke, insulin resistance/diabetes and a pro-thrombotic, pro-inflammatory state; CPAP lowers 24-h BP (modestly, ~2–4 mmHg, more in sleepy/resistant patients).
- ▶ **Neurobehavioural:** excessive daytime sleepiness, impaired concentration, mood disturbance, and a 2–3× increase in motor-vehicle and occupational accidents — relevant to driving fitness certification.
- ▶ **Screen high-risk groups:** resistant hypertension, type 2 diabetes, atrial fibrillation, heart failure, pre-operative patients, and professional drivers.
- ▶ Note **sex differences** — women report fatigue/insomnia rather than classic sleepiness and have REM-predominant, shorter apneas, causing under-recognition.

High-yield exam pointers

- ▶ **STOP-BANG** = Snoring, Tiredness, Observed apnea, Pressure (HTN), BMI >35, Age >50, Neck >40 cm, Gender male; score ≥3 = increased OSA risk.
- ▶ **Diagnostic AHI ≥5 with symptoms, or ≥15 without;** gold standard = **polysomnography**.
- ▶ **Severity:** Mild 5–14, Moderate 15–29, **Severe ≥30 events/h**.
- ▶ **Hypopnea** = ≥30% airflow drop ≥10 s with ≥3% desaturation or arousal.
- ▶ **Obesity accounts for 40–60% of OSA; 10% weight gain → >30% rise in AHI.**
- ▶ Commonest collapse site = **soft palate**; commonest paediatric cause = **adenotonsillar hypertrophy**.
- ▶ **CPAP = first-line / highest evidence;** oral appliance for mild–moderate or CPAP intolerance; hypoglossal nerve stimulation for CPAP-failure (AHI 15–65, BMI <35, no concentric velar collapse).
- ▶ **No FDA-approved drug;** GLP-1/GIP agonists (tirzepatide) reduce weight and AHI; modafinil/solriamfetol for residual sleepiness only.
- ▶ OSA is a recognised cause of **secondary and resistant hypertension** (a “non-dipping” BP pattern).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Sleep Apnea” (definition, AHI/severity tables, pathophysiology, risk factors/etiology, CPAP and surgical/neurostimulation therapy, pharmacotherapy); “Disorders of Sleep” (screening, Epworth) and “Disorders of Ventilation” (STOP-Bang reference).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Sleep-Disordered Breathing: A General Approach” (STOP-Bang, Berlin, ESS, PSQI screening pathway; PSG vs HSAT), “Obstructive Sleep Apnea,” and “Sleep-Disordered Breathing: Treatment” (PAP modes, oral appliances, positional, surgical and pharmacologic options).
- ▶ **CMDT 2026** — “Pulmonary Disorders / Sleep Apnea” (clinical features, diagnostic AHI thresholds, treatment including hypoglossal nerve stimulation eligibility, UPPP, tracheostomy, GLP-1/GIP weight-loss therapy).

Coverage note: The Epworth (>10/24) and STOP-BANG numerical risk bands and item thresholds (BMI >35, age >50, neck >40 cm) are standard, universally accepted sleep-medicine values stated to complete the screening tools; the corpus confirms the eight STOP-BANG components, the Berlin/ESS/PSQI instruments and all AHI/severity, etiology and treatment specifics quoted above.



Silicosis

Asked in: Paper IV Nov 2022 · Paper IV May 2022 (2×) — RGUHS MD General Medicine

Definition / Introduction — **Silicosis** is a fibrotic interstitial lung disease (a **pneumoconiosis**) caused by inhalation of **free crystalline silica (SiO₂)**, principally as **quartz**. It is one of the oldest known occupational lung hazards and remains a major cause of disease worldwide. Pulmonary fibrosis due to silica characteristically develops in a **dose-response fashion**, usually after many years of exposure, though intense exposure can cause fulminant disease within months. The hallmark lesion is the **upper-zone silicotic nodule**, which may coalesce into **progressive massive fibrosis (PMF)**.

Etiology, sources and pathogenesis

- ▶ **Hazardous agent:** free silica (SiO₂), i.e., **crystalline quartz**. Risk relates to the *free silica content* of the inhaled dust.
- ▶ **Respirable particle size:** only particles <10 µm deposit below the larynx; **coarse-mode** (2.5–10 µm) crustal particles such as silica deposit relatively high in the tracheobronchial tree. Particles >10–15 µm are filtered in the nose/throat.
- ▶ **Major occupational exposures:** mining; stone-cutting; sand-blasting; glass and cement manufacturing; foundry work; packing of silica flour; quarrying (particularly granite).

- ▶ **Recent outbreaks / emerging high-risk work:** sand-blasting of denim jeans to make them look “used,” and the manufacture and installation of artificial (“faux granite”/engineered quartz) stone kitchen countertops — a cause of acute silicosis in young workers.
- ▶ **Pathogenesis (source-grounded):** inhaled silica is ingested by **alveolar macrophages**; silica is directly cytotoxic and causes **alveolar macrophage dysfunction**. Silica also has **immunoadjuvant properties**, driving a fibrogenic and autoimmune-prone inflammatory response that produces the characteristic nodular fibrosis. The fibrosis may be **progressive even after exposure ceases**.
- ▶ **Dose–response and cumulative dose:** the probability and severity of fibrosis rise with **intensity × duration** of respirable-silica exposure; this explains why most chronic disease follows years of work while intense confined-space exposure can cause disease within months.
- ▶ **Macrophage defence is impaired**, leaving the silicotic lung vulnerable to intracellular pathogens — a single mechanism that links silicosis to both **tuberculosis** and the autoimmune/carcinogenic complications below.

Clinical–radiological types

Type	Exposure / latency	Key features
Acute silicosis (<i>silicoproteinosis</i>)	Very heavy exposure (sand-blasting in confined spaces , tunnelling rock of 15–25% quartz , artificial-stone work) — symptoms within months	Clinical & pathological features resemble pulmonary alveolar proteinosis ; rapidly progressive; severe even after exposure stops
Accelerated silicosis	Heavy exposure over ~5–10 years (standard textbook category)	Features intermediate between acute and chronic; faster progression to PMF
Chronic simple silicosis	Long-term, less intense exposure — opacities after 15–20 years	Small rounded opacities, upper lobes ; usually without functional impairment ; “eggshell” hilar node calcification in up to 20%
Complicated silicosis / PMF	Coalescence of nodules (may progress <i>without</i> further exposure)	Non-segmental conglomerate masses >1 cm in upper zones; significant restrictive + obstructive impairment

- ▶ **Acute silicosis imaging:** chest radiograph may show **profuse miliary infiltration or consolidation**; HRCT shows a “**crazy-paving**” pattern (ground-glass with thickened intralobular/interlobular septa producing polygonal shapes).
- ▶ **Complicated silicosis:** silicotic nodules coalesce into **irregular conglomerate masses >1 cm**; when these become large the term **progressive massive fibrosis (PMF)** is applied.

Investigations and radiology

- ▶ **Chest radiograph (ILO classification):** the International Labour Organisation (ILO) International Classification of Radiographs of Pneumoconioses grades opacities; **small rounded opacities** are typical of silicosis (and coal-worker's pneumoconiosis), contrasting with the **small linear/irregular opacities** of asbestosis. Useful for epidemiology/screening but limited in the individual worker.
- ▶ **HRCT:** more sensitive than plain film for detecting **silicotic nodules** and the **crazy-paving** pattern of acute disease; nodules are often **subpleural** and **upper-zone predominant**.
- ▶ **"Eggshell" calcification** of hilar lymph nodes is a classic supportive sign (up to ~20% of cases).
- ▶ **Pulmonary function tests:** often normal in **simple** silicosis; PMF produces **mixed restrictive and obstructive** deficits with reduced diffusing capacity.
- ▶ **Occupational history** is central — quantify type, intensity and duration of exposure; combine work history with any environmental sampling data to estimate cumulative exposure.

Complications and associations

- ▶ **Tuberculosis (silicotuberculosis):** because silica causes **alveolar macrophage dysfunction**, patients are at **increased risk of active TB** and other intracellular pathogens (*Mycobacterium tuberculosis*, atypical mycobacteria, fungi). Because of this risk, **treatment of latent TB** is given for a longer duration in silicotic patients.
- ▶ **Autoimmune connective-tissue disease:** silica's **immunoadjuvant** effect predisposes to rheumatoid arthritis and scleroderma.
- ▶ **Caplan syndrome:** combination of **pneumoconiotic nodules** and **seropositive rheumatoid arthritis** — first described in coal miners but subsequently recognised in silicosis.
- ▶ **Lung cancer:** the International Agency for Research on Cancer (IARC) lists silica as a **probable lung carcinogen**.
- ▶ **COPD / chronic airflow obstruction** may accompany dust exposure.
- ▶ **Related silicate/inorganic-dust exposures** to consider: fuller's earth, kaolin, mica, diatomaceous earths, silica gel, soapstone, carbonate and cement dusts; **talc** and **vermiculite** may be contaminated with asbestos (risk of fibrosis, lung cancer, mesothelioma).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Chest radiograph of chronic/complicated silicosis (frontal view).** Labels: *upper-zone small rounded nodules; "eggshell" calcification of hilar lymph nodes; conglomerate mass = progressive massive fibrosis (PMF); relatively spared lower zones; retracted hila.*
- ▶ **Diagram 2 — Pathogenesis flow.** Labels: *Inhaled crystalline silica (respirable, $<10\ \mu\text{m}$) → Alveolar macrophage ingestion → Macrophage cytotoxicity / dysfunction + immunoadjuvant effect → Release of inflammatory & fibrogenic mediators → Silicotic nodule formation →*

Fibrosis → coalescence → PMF; side-branches to ↑ TB risk, autoimmune disease (RA, scleroderma), probable lung carcinogen.

Clinical / Diagnostic significance

- ▶ **Diagnosis** rests on a triad of **compatible occupational exposure history**, **characteristic chest imaging** (upper-zone rounded nodules ± eggshell nodal calcification ± PMF on radiograph/HRCT), and **exclusion of mimics** (especially TB and sarcoidosis). Lung biopsy is rarely needed and is reserved for atypical presentations.
- ▶ **Differential diagnosis:** **pulmonary tuberculosis** (always exclude active disease before attributing upper-zone change to silicosis), **sarcoidosis** (bilateral hilar adenopathy, granulomas), **coal-worker's pneumoconiosis** and **chronic beryllium disease** (sarcoid-like, occupational), and for acute silicosis, **pulmonary alveolar proteinosis** (which it mimics clinically, radiologically and pathologically).
- ▶ **No specific curative therapy** exists; management is **supportive**, as for any diffuse interstitial lung disease — exposure cessation, smoking cessation, oxygen and pulmonary rehabilitation, and vaccination.
- ▶ **Whole-lung lavage** may provide **symptomatic relief and slow progression** in **acute silicosis** (mirroring its role in alveolar proteinosis).
- ▶ **Active TB surveillance** and **prolonged treatment of latent TB infection** are essential because of the markedly raised tuberculosis risk.
- ▶ **Prevention is paramount:** dust control (wet methods, enclosure, ventilation), substitution, respiratory protection, periodic chest imaging/PFT surveillance, and regulatory exposure limits — protection has improved in developed countries but risk persists in developing-country and engineered-stone settings.

High-yield exam pointers

- ▶ Causative agent = **free crystalline silica (SiO₂)/quartz**; only **respirable (<10 µm)** particles cause disease.
- ▶ **Upper-zone** small rounded nodules + “**eggshell**” **hilar nodal calcification** = classic silicosis radiology.
- ▶ **Acute silicosis** = **silicoproteinosis** — resembles **pulmonary alveolar proteinosis**, HRCT “**crazy paving**,” treat with **whole-lung lavage**; seen in **artificial-stone/quartz countertop** workers and **denim sand-blasting**.
- ▶ **Simple → complicated → PMF**: PMF = conglomerate masses >1 cm; may progress **even after exposure stops**.
- ▶ **Silicotuberculosis** — high active-TB risk; give **longer latent-TB treatment**.

- ▶ **Caplan syndrome** = pneumoconiotic nodules + **seropositive rheumatoid arthritis**.
- ▶ Silica is a **probable lung carcinogen (IARC)** and predisposes to **scleroderma & RA**.
- ▶ High-quartz tunnelling = **15–25% quartz**; tunnelling/sand-blasting in **confined spaces** → acute disease in **months**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 300 "Occupational and Environmental Lung Disease" (silicosis section, particle-deposition and ILO-classification sections, Table 300-1; Caplan syndrome cross-ref Ch 370). **Coverage note:** the chapter explicitly describes *acute, simple chronic* and *complicated/PMF* silicosis; the intermediate "**accelerated silicosis**" category and the generic **supportive-care/prevention** measures (smoking cessation, vaccination, dust control, surveillance) are universally accepted standard internal medicine added for completeness and are not verbatim subtypes in the provided text. Detailed molecular pathogenesis (e.g., NALP3/inflammasome) is beyond the provided chapter and is therefore not asserted.



Systemic manifestation of COPD

Asked in: Paper III Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Chronic obstructive pulmonary disease (COPD) is a disease state characterised by **persistent respiratory symptoms and airflow obstruction**, and encompasses *emphysema* (alveolar destruction with air-space enlargement), *chronic bronchitis* (chronic cough and phlegm) and *small airway disease*. Although defined by spirometric airflow limitation, COPD is now recognised as a **multi-system disorder**: a low-grade systemic inflammatory "spill-over" together with chronic hypoxaemia, physical inactivity and shared smoking-related risk drives extrapulmonary effects and **comorbidities** that independently determine symptoms, exacerbations, quality of life and mortality. Harrison explicitly directs the clinician to seek symptoms of common comorbidities — **cardiovascular disease, gastro-oesophageal reflux, osteoporosis, frailty, depression and anxiety** — in every COPD patient.

Why COPD becomes a systemic disease (mechanistic basis)

- ▶ **Systemic inflammation / cytokine spill-over** — the airway inflammatory process is mirrored by raised circulating inflammatory cytokines, notably **tumour necrosis factor- α (TNF- α)**, which mediate wasting and contribute to several extrapulmonary effects.
- ▶ **Chronic hypoxaemia** — develops as airflow obstruction worsens; drives secondary **erythrocytosis (elevated haematocrit)**, pulmonary vasoconstriction/pulmonary hypertension and cor pulmonale, and signals the need for long-term oxygen.

- ▶ **Autoimmune component** — lymphoid follicles of B and T cells, TH1/TH17 activation and autoantibodies against elastin fragments and pulmonary epithelium perpetuate chronic inflammation even after smoking cessation.
- ▶ **Deconditioning & shared exposure** — dyspnoea-limited inactivity plus the common risk factor of tobacco smoke link COPD with cardiovascular disease, lung cancer, osteoporosis and metabolic disturbance.

Systemic manifestations & comorbidities — at a glance

System	Manifestation	Mechanism / note (Harrison)
Nutritional	Cachexia, weight loss, loss of subcutaneous fat	Inadequate intake + raised cytokines (TNF- α); independent poor prognostic factor
Musculoskeletal	Skeletal-muscle dysfunction, accessory-muscle use, reduced exercise capacity	Deconditioning, hyperinflation; quantified by 6-min walk
Skeletal	Osteoporosis	Listed comorbidity; aggravated by inhaled/oral glucocorticoids
Cardiovascular	Cardiovascular disease; cor pulmonale / RV failure, pulmonary hypertension	Hypoxaemia + pulmonary vascular destruction
Haematological	Secondary polycythaemia (raised haematocrit)	Chronic hypoxaemia; <i>anemia of chronic disease may coexist</i> (see Coverage note)
Neuropsychiatric	Depression, anxiety, frailty	Common, under-recognised comorbidities
GI / Metabolic	GERD; glucose intolerance, weight gain	GERD a comorbidity; metabolic effects largely steroid-related
Neoplastic	Lung cancer	Smokers with COPD at high risk; new clubbing must prompt work-up
Thrombotic	Pulmonary embolism	Incidence increased during exacerbations

Nutritional & musculoskeletal manifestations

- ▶ **Cachexia** is a feature of advanced disease — *significant weight loss with diffuse loss of subcutaneous adipose tissue*. It is linked to both **inadequate oral intake** and **elevated inflammatory cytokines** (e.g., TNF- α).
- ▶ Such **wasting** is an **independent poor prognostic factor** in COPD — i.e., it predicts mortality over and above the degree of airflow obstruction.

- ▶ **Body mass index (BMI)** is therefore embedded in the **BODE index** (Body mass index, airflow Obstruction, Dyspnoea, Exercise capacity), a multifactorial tool that predicts mortality better than FEV₁ alone.
- ▶ **Skeletal-muscle dysfunction & deconditioning** — patients use accessory muscles (sternocleidomastoid, scalene, intercostals) and adopt the “tripod” position; exercise capacity is reduced and is quantified by the distance walked in 6 minutes.
- ▶ **Osteoporosis** is a listed comorbidity and is compounded by therapy: **inhaled corticosteroids** are associated with loss of bone density (and cataracts, oropharyngeal candidiasis, pneumonia), and **chronic oral glucocorticoids** cause osteoporosis, weight gain, cataracts, glucose intolerance and increased infection risk — hence chronic oral steroids are *not recommended*.

Cardiovascular & pulmonary-vascular manifestations

- ▶ **Cardiovascular disease** is among the most important comorbidities to screen for in the history.
- ▶ **Cor pulmonale** — signs of overt **right heart failure** (raised JVP, lower-extremity oedema). Pulmonary arterial hypertension severe enough to cause cor pulmonale and **right ventricular failure** typically occurs with FEV₁ <25 % predicted and chronic hypoxaemia (PaO₂ <55 mmHg).
- ▶ Some patients develop significant **pulmonary arterial hypertension from pulmonary vascular destruction, independent of COPD severity**.
- ▶ Cor pulmonale has become *relatively infrequent since supplemental oxygen therapy* became available, but pulmonary hypertension must be considered in any patient with persistent activity limitation or lower-extremity oedema.
- ▶ **Right ventricular hypertrophy** signs and an **elevated haematocrit** are clues to chronic hypoxaemia.

Haematological, neuropsychiatric, neoplastic & other systemic effects

- ▶ **Secondary polycythaemia / erythrocytosis** — an **elevated haematocrit** suggests chronic hypoxaemia; erythrocytosis is itself one of the qualifying signs (with pulmonary arterial hypertension or right heart failure) that lowers the oxygen-saturation threshold for long-term O₂ to ≤89 % (≤88 % otherwise).
- ▶ **Central cyanosis** — visible in the lips and nail beds, reflecting hypoxaemia.
- ▶ **Lung cancer** — smokers with COPD are at high risk; annual **low-dose chest CT** screening reduces lung-cancer mortality. **Clubbing is NOT a feature of COPD** — its appearance must trigger a search for another cause, most often **lung cancer**.
- ▶ **Depression, anxiety and frailty** — frequent neuropsychiatric/whole-patient comorbidities that should be actively elicited.
- ▶ **Gastro-oesophageal reflux disease (GERD)** — a recognised comorbidity and a contributor to exacerbations.

- ▶ **Metabolic** — glucose intolerance and weight gain occur chiefly as adverse effects of glucocorticoid therapy.
- ▶ **Venous thromboembolism** — the incidence of **pulmonary embolism** is increased during **COPD exacerbations**, and PE should be considered when an exacerbation is atypical or refractory.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **“Spokes-of-a-wheel” / systemic-effects schematic** — central hub labelled **“COPD: airflow obstruction + systemic inflammation (TNF- α) + chronic hypoxaemia”**, with labelled spokes: *Cachexia / weight loss, Skeletal-muscle dysfunction, Osteoporosis, Cardiovascular disease, Cor pulmonale / pulmonary hypertension, Secondary polycythaemia, Depression / anxiety / frailty, GERD, Lung cancer, Pulmonary embolism (exacerbations)*.
- ▶ **BODE index box** — four labelled components: **B** = Body-mass index, **O** = airflow Obstruction (FEV_1 % predicted), **D** = Dyspnoea (mMRC scale), **E** = Exercise capacity (6-minute walk distance); arrow to *“predicts mortality better than FEV_1 alone.”*

Clinical / Diagnostic significance

- ▶ **Assess every COPD patient for comorbidities** — cardiovascular disease, GERD, osteoporosis, frailty, depression and anxiety — because they drive symptoms, hospitalisation and death independent of lung function.
- ▶ **Nutritional assessment** (BMI/weight trend) and **6-minute walk distance** feed the **BODE index** for prognostication.
- ▶ **Elevated haematocrit / RV-hypertrophy signs / erythrocytosis** prompt evaluation for chronic hypoxaemia and may qualify the patient for **long-term oxygen therapy** (resting $SpO_2 \leq 88\%$, or $\leq 89\%$ with pulmonary arterial hypertension, right heart failure or erythrocytosis) — the only intervention other than smoking cessation, LVRS and transplant shown to improve survival in hypoxaemic patients.
- ▶ **New digital clubbing** → **investigate for lung cancer**; offer annual **low-dose CT** screening to eligible smokers with COPD.
- ▶ **Minimise glucocorticoid burden** (avoid chronic oral steroids; monitor bone density with ICS) to limit osteoporosis, cataracts and dysglycaemia.
- ▶ **Consider pulmonary embolism** in exacerbations that do not fit the usual pattern.

High-yield exam pointers

- ▶ **Cachexia/wasting = independent poor prognostic factor**, mediated by TNF- α — a favourite one-liner.
- ▶ **BODE index** = BMI + airflow Obstruction + Dyspnoea + Exercise capacity; better mortality predictor than FEV_1 .

- ▶ **Cor pulmonale/RV failure** appears at FEV₁ <25 % predicted and PaO₂ <55 mmHg; PAH can also be hypoxaemia-independent (vascular destruction).
- ▶ **Clubbing** is NOT due to COPD — its presence means look for **lung cancer**.
- ▶ **Raised haematocrit (erythrocytosis)** = marker of chronic hypoxaemia; one of the O₂-therapy qualifying signs (threshold ≤89 %).
- ▶ Listed comorbidities to recite: **cardiovascular disease, GERD, osteoporosis, frailty, depression, anxiety**.
- ▶ **Steroid-related systemic harms**: osteoporosis, weight gain, cataracts, glucose intolerance, infection (oral); bone-density loss, candidiasis, pneumonia (inhaled).
- ▶ **PE incidence is increased during exacerbations**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 303 "Chronic Obstructive Pulmonary Disease" (physical examination, laboratory findings, comorbidities, pharmacotherapy and exacerbations sections).

Coverage note: The provided chapter explicitly describes cachexia, cardiovascular disease, cor pulmonale/pulmonary hypertension, osteoporosis, secondary polycythaemia (elevated haematocrit/erythrocytosis), depression/anxiety/frailty, GERD, lung cancer and exacerbation-related PE. It does **not** describe **anaemia of chronic disease** as a COPD comorbidity (it discusses the opposite — polycythaemia); anaemia is listed here as a GOLD-recognised, universally accepted comorbidity and flagged as outside this Harrison chapter. The mMRC dyspnoea scale and standard SpO₂ figure (88 %) are referenced as universally accepted; specific BODE thresholds beyond its four components are not detailed in the chapter.



Interstitial Lung Disease Associated with Connective Tissue Disorders (CTD-ILD): Spectrum, Therapy and Complications

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — Connective-tissue-disease-associated interstitial lung disease (CTD-ILD) is a heterogeneous group of diffuse parenchymal lung diseases occurring as an extra-articular/systemic manifestation of an autoimmune rheumatic disorder, in which inflammation and fibrosis remodel the alveolar–interstitial unit. ILD is a leading cause of morbidity and mortality across the connective tissue diseases (CTDs) and may **precede, accompany, or be the sole presenting feature** of the underlying CTD. It occurs most commonly in **systemic sclerosis (SSc), rheumatoid arthritis (RA), and polymyositis/dermatomyositis (PM/DM)**, and less frequently in **Sjögren syndrome (SS), systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD)**. Compared with idiopathic

interstitial pneumonia, CTD-ILD patients are typically younger, female and non-smokers, and—stage for stage—carry a better prognosis than idiopathic pulmonary fibrosis (IPF).

Connective tissue diseases that cause ILD — prevalence and dominant pattern

CTD	Prevalence of ILD	Commonest radiologic/histologic pattern (others)	Key associations
Systemic sclerosis (SSc)	40–75% clinically significant; up to 65–70% on HRCT (~50% diffuse, ~30% limited)	NSIP (UIP)	Anti-topoisomerase-I (Scl-70) → ILD risk; anti-centromere → protective, PAH
Rheumatoid arthritis (RA)	Clinically evident ~10%; HRCT abnormalities 30–60%	UIP (NSIP, OP, LIP)	Male, smokers, high RF/anti-CCP, MUC5B variant
PM/DM (inflammatory myopathy)	ILD up to 32–45% (highest with anti-synthetase antibodies)	NSIP ± OP (UIP, DAD)	Anti-synthetase syndrome (Jo-1); anti-MDA5 → rapidly progressive
Sjögren syndrome (SS)	Clinically significant 8–27%; HRCT up to 30%	NSIP (often fibrotic) (LIP, UIP, OP)	Must exclude pulmonary lymphoma (risk ↑40–50×)
Systemic lupus (SLE)	Chronic diffuse ILD 1–15% (3–11%)	NSIP (LIP, OP, UIP)	Acute lupus pneumonitis & DAH distinct entities
MCTD	Pleuropulmonary 20–85%	NSIP (UIP)	Anti-U1-RNP defines disease

Histopathological and HRCT patterns in CTD-ILD

- ▶ **Nonspecific interstitial pneumonia (NSIP)** — the *overall most frequent* pattern: bilateral, symmetric, subpleural ground-glass opacity and reticulation with traction bronchiectasis, often peribronchovascular; relative *subpleural sparing*; honeycombing uncommon. Cellular NSIP responds better than fibrotic NSIP.
- ▶ **Usual interstitial pneumonia (UIP)** — second commonest and *the dominant pattern in RA*: subpleural, basal honeycombing, reticulation and traction bronchiectasis indistinguishable from IPF; in RA shows **fewer fibroblastic foci, more germinal centres**.
- ▶ **Organizing pneumonia (OP)** — patchy migratory subpleural consolidation (reversed-halo/atoll sign); strongly linked to PM/DM and RA; steroid-responsive.
- ▶ **Lymphocytic interstitial pneumonia (LIP)** — diffuse peribronchiolar lymphocytic infiltrate; classically Sjögren syndrome.

- ▶ **Diffuse alveolar damage (DAD)** — substrate of acute pneumonitis/acute exacerbation; seen in anti-MDA5/Jo-1 myositis, acute lupus pneumonitis.
- ▶ *Radiologic clues to an underlying CTD*: multi-compartment disease (dilated air-filled oesophagus, pleural/pericardial involvement, pulmonary artery enlargement), extensive subpleural sparing, and exuberant honeycombing being relatively rare.

Disease-specific features and serology

- ▶ **SSc** — ILD is the commonest pulmonary manifestation and a *leading cause of SSc death*. Velcro basal crackles, dry cough, exertional dyspnoea; clubbing rare. FVC may fall by up to 30%/year in the **first 3–5 years**. Risk factors: male sex, African ancestry, diffuse cutaneous disease, severe GERD/microaspiration, anti-Scl-70. **Pulmonary arterial hypertension (PAH)** may coexist or occur in isolation (commoner in limited SSc/CREST, anti-centromere) — an isolated/disproportionate fall in DLCO or rising FVC/DLCO ratio is the screening alert.
- ▶ **RA** — UIP-predominant; *male and smoker* predominance unlike articular RA. Spectrum is wide: ILD, OP, **obliterative (constrictive) bronchiolitis**, follicular bronchiolitis, bronchiectasis, rheumatoid nodules ($\pm$ **Caplan syndrome** with pneumoconiosis), pleural disease (exudate, low glucose, low pH). **Methotrexate pneumonitis** is an important mimic.
- ▶ **PM/DM** — **Anti-synthetase syndrome**: anti-tRNA-synthetase antibody (commonest **anti-Jo-1**) + myositis, ILD, arthritis, fever, Raynaud's and *mechanic's hands*. Anti-Jo-1 and especially **anti-MDA5** (often clinically amyopathic DM) predict rapidly progressive, DAD-type ILD. Low/normal CK does not exclude severe ILD. Screen for occult malignancy.
- ▶ **SLE** — ILD itself uncommon; the dangerous entities are **acute lupus pneumonitis** (DAD, >50% mortality), **diffuse alveolar haemorrhage (DAH)**, **shrinking lung syndrome** (restrictive defect with raised hemidiaphragms, diaphragmatic dysfunction), pleuritis (commonest manifestation) and PAH.
- ▶ **Sjögren** — fibrotic NSIP and LIP; xerotrachea, small-airway disease/bronchiolitis; always exclude **pulmonary lymphoma**.
- ▶ **Antibody panel**: ANA, RF and anti-CCP in all suspected cases; targeted ENA (Scl-70, anti-centromere, SSA/Ro, SSB/La, U1-RNP, Sm) and myositis antibodies (Jo-1, PL-7, PL-12, EJ, OJ, MDA-5) in selected cases; **repeat serology**, as seroconversion is common.

Diagnostic approach and severity staging

- ▶ **Multidisciplinary diagnosis** (pulmonologist, rheumatologist, radiologist, pathologist) integrating clinical features, serology, **HRCT**, and **PFTs** — no single test is diagnostic.
- ▶ **PFT**: restrictive defect — reduced TLC, FVC and DLCO with preserved/raised FEV1/FVC; **DLCO is the most sensitive early marker** and a disproportionate isolated fall suggests pulmonary vascular disease.

- ▶ **HRCT** is standard of care; surgical/transbronchial biopsy is rarely needed because histologic pattern seldom alters management or prognosis in CTD (RA-UIP is the main exception). BAL is mainly to exclude infection/haemorrhage.
- ▶ **UKRSA (Goh–Wells) staging** for SSc-ILD: **limited disease** if HRCT extent <20% (or, when indeterminate, FVC ≥70%) vs **extensive disease** if HRCT >20% (or FVC <70%) — extensive disease predicts progression and death and identifies who to treat.

Therapy

- ▶ **General principles:** Not all CTD-ILD needs treatment; *stabilisation*, not reversal, is the realistic goal in fibrotic disease. Decision to treat weighs ILD severity (extent on HRCT, FVC/DLCO), rate of progression, CTD subtype, age and comorbidity. Treat early, during the highest-risk first few years.
- ▶ **Immunosuppression (first-line for inflammatory/cellular disease):**
 - **Mycophenolate mofetil (MMF)** 1–3 g/day — now preferred first-line for SSc-ILD (Scleroderma Lung Study II: equivalent efficacy to cyclophosphamide with better tolerability).
 - **Cyclophosphamide** — oral 2 mg/kg/day or IV pulses (750–1000 mg/m² monthly) for 6–12 months; modest benefit on FVC/skin (Scleroderma Lung Study), significant toxicity (cystitis, marrow suppression, malignancy, gonadal failure) — reserve for severe/progressive disease.
 - **Azathioprine** (≤2.5 mg/kg/day, max 200 mg) and **calcineurin inhibitors** (ciclosporin, tacrolimus) as alternatives/steroid-sparing, especially in myositis-ILD.
 - **Glucocorticoids** (prednisolone) — mainstay for cellular NSIP, OP, acute pneumonitis, DAH and myositis-ILD; **use with caution/avoid high dose in SSc** (precipitates scleroderma renal crisis) and in UIP-pattern disease.
- ▶ **Biologics:** **Tocilizumab** (anti-IL-6R) slows FVC decline in early SSc-ILD (focuSSced/FaSSciate); **Rituximab** (anti-CD20) for refractory/rapidly progressive disease, most effective in myositis-ILD and anti-synthetase syndrome; abatacept used in RA-ILD.
- ▶ **Antifibrotic therapy:** **Nintedanib** (tyrosine-kinase inhibitor) 150 mg bid is approved for SSc-ILD (SENSCIS: FVC decline reduced by 41 mL/yr, ~44% relative, additive to MMF) and for **progressive pulmonary fibrosis** of any CTD (INBUILD); **pirfenidone** under study (RA-ILD/unclassifiable).
- ▶ **Adjunctive/supportive:** high-dose **proton-pump inhibitors** / **anti-reflux** measures in SSc (microaspiration drives fibrosis); pulmonary rehabilitation; supplemental **oxygen**; vaccination; *Pneumocystis* prophylaxis when heavily immunosuppressed.
- ▶ **Advanced disease:** **Autologous haematopoietic stem cell transplantation (HSCT)** for selected early, rapidly progressive SSc at risk of organ failure (ASTIS, SCOT trials — improved event-free/overall survival). **Lung transplantation** for end-stage disease unresponsive to therapy,

provided extrapulmonary activity and major oesophageal dysfunction are absent. **PAH-specific therapy** (endothelin antagonists e.g. bosentan, PDE-5 inhibitors e.g. sildenafil, riociguat, selexipag, prostacyclins) when pulmonary vascular disease is present.

Complications

- ▶ **Progressive pulmonary fibrosis** → chronic respiratory failure, the major cause of death in SSc-ILD and RA-ILD.
- ▶ **Acute exacerbation** (new DAD) — abrupt dyspnoea, fresh ground-glass on HRCT without infection; commonest/most severe in RA, very high mortality.
- ▶ **Pulmonary hypertension / cor pulmonale** — from fibrosis-hypoxia (Group 3) or pulmonary vascular disease (Group 1 PAH, esp. SSc, MCTD, SLE).
- ▶ **Diffuse alveolar haemorrhage and acute pneumonitis** — life-threatening in SLE and myositis.
- ▶ **Therapy-related:** drug-induced pneumonitis (methotrexate, anti-TNF, leflunomide), opportunistic infection, scleroderma renal crisis from steroids, malignancy from cyclophosphamide.
- ▶ **Increased risk of lung cancer** (SSc, RA) and **pulmonary lymphoma** (Sjögren).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — HRCT/histology patterns of CTD-ILD (panel):** label *UIP* (subpleural-basal honeycombing + traction bronchiectasis), *NSIP* (symmetric ground-glass + reticulation, subpleural sparing), *OP* (patchy migratory subpleural consolidation / reversed-halo sign), *LIP* (peribronchiolar cysts), and *dilated oesophagus* (SSc clue).
- ▶ **Diagram 2 — SSc-ILD screening/treatment algorithm:** boxes labelled *New SSc diagnosis* → *screening HRCT + PFT (FVC, DLCO)* → *No ILD / Limited ILD (FVC ≥70%, HRCT <20%)* / *Extensive ILD (FVC <70%, HRCT >20%)* → *Monitor PFT 3–6 monthly* → *Progression?* → *First-line MMF/cyclophosphamide* → *Add nintedanib* → *Rescue: HSCT, lung transplant, palliative care* (UKRSA staging arm shown).

Clinical / Diagnostic significance

- ▶ ILD may be the **first clue to an occult CTD** — any “idiopathic” NSIP demands a full autoimmune work-up; ~15% of apparent idiopathic interstitial pneumonia (30% of idiopathic NSIP) prove to be CTD.
- ▶ **IPAF (Interstitial Pneumonia with Autoimmune Features)** — ATS/ERS construct for ILD with autoimmune features (≥1 feature from ≥2 of clinical, serologic, morphologic domains) that does not meet full CTD criteria; a provisional, evolving entity.
- ▶ Distinguishing CTD-ILD from IPF is essential: it changes prognosis (generally better) and treatment direction (immunosuppression helps CTD but **harms IPF**). Serial **FVC and DLCO** monitoring guides therapy; FVC decline predicts mortality.

- ▶ Screen every new SSc patient for ILD and for PAH (baseline + annual echocardiography/DLCO).

High-yield exam pointers

- ▶ ILD is commonest in SSc > RA > PM/DM, less in SS, SLE, MCTD.
- ▶ NSIP is the overall commonest pattern; UIP predominates in RA (worse prognosis than NSIP).
- ▶ Anti-Scl-70 → SSc-ILD; anti-centromere → protective/PAH; anti-Jo-1 → anti-synthetase syndrome; anti-MDA5 → rapidly progressive DM-ILD.
- ▶ MMF is first-line; nintedanib (antifibrotic) for SSc-ILD & progressive fibrosis; avoid/limit steroids in SSc (renal crisis) and in UIP.
- ▶ DLCO is the most sensitive PFT abnormality; isolated low DLCO → think PAH.
- ▶ SSc-ILD: FVC can fall ~30%/year in the first 3–5 years — *treat early*.
- ▶ RA pulmonary spectrum beyond ILD: obliterative bronchiolitis, nodules, **Caplan syndrome**, pleural exudate (low glucose, low pH).
- ▶ SLE emergencies: acute lupus pneumonitis, DAH, shrinking lung syndrome; Sjögren → LIP & lymphoma risk.
- ▶ UKRSA (Goh) staging: HRCT >20% or FVC <70% = extensive disease = treat.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Interstitial Lung Disease” (ILD associated with connective tissue disease: SSc, RA, dermatomyositis/polymyositis) and “Systemic Sclerosis (Scleroderma) and Related Disorders” (pulmonary features, PAH, treatment algorithm Fig. 372-15).
- ▶ **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — “Connective Tissue Diseases” (Corte & Wells): prevalence/pattern table, disease-specific sections, autoantibody and drug tables, UKRSA staging, IPAF criteria.
- ▶ **CMDT 2026** — “Pulmonary Disorders” (interstitial lung disease, differential and management) and “Rheumatologic, Immunologic & Allergic Disorders” for current drug regimens.



Spirometry — Physiological Principle, Indications and Interpretation

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Spirometry is the most widely used pulmonary function test; it records the volume and rate (flow) of air that a subject can inhale and exhale as a function of time during standardised breathing manoeuvres. The two cardinal manoeuvres are the slow vital-capacity (VC) manoeuvre (lung-volume sub-divisions) and the forced vital-capacity (FVC) manoeuvre (dynamic

airflow), displayed as a **volume–time spirogram** and a **flow–volume loop**. It is *effort-dependent*, requiring patient cooperation and trained technique, and is the foundation for diagnosing and grading **obstructive** and **restrictive** ventilatory defects.

Physiological principle

- ▶ The lung behaves as **three coupled mechanical components** — lung (with airways), neuromuscular pump, and chest wall. Inspiratory muscles lower pleural and alveolar pressure below airway-opening pressure to drive **inflation**; expiratory muscles (and elastic recoil) raise alveolar pressure to drive **deflation**.
- ▶ During a forced expiration from **total lung capacity (TLC)** to **residual volume (RV)**, airflow becomes **flow-limited**: beyond an initial effort-dependent spike, expiratory flow at any given lung volume reaches a maximum that **cannot be increased by greater effort** (the *effort-independent* portion). This is the basis of the reproducible FVC manoeuvre.
- ▶ Flow limitation arises from **dynamic airway compression**: as gas accelerates toward the mouth, intraluminal pressure and airway transmural pressure fall (**Bernoulli effect**), collapsing the compliant bronchi. Maximal expiratory flow at any volume is set by **gas density, airway calibre/distensibility, lung elastic recoil pressure, and frictional resistance** to the flow-limiting site.
- ▶ Consequently, maximal flow **falls as lung volume falls** (lower recoil and smaller airways at low volume); diseases that reduce recoil (**emphysema**), narrow airways (**asthma, chronic bronchitis**) or increase collapsibility lower maximal flow, whereas increased recoil (**pulmonary fibrosis**) raises flow *relative to volume*.
- ▶ Spirometry discloses only **relative volume changes** during these manoeuvres; it **cannot measure absolute volumes that include RV** (RV, FRC, TLC). These require **body plethysmography** (Boyle's law) or **inert-gas dilution / washout** (helium dilution, nitrogen washout).

Lung volumes, capacities and spirometric indices

Index	Meaning	Measurable by spirometry?
Tidal volume (V _T)	Volume of a quiet breath	Yes
Inspiratory capacity (IC), ERV	IC = TV + IRV; ERV = expiratory reserve	Yes
Vital capacity (VC)	TLC – RV; maximal slow excursion	Yes
FVC	Volume forcibly exhaled from TLC to RV	Yes
FEV ₁	Volume exhaled in the first second of FVC (a flow)	Yes

Index	Meaning	Measurable by spirometry?
FEV1/FVC ratio	Proportion of VC exhaled in 1 s — key obstruction marker	Yes
FEF25–75%	Mid-expiratory flow; reputed small-airway marker (high variability)	Yes
PEF	Peak expiratory flow	Yes
FEV6 / FEV1/FEV6	6-s surrogate for FVC (FEV1/FEV6 <0.73 ≈ FEV1/FVC <0.70)	Yes
MVV	Maximal voluntary ventilation (overall reserve)	Yes
RV, FRC, TLC, RV/TLC	Static volumes containing RV	No — need plethysmography / gas dilution

Indications and contraindications

- ▶ **Diagnose airflow obstruction and quantify its severity** (asthma, COPD — FEV1/FVC and FEV1 are part of the disease definitions).
- ▶ Evaluate **dyspnoea, chronic cough, wheeze, hypoxaemia or an abnormal chest image**; narrow the differential and trigger specific further testing.
- ▶ **Monitor disease activity and treatment response** over time; assess **bronchodilator reversibility** and **bronchial hyper-responsiveness** (methacholine challenge).
- ▶ **Pre-operative / fitness assessment** (e.g. predicting post-pneumectomy reserve; MVV estimable from FEV1) and **occupational / disability and impairment** evaluation.
- ▶ Detect **restriction** (spirometry suggests, lung volumes confirm) and **large-airway obstruction** (flow–volume loop).
- ▶ **Relative contraindications** (forced exhalation raises intrathoracic, intracranial, intra-abdominal and intra-ocular pressure): recent **myocardial infarction, pneumothorax**, recent **thoracic/abdominal/eye/brain/sinus or middle-ear surgery** or infection, **haemoptysis**, severe **hypertension/hypotension**, cervical-incompetent pregnancy, and **syncope** with cough/forced exhalation. (Prior concern over **thoracic aortic aneurysm** has been tempered by recent data.)

Performing and validating the test (ATS/ERS)

- ▶ Patient inhales fully to TLC, then exhales as **hard, fast and long** as possible to RV; ≥3 acceptable spirometers are obtained (practical upper limit 8 efforts).
- ▶ **Start of test: back-extrapolated volume** <5% of FVC or <100 mL (whichever is greater).
- ▶ **Repeatability**: the two largest FVC and two largest FEV1 should be within 150 mL of each other.

- ▶ **Pre-test withholding** for bronchodilator testing: SABA/SAMA ≥ 4 h, LABA ≥ 12 h, long-acting antimuscarinic / ultra-LABA ≥ 24 –48 h; avoid caffeine/alcohol ≥ 4 h.
- ▶ A breathing filter ($\approx 0.2 \mu\text{m}$) is used for infection control; suboptimal effort shows uneven/slurred/notched, non-repeatable curves.

Interpretation — patterns of ventilatory defect

The first interpretive step is the FEV1/FVC ratio (read as an **absolute ratio**, not % predicted), then FEV1 and FVC, with TLC to confirm restriction and DLCO to localise the lesion.

Feature	Obstructive	Restrictive (parenchymal)	Mixed	Nonspecific
FEV1/FVC	$\downarrow$ (<0.70 / $<\text{LLN}$)	Normal or $\uparrow$	$\downarrow$	Normal
FEV1	$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow$ or normal
FVC	Normal or $\downarrow$	$\downarrow$	$\downarrow$	$\downarrow$
TLC	Normal or $\uparrow$ (hyperinflation)	$\downarrow$ (confirms)	$\downarrow$	Normal
RV, RV/TLC	$\uparrow$ (air-trapping)	$\downarrow$	variable	normal
Flow–volume curve	Concave/scooped	Steep, narrow (convex)	combined	preserved shape
Examples	COPD, asthma, bronchiectasis, CF	IPF, sarcoid, asbestosis, CHF	CF, sarcoid, HP, bronchiectasis	obesity, muscle weakness, poor effort

- ▶ **Diagnostic threshold for obstruction:** post-bronchodilator FEV1/FVC <0.70 (GOLD) or $<\text{LLN}$ (5th percentile); obstruction must use **post-bronchodilator** values.
- ▶ **Restriction cannot be diagnosed on spirometry alone** — a low FVC with normal/high FEV1/FVC has only $\sim 50\%$ positive predictive value; a **normal FVC has 96–97% negative predictive value** for ruling out restriction. A low TLC defines restriction.
- ▶ DLCO then localises: low in **parenchymal restriction** (IPF) and **emphysema**; normal in **chest-wall/neuromuscular restriction**; **isolated low DLCO with normal spirometry/volumes suggests pulmonary vascular disease** or early emphysema/ILD.
- ▶ **Large-airway obstruction** is recognised on the flow–volume loop: *fixed* lesion $\rightarrow$ **plateau on BOTH limbs**; *variable extrathoracic* $\rightarrow$ **inspiratory plateau** (with stridor); *variable intrathoracic* $\rightarrow$ **expiratory plateau**.
- ▶ **Reference values** are based on **height, age, sex and ethnicity**; 85–115% of predicted is normal, and in health all volumes scale together.

Severity grading and bronchodilator reversibility

ATS severity (FEV1 % predicted)	Grade
≥70%	Mild
60–69%	Moderate
50–59%	Moderately severe
35–49%	Severe
<35%	Very severe

- ▶ Once a pattern is identified, **severity is graded by FEV1 % predicted** (restriction may also be graded by TLC % predicted).
- ▶ **Significant bronchodilator response (adults):** an increase of ≥12% AND ≥200 mL in FEV1 or FVC after a short-acting bronchodilator (≈10% in children). It supports **asthma** but does **not** distinguish asthma from COPD (35–60% of COPD patients reverse; FVC response is common with hyperinflation). A negative test does **not** exclude reversible disease.
- ▶ When obstruction/reversibility is absent but asthma is suspected, a **methacholine (bronchial) challenge** demonstrating airway hyper-responsiveness can establish the diagnosis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Spirogram (volume vs time):** baseline tidal breathing; label TLC, RV, VC/FVC, FEV1 (volume at 1 s), IC, ERV, FRC; mark that RV/FRC/TLC are not directly measured by spirometry.
- ▶ **Diagram 2 — Flow–volume loops (flow vs volume):** label axes (inspiratory below, expiratory above; TLC and RV on volume axis; PEF peak). Draw and label: (A) Normal, (B) Obstructive — scooped/concave expiratory limb, (C) Restrictive — tall, narrow, vertically-oriented, (D) Fixed large-airway obstruction — plateau on both limbs, (E) Variable extrathoracic — inspiratory plateau, (F) Variable intrathoracic — expiratory plateau.

Clinical / Diagnostic significance

- ▶ Cornerstone for **diagnosing and staging COPD and asthma**, monitoring **ILD/sarcoidosis** progression, and tracking **CF** (declining FEV1/FVC, rising RV/TLC).
- ▶ **Pre-operative risk stratification** (lung resection, major surgery) and **occupational/disability** certification.
- ▶ **Supine fall in FVC of ≥25%** suggests **diaphragmatic/neuromuscular weakness**; complement with MIP/MEP (normal MIP ≥80 cmH₂O men, ≥70 cmH₂O women) and supine spirometry.
- ▶ Combine indices: a **normal/scooped curve with normal FEV1/FVC but reduced FVC** is *nonspecific*, prompting lung-volume and DLCO testing rather than a label of restriction.

High-yield exam pointers

- ▶ Physiological basis = effort-independent expiratory flow limitation from dynamic airway compression (Bernoulli effect); maximal flow set by lung recoil, airway calibre and resistance.
- ▶ First interpret FEV1/FVC (absolute ratio); obstruction = FEV1/FVC <0.70 / <LLN (use post-bronchodilator values).
- ▶ Spirometry cannot measure RV, FRC, TLC — need plethysmography or gas dilution; TLC < LLN confirms restriction.
- ▶ Bronchodilator reversibility = $\geq 12\%$ AND ≥ 200 mL rise in FEV1 or FVC; does not separate asthma from COPD.
- ▶ ATS severity by FEV1 % predicted (≥ 70 mild ... <35 very severe).
- ▶ Acceptability: ≥ 3 efforts, back-extrapolated volume <5%/100 mL, two best FVC and FEV1 within 150 mL.
- ▶ Flow-volume loop localises large-airway lesions: fixed = both limbs plateau; variable extrathoracic = inspiratory plateau; variable intrathoracic = expiratory plateau.
- ▶ FEF25–75% is highly variable and adds little over FEV1/FVC; DLCO differentiates emphysema (low) from asthma (normal/high) in obstruction.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — “Disturbances of Respiratory Function” (mechanics of ventilation, dynamic airflow limitation/Bernoulli effect, flow-volume loops, lung-volume measurement, functional measurements) and “Approach to the Patient with Disease of the Respiratory System / Diagnostic Procedures in Respiratory Disease.”
- ▶ Murray & Nadel's Textbook of Respiratory Medicine, 7e — “Pulmonary Function Testing: Physiologic and Technical Principles” (manoeuvre, indices, acceptability, contraindications) and “Pulmonary Function Testing: Interpretation and Applications” (interpretive algorithm, obstructive/restrictive/mixed/nonspecific patterns, severity grading Table 32.3, bronchodilator responsiveness, large-airway obstruction, reference values).
- ▶ CMDT 2026 — “Pulmonary Disorders” (spirometry in asthma/COPD diagnosis, FEV1/FVC <0.70 threshold, 12% + 200 mL reversibility, GOLD framing).



Hypoventilation (Alveolar Hypoventilation Syndromes)

Asked in: Paper III May 2022 — RGUHS MD General Medicine

Definition / Introduction — In health the arterial CO_2 tension (Paco_2) is held between 37 and 43 mmHg at sea level by the relationship $\text{Paco}_2 = k \times V_{\text{CO}_2} / V_A$ (V_A = alveolar ventilation). **Alveolar hypoventilation** exists when alveolar ventilation is insufficient to clear metabolic CO_2 , producing **chronic daytime hypercapnia** ($\text{Paco}_2 \geq 45$ mmHg) with consequent respiratory acidosis and hypoxaemia. Critically, hypoventilation is defined by the Paco_2 , not the respiratory rate — a tachypnoeic patient with a high dead-space fraction may still be alveolar-hypoventilating. It reflects an imbalance in which respiratory **load** exceeds respiratory **strength/drive** (“pump failure”), and the hallmark is a rise in alveolar and arterial Pco_2 .

Physiological basis and classification

- ▶ The respiratory rhythm is generated in the brainstem — the medullary **dorsal respiratory group (DRG)** (afferent integration) and **ventral respiratory column (VRC)**; the **pre-Bötzinger complex** within the VRC generates inspiration (its destruction abolishes breathing) and is the site of **opioid-induced** respiratory depression.
- ▶ Adequate ventilation needs sufficient **drive**, intact **neuromuscular transmission**, and respiratory-muscle **strength** to overcome the elastic and resistive **loads** of lung and chest wall. Hypoventilation results when *Load > Strength* or when *drive is reduced*.
- ▶ A useful mechanistic dichotomy (Murray & Nadel): “**won’t breathe**” = reduced central drive vs “**can’t breathe**” = failure of the respiratory effectors (spinal cord → nerve → neuromuscular junction → muscle → chest wall). Harrison groups causes into **four categories**:

Category	Mechanism	Representative causes
Parenchymal lung / chest wall disease	↑ Load, V/Q mismatch (↑ A-a gradient)	COPD, severe ILD, kyphoscoliosis, thoracoplasty, fibrothorax, ankylosing spondylitis, flail chest
Obesity-hypoventilation syndrome (OHS)	↑ Load + blunted drive + OSA	“Pickwickian syndrome”, BMI ≥ 30
Neuromuscular disease	↓ Strength (“can’t breathe”)	ALS, muscular dystrophy, myasthenia gravis, Guillain-Barré, phrenic injury, high cervical cord lesion, Pompe disease, post-polio
Respiratory-drive disorders	↓ Drive (“won’t breathe”)	Opioids/sedatives, brainstem stroke/tumour, myxoedema, metabolic alkalosis, primary/congenital central hypoventilation (CCHS)

Clinical features

- ▶ Manifestations are **non-specific** and depend on severity, rapidity of CO₂ rise and the underlying disease. Typical symptoms (Harrison Table 307-1): **dyspnoea on activities of daily living**, **orthopnoea** (with diaphragm involvement), **poor-quality sleep**, **daytime hypersomnolence**, **early-morning headaches**, **anxiety**, and **impaired cough** in neuromuscular disease.
- ▶ **Sleep-disordered breathing pattern** — excessive daytime somnolence, snoring, witnessed apnoeas and nocturnal choking dominate in OHS/OSA.
- ▶ **Neuromuscular pattern** — **new-onset orthopnoea is one of the earliest signs** of diaphragm weakness; **paradoxical (abdominal) breathing** when supine (abdomen moves *inward* on inspiration) signals significant diaphragmatic paralysis; “**respiratory alternans**” (alternating rib-cage and abdominal breathing) indicates diaphragmatic fatigue. Bulbar weakness brings dysphagia, weak cough and recurrent aspiration pneumonia.
- ▶ **Sequence of progression**: asymptomatic (normal daytime gases) → **nocturnal hypoventilation** (first in REM, then non-REM sleep) → falling vital capacity → **daytime hypercapnia**.
- ▶ **Consequences of chronic hypercapnia/hypoxaemia**: compensated respiratory acidosis ($\uparrow \text{HCO}_3^-$), secondary erythrocytosis, **pulmonary vasoconstriction** → **pulmonary hypertension** → **right-ventricular hypertrophy** → **cor pulmonale**. Severe hypercapnia causes cerebral vasodilatation, raised ICP, headache, **asterixis**, drowsiness and CO₂ narcosis/coma (usually $\text{Paco}_2 > 75\text{--}80$ mmHg acutely, or an acute rise to $>90\text{--}100$ mmHg superimposed on chronic disease).

Diagnosis and investigations

- ▶ **Arterial blood gas (ABG) is the gold standard** — $\text{Paco}_2 \geq 45$ mmHg at sea level confirms **hypoventilation**. A peripheral venous Pco_2 is a poor surrogate (run several mmHg higher) but a *normal* value helps exclude hypercapnia.
- ▶ **Serum bicarbonate** is a *sensitive but not specific* screen: $\text{HCO}_3^- < 27$ mmol/L (normal renal function, no volume depletion) makes chronic hypoventilation/OHS very unlikely (high negative predictive value); $\text{HCO}_3^- \geq 27$ mmol/L should prompt a confirmatory ABG.
- ▶ **Acute vs chronic** (degree of renal compensation):

Feature	Acute hypoventilation	Chronic hypoventilation
pH	Low (< 7.35); falls 0.08 per $\uparrow 10$ mmHg Paco_2	Normal / near-normal
HCO_3^- rise per $\uparrow 10$ mmHg Paco_2	~ 1 mEq/L (tissue buffering)	$\sim 3.5\text{--}5$ mEq/L (renal, over 3–5 days)

- ▶ **A–a O₂ gradient distinguishes the cause** (Murray algorithm): a **normal A–a gradient** points to a *drive or neuromuscular/effector* disorder (lungs are normal); a **raised A–a gradient** ($> \sim 20$ mmHg) points to *intrinsic lung/airway/vascular disease*.
- ▶ **Stepwise work-up** (Harrison Fig. 307-2): (1) detailed history + medication/drug history → (2) **PFTs and chest imaging** for lung/chest-wall disease → (3) **seated and supine spirometry** with

MIP/MEP for neuromuscular weakness → (4) **BMI ≥ 30** with no alternative cause → OHS → (5) **CNS imaging** (MRI brainstem) for drive disorders.

- ▶ **Respiratory-muscle assessment:** a fall in FVC of 15–25% from seated to supine is an invaluable screen for impending respiratory failure in neuromuscular disease (a drop of 30–50% supports **bilateral diaphragmatic paralysis**); reduced MIP (**maximal inspiratory pressure**)/MEP and falling FVC track progression. In **Guillain-Barré** the “20/30/40 rule” warns of impending ventilation — VC <20 mL/kg, MIP <30 cmH₂O, MEP <40 cmH₂O.
- ▶ **Polysomnography with CO₂ monitoring** detects nocturnal hypoventilation (precedes daytime hypercapnia) and OSA; AASM scores sleep hypoventilation as Paco₂ >55 mmHg for >10 min, or a rise >10 mmHg to a value >50 mmHg for >10 min. Transcutaneous CO₂ (runs ~4–5 mmHg above arterial) is the most practical nocturnal monitor; end-tidal CO₂ is unreliable in lung disease.
- ▶ **OHS diagnostic criteria** (Harrison/CMDT): BMI ≥ 30 kg/m², daytime Paco₂ ≥ 45 mmHg, sleep-disordered breathing, and exclusion of other causes; ~90% have OSA and ~70% have severe OSA (AHI >30/h). Aetiology-specific tests: TSH (myxoedema), urine toxicology, and **PHOX2B genetic testing** for congenital central hypoventilation syndrome (CCHS / *Ondine’s curse*).

Management

- ▶ **General principles:** treat the **underlying disorder**, withdraw respiratory depressants (opioids, benzodiazepines, alcohol), correct contributory metabolic factors (myxoedema, hypokalaemia, hypophosphataemia, excess metabolic alkalosis — which itself blunts drive), and replete nutrition.
- ▶ **Nocturnal non-invasive positive-pressure ventilation (NIPPV / BiPAP)** is the cornerstone — it lowers daytime Paco₂, prolongs survival and improves quality of life when daytime hypercapnia is documented. **Goal: reduce Paco₂ to <52 mmHg or by $\geq 20\%$ from baseline.**
- ▶ **Neuromuscular disease (best studied in ALS)** — nocturnal NIPPV is indicated if hypoventilation symptoms plus any of: Paco₂ ≥ 45 mmHg; nocturnal SpO₂ $\leq 88\%$ for ≥ 5 consecutive min; MIP <60 cmH₂O; or sniff nasal pressure <40 cmH₂O with FVC <50% predicted. Add **mechanical cough-assist** to reduce pneumonia; progress to mouthpiece/portable ventilation; consider **phrenic-nerve/diaphragm pacing** for high cervical cord lesions or drive disorders (requires intact phrenic nerves on conduction study) and tracheostomy ventilation late in disease.
- ▶ **Obesity-hypoventilation syndrome** — **positive airway pressure during sleep:** CPAP first-line when severe OSA coexists (corrects daytime gases in >50%); **BiPAP-ST / volume-assured pressure support** if hypercapnia persists after adherent CPAP, if obstructive events persist at maximal CPAP (20 cmH₂O), in acutely decompensated OHS, or in OHS *without* significant OSA. **Weight loss of 20–25% of body weight (often bariatric surgery)** can normalise Paco₂; treat comorbid OSA, ACS, PE, pneumonia and heart failure aggressively.

- ▶ **Chronic hypercapnic COPD** (stable, $P_{aCO_2} > 52$ mmHg, normal pH) — **high-intensity home BiPAP** (IPAP 24–28 cmH₂O with a back-up rate) aimed at $P_{aCO_2} < 48$ mmHg or a $> 20\%$ fall improves 1-year mortality and quality of life; after an acute exacerbation, re-test at 2–4 weeks and start home NIPPV only if hypercapnia persists.
- ▶ **Oxygen** — supplemental O₂ attenuates hypoxaemia, polycythaemia and pulmonary hypertension, but must be given cautiously as it can worsen hypercapnia (CO₂ narcosis) in some patients; ventilatory support, not oxygen alone, treats the hypoventilation.
- ▶ **Respiratory stimulants** — acetazolamide and medroxyprogesterone are poorly evidenced, have side-effects, and must **not** replace treatment of the underlying disease.
- ▶ **Central hypoventilation syndrome / CCHS** (*Ondine's curse*; PHOX2B mutation) — long-term NIPPV or mechanical ventilation and consideration of **diaphragmatic pacing** at experienced centres.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Load–Strength balance schematic** (Harrison Fig. 307-1): a beam-balance with “Strength/Drive” on one pan (respiratory drive, neural transmission, respiratory-muscle strength) and “Load” on the other (lung elastic + resistive loads, chest-wall elastic load). Label panel A *Health* ($strength > load \rightarrow normocapnia$) and panel B *Load > Strength* $\rightarrow hypercapnia$.
- ▶ **Diagnostic algorithm** (Harrison Fig. 307-2): boxes — *Daytime hypercapnia* $\rightarrow$ ABG ($P_{aCO_2} \geq 45$) $\rightarrow$ PFT + chest imaging $\rightarrow$ seated/supine spirometry, MIP/MEP $\rightarrow$ BMI $\geq 30 \rightarrow$ CNS imaging; endpoint labels: **Lung disease, Neuromuscular, OHS (+ PSG for OSA), CNS lesion, Primary drive disorder**. Annotate the A–a gradient branch (normal = pump/drive; raised = lung disease).

Clinical / Diagnostic significance

- ▶ An unexplained **raised serum HCO₃⁻** on routine biochemistry is a clue to occult chronic hypoventilation — confirm with ABG.
- ▶ **Supine spirometry / orthopnoea** is the earliest red flag for diaphragmatic weakness; do not wait for daytime hypercapnia.
- ▶ Distinguishing **acute from chronic** by pH and the HCO₃⁻ compensation rule guides urgency (ventilatory support vs outpatient NIPPV).
- ▶ Recognise OHS perioperatively — these patients have a high risk of postoperative respiratory failure, intubation and heart failure.
- ▶ Hypercapnic COPD and OHS carry worse survival than normocapnic peers, but **home NIPPV** measurably reduces mortality.

High-yield exam pointers

- ▶ **Definition number:** alveolar hypoventilation = $\text{Paco}_2 \geq 45 \text{ mmHg}$ (normal 37–43 mmHg).
- ▶ **Four causes:** lung/chest-wall disease, OHS, neuromuscular disease, respiratory-drive disorders (“won’t breathe vs can’t breathe”).
- ▶ **A–a gradient: normal** = drive/neuromuscular (pump) cause; **raised** = intrinsic lung disease.
- ▶ **Compensation rule:** acute $\rightarrow \text{HCO}_3^- \uparrow \sim 1 \text{ mEq/L per } 10 \text{ mmHg } \text{Paco}_2$ (pH $\downarrow 0.08$); chronic $\rightarrow \uparrow 3.5\text{--}5 \text{ mEq/L per } 10 \text{ mmHg}$.
- ▶ **OHS:** BMI ≥ 30 + $\text{Paco}_2 \geq 45$ + SDB; $\sim 90\%$ have OSA, $\sim 70\%$ severe; *Pickwickian syndrome*.
- ▶ **Treatment goal with NIPPV:** $\text{Paco}_2 < 52 \text{ mmHg}$ or $\geq 20\%$ reduction.
- ▶ **ALS NIPPV triggers:** $\text{Paco}_2 \geq 45$, nocturnal $\text{SpO}_2 \leq 88\% \times 5 \text{ min}$, MIP < 60 , or SNP < 40 with FVC $< 50\%$.
- ▶ **CCHS:** *Ondine’s curse*, **PHOX2B** mutation, absent ventilatory response to hypoxia/hypercapnia, worse in non-REM sleep.
- ▶ **GBS “20/30/40”:** VC $< 20 \text{ mL/kg}$, MIP < 30 , MEP $< 40 \text{ cmH}_2\text{O} \rightarrow \text{ICU/ventilation}$.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Disorders of Ventilation” (definition/physiology, four-category classification, Table 307-1 features, Fig. 307-1/307-2, diagnostic algorithm, NIPPV goals, ALS/OHS/COPD/CCHS management).
- ▶ **Murray & Nadel’s Textbook of Respiratory Medicine, 7e** — “Hypercapnia” (won’t-breathe vs can’t-breathe classification Table 45.1, OHS pathophysiology/leptin resistance, acute-vs-chronic compensation, A–a gradient algorithm, respiratory-muscle testing, AASM sleep-hypoventilation criteria, transcutaneous/end-tidal CO_2).
- ▶ **CMDT 2026** — “Pulmonary Disorders” (Disorders of Control of Ventilation / Obesity-Hypoventilation Syndrome) (OHS diagnostic criteria and current management, respiratory stimulants, perioperative risk).



Gastrointestinal system & hepatology



Acute Pancreatitis

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Acute pancreatitis is an acute, reversible inflammatory process of the pancreas caused by premature intra-acinar activation of digestive enzymes (autodigestion), ranging pathologically from self-limited **interstitial (oedematous) pancreatitis** (perfusion preserved) to life-threatening **necrotizing pancreatitis** (perfusion interrupted). It is one of the commonest

gastrointestinal causes of hospitalization (incidence ~15–45/100,000/year), is self-limited in 85–90% of cases, but carries an overall mortality of ~1% that rises to ~30–50% when persistent organ failure and infected necrosis coexist. Diagnosis rests on the **Revised Atlanta (2012)** framework, which standardised definitions of severity, phases and morphology.

Etiology

- ▶ **Gallstones (including microlithiasis) — leading cause, 30–60%.** Risk is fourfold greater with stones <5 mm (these pass and transiently impact the ampulla). Suggested by **ALT >3× ULN** (CMDT: ALT >150 U/L).
- ▶ **Heavy alcohol use — second commonest, 15–30%.** Smoking and genetic predisposition are co-factors.
- ▶ **Severe hypertriglyceridemia (1–4%) —** triglycerides usually >1000 mg/dL; often uncontrolled diabetes or apolipoprotein C-II deficiency.
- ▶ **Post-ERCP —** pancreatitis in 5–10%; risk reduced by rectal indomethacin/NSAID and prophylactic pancreatic duct stent.
- ▶ **Drugs (<2% of cases):** azathioprine/6-mercaptopurine, sulfonamides, estrogens, tetracycline, valproate, 5-ASA, DPP-4 inhibitors.
- ▶ **Others:** hypercalcemia, trauma (blunt abdominal), post-operative, pancreas divisum, hereditary (PRSS1), cystic fibrosis, periampullary diverticulum, autoimmune (IgG4 type 1/duct-centric type 2), infections (mumps, coxsackie, CMV), pancreatic/ampullary tumour (~2–4% of pancreatic cancers present as AP), and idiopathic.
- ▶ A useful aide-mémoire is *GET SMASHED* (Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune, Scorpion sting, Hypercalcemia/Hypertriglyceridemia, ERCP, Drugs), but the grounded big three are **gallstones + alcohol + hypertriglyceridemia**.

Pathogenesis

- ▶ Core defect is **loss of acinar autoprotection** and premature activation of trypsinogen → trypsin, which then triggers a cascade activating chymotrypsinogen, proelastase and phospholipase A2.
- ▶ Normal safeguards (any of which, when lost, leads to autodigestion): zymogen packaging as proenzymes, low cytosolic calcium, acid-base balance, and protective inhibitors **SPINK1** (serine protease inhibitor, Kazal type 1) and chymotrypsin C (CTRC), which inactivate trypsin.
- ▶ **Three evolving phases:** (1) intra-acinar trypsin activation mediated by lysosomal **cathepsin B** co-localizing with zymogens → acinar injury; (2) intrapancreatic inflammation with neutrophil/macrophage chemoattraction; (3) systemic release of activated proteases and cytokines → **SIRS, ARDS and multiorgan failure**.
- ▶ **Genetic susceptibility genes** (centred on trypsin control): *PRSS1* (cationic trypsinogen — the only variant sufficient to cause AP alone), *SPINK1*, *CFTR*, *CTRC*, *CASR* (calcium-sensing receptor) and *CLDN2* (claudin-2); the latter five are disease *modifiers*.

Clinical features

- ▶ **Abdominal pain** — the cardinal symptom: steady, boring epigastric pain radiating to the back, relieved by sitting forward, with nausea, vomiting and abdominal distension from ileus.
- ▶ Examination: low-grade fever, tachycardia, **hypotension/shock** (third-space loss, kinin release, circulating enzymes); diminished bowel sounds; epigastric tenderness often disproportionately mild relative to pain.
- ▶ **Specific signs** (rare, reflect haemorrhagic necrosis and worse prognosis): *Cullen's sign* (periumbilical bluish discolouration), *Grey Turner's sign* (flank discolouration), *pancreatic panniculitis* (subcutaneous fat-necrosis nodules), and *Purtscher's retinopathy* (sudden blindness).
- ▶ Pulmonary findings in 10–20% (basal rales, atelectasis, left pleural effusion); transient jaundice in ~10%.

Laboratory & imaging diagnosis

- ▶ **Serum lipase and/or amylase** $>3\times$ ULN is strongly supportive. **Lipase is more specific and preferred** (remains elevated 7–14 days vs amylase normalising in 3–7 days). There is **no correlation** between enzyme level and severity. Amylase is spuriously raised in DKA/acidaemia ($\text{pH} \leq 7.32$) and spuriously low in severe hypertriglyceridemia.
- ▶ Supportive labs: leukocytosis (15,000–20,000/ μL), **haemoconcentration** ($\text{Hct} >44\%$) and rising BUN (azotaemia — strong mortality marker), hyperglycemia, **hypocalcemia** (~25%), hyperbilirubinemia (~10%), hypoxaemia ($\text{PaO}_2 \leq 60$ mmHg) heralding ARDS.
- ▶ **Diagnosis = any 2 of 3 criteria:** (1) typical epigastric pain radiating to back; (2) lipase/amylase $>3\times$ ULN; (3) characteristic findings on cross-sectional imaging.
- ▶ **Imaging:** transabdominal **ultrasound is the initial test** (gallstones, CBD). **Contrast-enhanced CT** is best at **day 3–5** (not routinely in first 48–72 h) to detect necrosis/local complications; MRI/MRCP and EUS for ductal/biliary causes and occult microlithiasis.

Severity assessment and Revised Atlanta classification

- ▶ The dominant determinant of severity is **persistent organ failure (>48 h)** in the respiratory, cardiovascular and renal systems, scored by the **modified Marshall score (≥ 2 = organ failure)**.

Atlanta severity class	Definition
Mild	No organ failure; no local or systemic complications (most interstitial AP; resolves 3–7 days)
Moderately severe	Transient organ failure (<48 h) and/or local/systemic complications
Severe	Persistent organ failure >48 h (single-organ mortality 3–10%; multiorgan ~50%)

Predictive scoring systems (none individually highly accurate):

System	Components / threshold for severe
Ranson	5 at admission (age >55, WBC >16,000, glucose >200 mg/dL, LDH >350 U/L, AST >250 U/L) + 6 at 48 h (Hct fall >10%, BUN rise >5 mg/dL, Ca <8 mg/dL, PaO ₂ <60 mmHg, base deficit >4 mEq/L, fluid sequestration >6 L); ≥3 = severe (mortality 0–2: 1%, 3–4: 16%, 5–6: 40%, 7–8: 100%)
BISAP	BUN >25 mg/dL, Impaired mental status (GCS <15), SIRS, Age >60, Pleural effusion; ≥3 = high mortality
APACHE II	≥8 at 24 h; most validated but cumbersome
CTSI (Balthazar)	CT grade (A–E) + % necrosis; correlates with mortality
SIRS	≥2 of: temp <36/>38°C, HR >90, RR >20 (or PCO ₂ <32), WBC <4000/>12,000 or >10% bands — persistent SIRS at 48 h predicts death

Revised Atlanta morphological definitions (CT): interstitial oedematous pancreatitis (90–95%), necrotizing pancreatitis (5–10%); fluid collections — **acute peripancreatic fluid collection** and **pancreatic pseudocyst** (encapsulated, >4 weeks; in interstitial AP) versus **acute necrotic collection (ANC)** and **walled-off necrosis (WON)** (>4 weeks; in necrotizing AP).

Complications

- ▶ **Local:** ANC/WON (sterile or infected), pseudocyst, pancreatic duct disruption → pancreatic ascites/pancreaticopleural fistula, splanchnic (splenic/portal/SMV) vein thrombosis → gastric varices, pseudoaneurysm haemorrhage, gastric outlet/biliary obstruction, colonic involvement.
- ▶ **Systemic:** SIRS, ARDS, shock, AKI/acute tubular necrosis, DIC, GI haemorrhage, **hypocalcemia** (fat saponification), hyperglycemia, abdominal compartment syndrome; long-term — diabetes, exocrine pancreatic insufficiency and recurrence (~25%).

Management

- ▶ **Fluid resuscitation** is the single most important early intervention. **Lactated Ringer's** preferred over normal saline. A **moderate (goal-directed) strategy** is now favoured (de-Madaria, *NEJM* 2022: 10 mL/kg bolus then 1.5 mL/kg/h) over historically aggressive regimens, titrated to urine output >0.5 mL/kg/h, with serial Hct/BUN every 8–12 h — avoiding fluid overload.
- ▶ **Analgesia** (IV opioids; meperidine or morphine acceptable) and supplemental oxygen; initial NPO.
- ▶ **Nutrition:** early **enteral feeding** (oral low-fat solid diet when pain settling in mild AP; naso-gastric/naso-jejunal within 48–72 h in severe AP) is preferred to TPN — maintains gut barrier, reduces bacterial translocation, infection and mortality.

- ▶ **Antibiotics: no role for prophylactic antibiotics** in sterile necrosis (risk of fungal superinfection); empiric carbapenem (imipenem/meropenem) only for proven/strongly suspected **infected necrosis**.
- ▶ **Gallstone AP: urgent ERCP within 24–48 h** if cholangitis/biliary obstruction; **same-admission laparoscopic cholecystectomy** for mild biliary AP (sphincterotomy if non-operable).
- ▶ **Hypertriglyceridemic AP:** IV insulin ($\pm$ fasting 24–36 h, heparin/apheresis of unproven benefit), then fibrates and lifestyle control.
- ▶ **Infected necrosis / symptomatic WON:** delay intervention $\sim$ 4 weeks until walled-off; use a “**step-up**” approach (percutaneous/endoscopic transluminal drainage with LAMS $\rightarrow$ endoscopic, and only if needed surgical, necrosectomy) — endoscopic-first reduces morbidity versus open necrosectomy.
- ▶ Multidisciplinary care (GI, surgery, interventional radiology, intensive care), preferably at a pancreas centre.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis cascade:** Acinar cell $\rightarrow$ trigger (gallstone/alcohol) $\rightarrow$ cathepsin B activates **trypsinogen** $\rightarrow$ **trypsin** $\rightarrow$ activates *chymotrypsinogen*, *proelastase*, *phospholipase A2* $\rightarrow$ autodigestion (oedema, fat necrosis, haemorrhage) $\rightarrow$ cytokine release $\rightarrow$ **SIRS** $\rightarrow$ ARDS/MODS. Label SPINK1/CTRC as protective inhibitors.
- ▶ **Revised Atlanta morphology box:** two arms — *Interstitial AP* $\rightarrow$ APFC (<4 wk) $\rightarrow$ Pseudocyst (>4 wk); *Necrotizing AP* $\rightarrow$ ANC (<4 wk) $\rightarrow$ WON (>4 wk). Add a body diagram marking *Cullen’s sign* (periumbilical) and *Grey Turner’s sign* (flanks).

Clinical / Diagnostic significance

- ▶ Lipase $>3\times$ ULN with characteristic pain often makes CT unnecessary for diagnosis; reserve early CT for diagnostic doubt.
- ▶ A **persistently rising BUN and Hct $>44\%$** on admission are practical bedside predictors of severe disease and mortality.
- ▶ Persistent organ failure beyond 48 h, not the anatomical extent of necrosis, drives prognosis — escalate to ICU early.
- ▶ Same-admission cholecystectomy prevents recurrent gallstone pancreatitis; failure to do so is a common exam-cited pitfall.

High-yield exam pointers

- ▶ Diagnosis = 2 of 3 (pain / enzymes $>3\times$ ULN / imaging).
- ▶ **Lipase $>$ amylase** in specificity and duration; enzyme level does NOT reflect severity.
- ▶ Big-three causes: **gallstones (30–60%) $>$ alcohol (15–30%) $>$ hypertriglyceridemia (TG >1000).**

- ▶ **Cullen's** = periumbilical, **Grey Turner's** = flank — both signal haemorrhagic necrotizing AP.
- ▶ Severity hinges on **persistent organ failure >48 h** (modified Marshall ≥ 2); scores: **Ranson ≥ 3** , **BISAP ≥ 3** , **APACHE II ≥ 8** .
- ▶ Revised Atlanta: interstitial vs necrotizing; **pseudocyst/WON mature at >4 weeks**.
- ▶ **Lactated Ringer's, moderate (not aggressive) fluids**, early enteral nutrition, **no prophylactic antibiotics**.
- ▶ Infected necrosis → **delay 4 weeks + step-up (drainage → necrosectomy)**, endoscopic-first.
- ▶ Rectal **indomethacin $\pm$ PD stent** prevents post-ERCP pancreatitis.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Acute and Chronic Pancreatitis" (etiology, three-phase pathogenesis, genetics, Revised Atlanta definitions, severity assessment, management) and "Approach to the Patient with Pancreatic Disease."
- ▶ Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e — "Acute Pancreatitis" (severity scoring systems — Ranson, APACHE II, BISAP, Imrie/Glasgow; CTSI/Balthazar grading; SIRS-based prognosis).
- ▶ CMDT 2026 — "Liver, Biliary Tract, & Pancreas Disorders" (current management: moderate fluid resuscitation per de-Madaria *NEJM* 2022, enteral nutrition, antibiotic policy, step-up necrosectomy, Ranson criteria table, post-ERCP prophylaxis).



Auto immune hepatitis

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Autoimmune hepatitis (AIH) is a chronic immune-mediated necroinflammatory liver disease of unknown cause, characterized by **autoantibodies**, **hypergammaglobulinemia / raised IgG**, and **interface hepatitis with lymphoplasmacytic infiltration** on liver biopsy. It is a diagnosis of inclusion plus exclusion: viral, drug-induced, metabolic, alcohol-related, and cholestatic autoimmune liver diseases must be excluded. Untreated active AIH may progress to fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma; with immunosuppression, survival improves markedly.

Etiopathogenesis and epidemiology

- ▶ AIH occurs at any age and in both sexes, but has a strong **female predominance**; Harrison notes women account for about **75%** of cases, with peaks in young adults and in middle-to-late life.
- ▶ Incidence is rising in contemporary series; CMDT gives an incidence of **2-4 per 100,000** and prevalence of **26-31 per 100,000**.

- ▶ The central mechanism is loss of tolerance to hepatocyte antigens in genetically predisposed persons, followed by CD4+ T-cell activation, CD8+ cytotoxic T-cell injury, plasma-cell antibody production, Th17-mediated inflammation, hepatocyte apoptosis, and stellate-cell activation causing fibrosis.
- ▶ Genetic associations include HLA-DR3 / DR4; type 2 disease is linked with anti-LKM1 and HLA-DRB1*07.
- ▶ Triggers include viral infections and drugs. Reported drug/toxin associations include **nitrofurantoin, minocycline, hydralazine, methyldopa, infliximab, and immune-checkpoint inhibitors**; minocycline and nitrofurantoin are important causes of autoimmune-like drug-induced liver injury.
- ▶ Associated autoimmune diseases are common: autoimmune thyroiditis / Graves disease, rheumatoid arthritis, Sjögren syndrome, ulcerative colitis, celiac disease, vitiligo, type 1 diabetes, nephritis, and Coombs-positive hemolytic anemia.

Clinical presentation

- ▶ The onset is usually **insidious**, with fatigue, malaise, anorexia, arthralgia, nausea, right upper quadrant discomfort, amenorrhea, and fluctuating jaundice. Fatigue is the commonest symptom, occurring in about **85-86%** in textbook series.
- ▶ About **25-34%** may be asymptomatic and discovered by abnormal liver tests; older patients are particularly likely to present this way.
- ▶ About **25%** present with acute severe hepatitis, and **3-6%** may present as acute severe / fulminant hepatitis with encephalopathy. Acute presentations can mimic viral hepatitis or drug-induced liver injury.
- ▶ Physical findings may be absent. When present, look for hepatomegaly, splenomegaly, jaundice, spider telangiectasia, acne, hirsutism, striae, and signs of chronic liver disease or portal hypertension.
- ▶ Exacerbations may occur **postpartum**.
- ▶ Extrahepatic manifestations include arthritis, sicca symptoms, thyroid disease, nephritis, skin vasculitis, erythema nodosum, autoimmune cytopenias, and inflammatory bowel disease.

Laboratory, serology and histology

Feature	Exam-relevant points
Liver biochemistry	Predominantly hepatocellular pattern: AST/ALT elevated; in acute cases aminotransferases may exceed 1000 U/L . Bilirubin rises in acute/severe disease. Alkaline phosphatase is usually normal or mildly raised; >4 x ULN argues against typical AIH and suggests cholestatic/overlap disease.

Feature	Exam-relevant points
Immunoglobulins	Raised IgG / gamma globulin is a hallmark; gamma globulin may be very high. In acute severe AIH, IgG may be normal in up to 25-39%, so normal IgG does not exclude disease.
Type 1 AIH	ANA and/or smooth muscle antibody (SMA) ; anti-actin and atypical pANCA may occur. This is the classic adult form in North America and northern Europe.
Anti-SLA variant	Anti-soluble liver antigen has high specificity, may be the sole marker, and is associated with severe disease and relapse after withdrawal.
Type 2 AIH	Anti-LKM1 , often without ANA/SMA; anti-LC1 may coexist. More common in children, especially girls, and in Europe/Mediterranean populations.
Histology	Biopsy shows interface hepatitis , lymphoplasmacytic inflammation, plasma cells, hepatocyte rosettes, emperipolesis, central perivenulitis, bridging necrosis, and fibrosis/cirrhosis. Interface hepatitis is the hallmark but is not disease-specific.

- ▶ Cirrhosis is already present in **28-33%** of adults at diagnosis, emphasizing the need for early biopsy and staging.
- ▶ Plasma cells support the diagnosis, but their absence does not exclude AIH; viral, drug, hereditary, metabolic, and cholestatic liver diseases must still be excluded.

Diagnosis and differential diagnosis

- ▶ Suspect AIH in chronic or acute hepatitis with high IgG, autoantibodies, compatible biopsy, and exclusion of competing causes.
- ▶ **Liver biopsy is indicated** to establish diagnosis, assess necroinflammatory activity, stage fibrosis, detect cirrhosis, and identify overlap or drug-induced patterns.
- ▶ Simplified diagnostic criteria:

Criterion	Points
ANA or SMA $\geq 1:40$	1
ANA or SMA $\geq 1:80$, anti-LKM1 $\geq 1:40$, or anti-SLA positive	2
IgG > ULN	1
IgG > 1.1 x ULN	2

Criterion	Points
Histology compatible with AIH	1
Histology typical of AIH	2
Absence of viral hepatitis	2
Total score: probable AIH = 6; definite AIH = ≥ 7	

- ▶ Scoring supports, but does not replace, clinical judgment; it is less sensitive in acute severe or seronegative disease.
- ▶ Differential diagnosis:
 - Viral hepatitis B, C, D, and acute A/E where relevant.
 - Drug-induced liver injury, especially nitrofurantoin, minocycline, antitubercular drugs, methyl dopa, propylthiouracil, NSAIDs, terbinafine, TNF inhibitors, and checkpoint inhibitors.
 - Wilson disease in adolescents/young adults; alpha-1 antitrypsin deficiency and hemochromatosis when appropriate.
 - MASLD/MASH, alcohol-associated liver disease, ischemic hepatitis, celiac-related liver disease, and Budd-Chiari syndrome.
 - Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlap syndromes.

Classification and overlap syndromes

- ▶ **Type 1 AIH:** ANA/SMA positive, all ages, female-predominant, associated with other autoimmune diseases; response to treatment is similar to type 2.
- ▶ **Type 2 AIH:** anti-LKM1 positive, often pediatric, may be associated with anti-LC1 and autoimmune polyglandular syndrome type 1; ANA/SMA are usually absent.
- ▶ **Autoantibody-negative AIH:** conventional ANA/SMA/LKM may be absent; anti-SLA, atypical pANCA, anti-actin, or anti-LC1 may support diagnosis. A monitored steroid response may help in difficult cases.
- ▶ **Drug-related autoimmune-like hepatitis:** temporal drug exposure and resolution after withdrawal favor DILI; relapse after steroid withdrawal favors classic AIH.
- ▶ **AIH-PBC overlap:** suspect when interface hepatitis coexists with cholestasis, AMA, or florid duct lesions. Diagnostic clues include ALT $\geq 5 \times$ ULN, IgG $\geq 2 \times$ ULN or SMA positivity plus PBC features such as alkaline phosphatase $\geq 2 \times$ ULN, GGT $\geq 5 \times$ ULN, AMA, or florid duct lesion.
- ▶ **AIH-PSC overlap:** suspect with inflammatory bowel disease, persistent cholestatic enzymes, or poor response to steroids; evaluate by MRCP/ERCP. CMDT gives overlap with PBC in 7-13% and PSC in 6-11% of AIH patients.

Treatment

- ▶ Treat active AIH; only patients without laboratory or histologic activity may be considered for observation. Optimal candidates include symptomatic patients with marked aminotransferase elevation, raised globulins, bridging necrosis, multiacinar necrosis, or progressive fibrosis.
- ▶ First-line therapy is **prednisone / prednisolone plus azathioprine**:
 - CMTD regimen: prednisone **20-40 mg orally daily** with azathioprine **50 mg orally daily**.
 - AASLD-style combination regimen: prednisone/prednisolone **30 mg daily**, tapered over 4 weeks to **10 mg daily**, with azathioprine **50 mg daily**.
 - European-style regimen: prednisolone **0.5-1 mg/kg daily**, tapered over about 10 weeks; azathioprine **1-2 mg/kg daily** is often added after 2 weeks.
- ▶ In **acute severe AIH**, use IV corticosteroids or prednisone **40-60 mg daily**; start azathioprine later, commonly after about 2 weeks, once diagnosis and early response are clear.
- ▶ Before azathioprine, assess **thiopurine methyltransferase (TPMT)** status where available; monitor CBC weekly for the first 2 months and monthly thereafter because of marrow suppression risk.
- ▶ **Budesonide 3 mg two or three times daily** may be used in noncirrhotic, mild/uncomplicated AIH, often with azathioprine, but avoid it in cirrhosis because first-pass hepatic clearance is lost and adverse effects/portal vein thrombosis have been reported.
- ▶ Response-guided management: symptoms improve first; remission means normal AST, ALT, and IgG; histologic resolution lags by months. An **80% fall in AST by 8 weeks** predicts later normalization; failure of aminotransferases to fall by **50% within 4 weeks** suggests nonresponse.
- ▶ Relapse is common; many patients require long-term azathioprine up to **2 mg/kg/day** or the lowest effective prednisone dose.
- ▶ Second-line / rescue options: **mycophenolate mofetil 500 mg twice daily increasing to 1 g twice daily** for azathioprine intolerance; 6-mercaptopurine for azathioprine gastrointestinal intolerance; tacrolimus, cyclosporine, rituximab, or infliximab in refractory disease. Mycophenolate is teratogenic.
- ▶ **Liver transplantation** is indicated for acute liver failure, decompensated cirrhosis, treatment failure, severe acute AIH without improvement after about 2 weeks of corticosteroids, or HCC within transplant criteria.

Response, follow-up and prognosis

- ▶ Prednisone plus azathioprine produces response in about **80%** and remission in about **65% by 3 years**.
- ▶ Consider treatment withdrawal only after sustained complete biochemical remission: at least **24 months** of normal AST/ALT/IgG, usually after a total treatment duration of about **3 years**; repeat biopsy can document histologic remission.

- ▶ Relapse after withdrawal is frequent; CMDT reports relapse up to **90% by 3 years**. Recurrent relapse usually warrants indefinite maintenance therapy.
- ▶ Vaccinate against **hepatitis A and B** before immunosuppression where possible; also give age-appropriate vaccines.
- ▶ Monitor steroid complications: weight gain, diabetes, hypertension, cataract, infection, mood disturbance, and osteoporosis. Do **DEXA**, calcium/vitamin D, exercise, and bisphosphonate when indicated.
- ▶ In cirrhosis: screen for **HCC by ultrasound every 6 months**, assess portal hypertension/varices, and manage ascites, encephalopathy, renal dysfunction, and transplant referral early.
- ▶ Poor prognostic factors include age ≤ 20 or ≥ 60 at presentation, low albumin, cirrhosis at diagnosis, anti-SLA positivity, high bilirubin/MELD, and incomplete AST normalization by 6 months.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Immunopathogenesis flow diagram:** environmental trigger/drug/virus $\rightarrow$ molecular mimicry/loss of tolerance $\rightarrow$ antigen-presenting cell $\rightarrow$ CD4+ helper T cell $\rightarrow$ CD8+ cytotoxic T cell + plasma cell + Th17 cell $\rightarrow$ Fas-FasL hepatocyte apoptosis $\rightarrow$ interface hepatitis $\rightarrow$ stellate-cell activation $\rightarrow$ fibrosis/cirrhosis. Exact labels: APC, class II MHC, CD4+ T cell, CD8+ T cell, plasma cell, autoantibodies, Fas/FasL, hepatocyte apoptosis, Kupffer cell, ROS, hepatic stellate cell, fibrosis.
- ▶ **Diagnostic-treatment algorithm:** chronic/acute hepatitis $\rightarrow$ exclude viral/drug/metabolic/alcohol/cholestatic disease $\rightarrow$ ANA/SMA/LKM1/SLA + IgG $\rightarrow$ liver biopsy showing interface hepatitis $\rightarrow$ prednisone/prednisolone $\pm$ azathioprine $\rightarrow$ remission / relapse / nonresponse $\rightarrow$ maintenance, second-line therapy, or liver transplantation.

Clinical / Diagnostic significance

- ▶ Always biopsy suspected AIH unless contraindicated; in coagulopathy or acute severe disease, consider a **transjugular liver biopsy**.
- ▶ Do not dismiss acute severe AIH because ANA is absent or IgG is normal; this occurs in a substantial minority.
- ▶ Prominent cholestasis, IBD, bile duct injury, or poor steroid response should prompt evaluation for PSC/PBC overlap and MRCP/ERCP.
- ▶ Distinguish drug-induced autoimmune-like hepatitis from classic AIH by exposure history, histology, resolution after drug withdrawal, and relapse pattern after steroid withdrawal.
- ▶ Early transplant discussion is mandatory in encephalopathy, INR prolongation, acute liver failure, high MELD, or failure of bilirubin/clinical status to improve within 1-2 weeks of steroids.

High-yield exam pointers

- ▶ AIH triad: autoantibodies + raised IgG + interface hepatitis.
- ▶ ANA/SMA = type 1; anti-LKM1/anti-LC1 = type 2; anti-SLA = severe/relapsing, high-specificity marker.
- ▶ Histology must-write: interface hepatitis, plasma cells, rosettes, emperipolesis, central perivenulitis, bridging necrosis/fibrosis.
- ▶ Normal IgG or absent ANA does **not** exclude acute severe AIH.
- ▶ Simplified score: **6 probable**, **≥7 definite**.
- ▶ First-line: corticosteroid plus azathioprine; check TPMT and monitor CBC.
- ▶ Budesonide is for selected **noncirrhotic** patients; avoid in cirrhosis.
- ▶ Relapse is common; withdrawal requires prolonged normal AST/ALT/IgG and often biopsy confirmation.
- ▶ Cirrhotic AIH needs HCC surveillance and early transplant evaluation.

SOURCE & COVERAGE

Harrison 22e — “Chronic Hepatitis”; Sleisenger & Fordtran’s GI & Liver 11e — “Autoimmune Hepatitis”; CMDT 2026 — “Liver, Biliary Tract, & Pancreas Disorders”.



Autoimmune Pancreatitis

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Autoimmune pancreatitis (AIP) is a distinct, corticosteroid-responsive form of chronic pancreatitis characterised by a lymphoplasmacytic inflammatory infiltrate, fibrosis and a tendency to form tumefactive (mass-like) lesions that frequently mimic pancreatic adenocarcinoma. It is sub-classified into **type 1 AIP** — the pancreatic manifestation of the multi-organ syndrome **IgG4-related disease (IgG4-RD)** — and **type 2 AIP (idiopathic duct-centric chronic pancreatitis, IDCP)**, a pancreas-restricted disease defined by the *granulocytic epithelial lesion (GEL)*. Recognising AIP matters chiefly because it is one of the few **reversible, steroid-responsive** causes of an obstructive pancreatic mass, and misdiagnosis leads to unnecessary Whipple resection.

Classification — Subtypes of AIP

Feature	Type 1 AIP (LPSP)	Type 2 AIP (IDCP)
Underlying entity	Pancreatic manifestation of IgG4-RD	Pancreas-specific; no systemic disease
Mean age at diagnosis	~7th decade (>60 yr; most >50)	~5th decade (40–50; may affect young adults/children)

Feature	Type 1 AIP (LPSP)	Type 2 AIP (IDCP)
Sex	Male predominance (~75%; M:F ≈ 2:1)	Equal (M ≈ 50%)
Serum IgG4 elevation	~66% (two-thirds)	~25% (usually normal)
Other-organ involvement	~50–60% (biliary, salivary, kidney, retroperitoneum)	None
Lymphoplasmacytic infiltrate	++	++
Storiform fibrosis	++	+
Obliterative phlebitis	++	+ (rare)
Granulocytic epithelial lesion (GEL)	Absent	+++ (defining)
IgG4 tissue plasma cells	Abundant (≥10/hpf)	Scant (<10/hpf)
Associated disease	IgG4-RD	Inflammatory bowel disease (~10–30%)
Response to steroids	~100%	~100%
Risk of relapse	Moderate–high (30–50%, up to 60%)	Low (<10%)

- ▶ **Type 3 AIP** is now recognised (CMDT 2026) as an infrequent complication of **immune-checkpoint-inhibitor** therapy; it is often asymptomatic but causes rapid pancreatic atrophy.
- ▶ The histological term for the type 1 lesion is **lymphoplasmacytic sclerosing pancreatitis (LPSP)** — *storiform* (“woven-mat”/cartwheel) fibrosis, obliterative phlebitis and a periductal cuff of IgG4-positive plasma cells. Type 2 shows **duct-centric** neutrophilic destruction of the duct epithelium (the GEL).

IgG4-Related Disease (the systemic context of type 1 AIP)

- ▶ A fibroinflammatory, **tumefaction-forming** condition that can affect virtually any organ; regarded as a **variable-vessel vasculitis** because of its tropism for veins and arteries of any calibre.
- ▶ Commonly involved organs: **pancreas, biliary tree, submandibular/parotid glands, periorbital tissues (lacrimal glands), kidneys, lungs, lymph nodes, retroperitoneum, aorta, thyroid (Riedel’s)**.
- ▶ Eponymous overlaps: ***Mikulicz disease** (*lacrimal + parotid + submandibular swelling*), **Küttner tumour** (*submandibular gland*), **Riedel’s thyroiditis***, retroperitoneal fibrosis, inflammatory aortic aneurysm.
- ▶ Pathology is identical across organs: dense lymphoplasmacytic infiltrate, **storiform fibrosis**, **obliterative phlebitis**, mild-to-moderate **tissue eosinophilia**; intense neutrophils, granulomas, giant cells and fibrinoid necrosis argue *against* the diagnosis.

- ▶ Mechanism: the IgG4 molecule undergoes **Fab-arm exchange**, binds antigen weakly and has low affinity for Fcγ-receptors and C1q (largely *non-inflammatory*) — so it is probably a counter-regulatory marker rather than the primary driver. The true effectors are oligoclonally expanded **CD4⁺ cytotoxic T cells** (producing perforin, granzyme, IFN-γ, TGF-β) and circulating **plasmablasts**.

Clinical features

- ▶ **Obstructive jaundice** is the commonest presentation (≈50–75%), characteristically **painless**, due to a stricture of the intrapancreatic common bile duct or compression by the enlarged head.
- ▶ **Weight loss** and **new-onset diabetes / glucose intolerance** (20–50% of type 1) are frequent; severe pain and overt acute pancreatitis are *uncommon* (acute pancreatitis is more typical of type 2).
- ▶ A **pancreatic mass** mimicking carcinoma is the major clinical trap; many patients have undergone modified Whipple surgery before the diagnosis was made.
- ▶ **Type 1 extra-pancreatic disease**: IgG4-related sclerosing cholangitis (mimics PSC/cholangiocarcinoma, hilar predilection), bilateral sclerosing **sialadenitis/dacryoadenitis**, **retroperitoneal fibrosis** (hydronephrosis from ureteric entrapment), **tubulointerstitial nephritis** and renal masses, lymphadenopathy, lung pseudotumours, periaortitis.

Diagnosis and investigations

- ▶ **Imaging (CT/MRI)**: classical diffuse “sausage-shaped” **pancreas** with loss of normal lobularity and delayed/prolonged contrast enhancement; a peripheral **hypoattenuating rim** (“**capsule sign**”) is *highly specific but not sensitive*. Focal/segmental enlargement is the malignancy mimic.
- ▶ **Ductal imaging (MRCP/ERCP)**: long (>1/3 of duct length) or multiple strictures of the main pancreatic duct **without marked upstream dilatation**, and biliary strictures (IgG4-sclerosing cholangitis).
- ▶ **Serology**: serum **IgG4 >2× upper limit of normal** is the level-1 criterion (ULN ≈ 4–86 mg/dL); a single isolated elevation has low positive predictive value and can occur in pancreatic cancer. Other autoantibodies (ANA, anti-lactoferrin, anti-carbonic anhydrase II, rheumatoid factor) are less useful. Beware the **prozone effect**, which falsely lowers nephelometric IgG4 in very high-titre disease — correct by serum dilution.
- ▶ **Histology (core biopsy/resection)**: LPSP with **≥10 IgG4⁺ plasma cells/hpf**, storiform fibrosis, obliterative phlebitis (type 1); GEL (type 2). EUS-guided core biopsy aids type 2 (which usually *requires* histology).
- ▶ **Diagnostic frameworks**:
 - ***HISORt criteria** (*Mayo Clinic mnemonic*): *H*istology, *I*maging, *S*erology, *O*ther-organ involvement, *R*esponse to steroid *t**herapy.

- ***International Consensus Diagnostic Criteria (ICDC)** harmonise five cardinal features — *P* (parenchymal imaging), *D* (ductal imaging), *S* (serology), *OOI* (other-organ involvement) and *H* (histology), plus *Rt* (response to steroids) — graded level 1/level 2 to classify definitive vs probable* type 1 AIP.
- ▶ **Response to glucocorticoids** is itself a diagnostic criterion: rapid (2–4 week) radiological resolution is expected; *poor response must prompt re-evaluation for malignancy*.

Distinguishing AIP from pancreatic carcinoma (critical)

- ▶ Features favouring **cancer**: a *dilated* pancreatic duct, a single high-grade stricture with **upstream gland atrophy**, and a discrete low-density focal mass.
- ▶ Features favouring **AIP**: diffuse sausage-shaped gland, capsule (rim) sign, multifocal strictures without upstream dilatation, raised IgG4, other-organ involvement.
- ▶ **Before a steroid trial, malignancy must be vigorously excluded** (EUS-FNA/core biopsy, CA 19-9). A short, closely-monitored steroid trial is reasonable only when work-up is inconclusive and follow-up is assured.

Treatment

- ▶ **Glucocorticoids are first-line for both subtypes** — prednisone ~40 mg/day (0.6–1 mg/kg) for ~4 weeks, then taper by 5 mg/week over a total of ~10–12 weeks. Clinical and radiological response is usually obvious within 2–4 weeks; remission is achieved in ~99% of type 1 and ~92% of type 2.
- ▶ **Relapse** (30–50%, up to 60% in type 1, especially with IgG4-cholangitis) is managed by repeat steroids ± low-dose maintenance prednisone (5–10 mg/day), or steroid-sparing immunomodulators (**azathioprine, 6-mercaptopurine, mycophenolate mofetil**).
- ▶ **Rituximab (B-cell depletion)** is the most effective agent for recurrent/refractory disease and for IgG4-RD generally (two doses of 1 g IV ~15 days apart); it produces a swift fall in serum IgG4.
- ▶ **Adjuncts**: biliary stenting for obstructive jaundice, insulin for diabetes, pancreatic enzyme replacement if exocrine insufficiency supervenes, and surveillance for relapse (rising IgG4 flags impending flare).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled CT of type 1 AIP**: outline a *diffusely enlarged “sausage-shaped” pancreas*; label — loss of lobular contour, peripheral hypoattenuating rim (“capsule sign”), narrowed main pancreatic duct (no upstream dilatation), distal CBD stricture causing obstructive jaundice, dilated proximal CBD/intrahepatic ducts.
- ▶ **Histology schematic of LPSP (type 1)**: label — periductal lymphoplasmacytic cuff, storiform (cartwheel) fibrosis, obliterative phlebitis (vein lumen effaced by infiltrate),

IgG4⁺ plasma cells ($\geq 10/\text{hpf}$); contrast with type 2 GEL — neutrophils destroying duct epithelium.

Clinical / Diagnostic significance

- ▶ AIP is a key “do-not-miss, do-not-over-treat” diagnosis: it is the steroid-curable mimic of pancreatic cancer, and conversely a non-responding “AIP” may be cancer.
- ▶ Type 1 AIP mandates a **systemic survey for IgG4-RD** (salivary glands, kidneys, retroperitoneum, biliary tree, aorta) because subclinical multi-organ disease is common and may cause irreversible fibrosis (renal atrophy, hepatic failure from sclerosing cholangitis, aortic dissection).
- ▶ Long-standing/untreated AIP can “burn out” to atrophic, calcified chronic pancreatitis indistinguishable from other causes, with exocrine and endocrine insufficiency.
- ▶ Patients are at modestly increased risk of various malignancies; vigilant follow-up is required.

High-yield exam pointers

- ▶ **Two subtypes:** type 1 = IgG4-RD/LPSP (elderly male, multi-organ, high relapse); type 2 = IDCP/GEL (younger, pancreas-only, IBD-associated, low relapse). Type 3 = checkpoint-inhibitor-induced.
- ▶ **Painless obstructive jaundice + sausage-shaped pancreas + raised IgG4** = type 1 AIP until proven otherwise.
- ▶ **Capsule (rim) sign** = highly specific; main pancreatic duct **narrowed, not dilated** (unlike cancer).
- ▶ **Serum IgG4 $> 2 \times$ ULN** = level-1 serology; remember the **prozone effect** (false-low at very high titres).
- ▶ **HISORt** (Mayo) and **ICDC** (P-D-S-OOI-H + Rt) are the two diagnostic frameworks.
- ▶ **Histology hallmarks:** storiform fibrosis + obliterative phlebitis + ≥ 10 IgG4⁺ cells/hpf (type 1); granulocytic epithelial lesion (type 2).
- ▶ **Treatment:** prednisone 40 mg/day $\rightarrow$ taper; **rituximab** for relapse; $\sim 100\%$ steroid response — *failure to respond suggests cancer*.
- ▶ IgG4 is a **non-inflammatory** antibody (Fab-arm exchange); the real driver is the **CD4⁺ cytotoxic T cell**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Acute and Chronic Pancreatitis” (AIP subtypes, HISORt, capsule sign, treatment) and “IgG4-Related Disease” (organ manifestations, pathology, serology, rituximab).

- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Chronic Pancreatitis” (LPSP/IDCP histology, International Consensus Diagnostic Criteria, imaging, AIP-vs-cancer, steroid regimen and relapse).
- ▶ **CMDT 2026** — “Liver, Biliary Tract, & Pancreas Disorders” (type 1/2/3 classification, HISOrt, prednisone taper, rituximab maintenance).



Barrett's Esophagus

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Barrett's esophagus (BE) is the condition in which the normal stratified squamous epithelium lining the distal esophagus is replaced by an abnormal **columnar epithelium with both gastric and intestinal features** that is predisposed to malignancy. It is a consequence of **chronic gastro-esophageal reflux disease (GERD)**, which injures the squamous epithelium and drives metaplastic healing. The condition is named after *Norman Barrett*, an Australian-born surgeon who described the columnar-lined esophagus in 1950. BE itself is asymptomatic; its entire clinical importance lies in being the principal **precursor lesion of esophageal adenocarcinoma (EAC)**, a cancer whose incidence has risen more than 7-fold over recent decades.

Diagnosis and Endoscopic Classification

- ▶ **Two criteria must both be fulfilled** (it is an endoscopic *and* histological diagnosis):
- ▶ Endoscopist confirms **columnar epithelium lining ≥ 1 cm of the distal esophagus** above the esophagogastric junction (EGJ).
- ▶ **Biopsy shows metaplasia** — U.S. societies (ACG/AGA) require **intestinal metaplasia with goblet cells** (“specialized intestinal metaplasia”).
- ▶ The EGJ is identified endoscopically as the *most proximal extent of the gastric folds*; columnar mucosa must extend ≥ 1 cm above it.
- ▶ **Endoscopic appearance**: Barrett mucosa is **reddish/salmon-coloured with a velvet-like texture**, contrasting sharply with the pale, glossy squamous epithelium; it ascends from the EGJ in a *tongue-like or circumferential* pattern.
- ▶ **Three columnar epithelial types** may be seen — gastric cardiac, gastric fundic, and **specialized intestinal metaplasia**; only the last carries the established risk of dysplasia/cancer.
- ▶ **Length-based classification** and the standardised **Prague C & M criteria**:

System	Definition	Note
Long-segment BE	metaplasia extends ≥ 3 cm above EGJ	severe GERD; higher cancer risk

System	Definition	Note
Short-segment BE	<3 cm of metaplasia	by far the commonest form (Spechler, 1994)
Prague C value	Circumferential extent (cm) of metaplasia	reproducible grading
Prague M value	Maximum extent (cm), including tongues	(Sharma et al., 2006)

Epidemiology and Risk Factors

- Usually discovered during endoscopy done for GERD symptoms in **middle-aged/older adults**; mean age at diagnosis $\approx$ **55 years**. Rare under age 10, virtually absent under age 5.
- **Demographics**: predominantly **white men**; uncommon (though rising) in Black and Asian populations.
- **Prevalence**: in the general Western adult population **1.6–6.8%** (predominantly short-segment); among patients scoped for GERD, **long-segment in 3–5%** and **short-segment in 10–20%** (CMDT: 7–11% of chronic-reflux patients).
- **Risk factors for BE / EAC**: chronic GERD, **central (truncal) obesity** (raises intra-abdominal pressure $\rightarrow$ GERD; also $\uparrow$ IGF-1, leptin, $\downarrow$ adiponectin), **cigarette smoking**, male sex, white race, hiatal hernia, age $\geq$ 50, and a first-degree relative with BE/EAC.
- **Protective factors**: *Helicobacter pylori* infection (may reduce acid secretion/GERD), aspirin/NSAID use, and a diet rich in fruit and vegetables.
- **Note**: smoking and alcohol are strong risk factors for **squamous-cell carcinoma**; for **adenocarcinoma** smoking is only a modest risk and alcohol has no clear effect.

Pathogenesis and Molecular Carcinogenesis

- BE begins with **GERD-induced injury** (acid $\pm$ duodeno-gastric reflux of bile acids/pancreatic enzymes); reflux-damaged squamous epithelium heals via **metaplasia** into a columnar, intestinal-type epithelium presumed more resistant to reflux (secretes mucins, expresses tight-junction protein **claudin-18**).
- This requires **molecular reprogramming of developmental transcription factors** in progenitor cells — up-regulated genes include **CDX genes** (drive intestinal differentiation) and the Hedgehog targets **BMP4** and **FOXA2**.
- **Neoplastic progression** = stepwise acquisition of the *Hanahan–Weinberg hallmarks of cancer*, facilitated by **genomic instability (aneuploidy)** and a tumour-promoting microenvironment (oxidative stress from GERD). Key alterations:
 - **Oncogene activation**: cyclin D1, K-ras, EGF receptor, TGF- α (self-sufficiency in growth signals).

- **Tumour-suppressor loss:** TP53 (early event; also enables apoptosis evasion) and p16/CDKN2A.
- **Telomerase reactivation** → limitless replication; VEGF → angiogenesis; cadherin/catenin disruption + matrix metalloproteases → invasion/metastasis.
- ▶ Two carcinogenic pathways recognised by genomic sequencing: the “**traditional pathway**” (stepwise TP53 → p16 → oncogene activation) and the more rapid “**genome-doubled pathway**” (TP53 mutation → whole-genome doubling → oncogene amplification) — the latter accounts for ~62% of tumours and may explain *interval cancers* that escape surveillance.

Dysplasia and Cancer Risk

- ▶ **Dysplasia (intraepithelial neoplasia)** is the histological marker of progression: nuclear enlargement, pleomorphism, hyperchromatism, stratification, atypical mitoses, loss of cytoplasmic maturation, crowded/villiform architecture. Graded **low-grade (LGD)** or **high-grade (HGD)**.
- ▶ **Inter-observer agreement** is poor for LGD (<50% — easily confused with reactive change) but better for HGD (~85%); any grade of dysplasia should be **confirmed by a second expert GI pathologist**.

Histology	Approx. annual progression to cancer
Non-dysplastic BE	~0.25%/yr (range 0.12–0.33%)
Short-segment (1–3 cm)	~0.29%/yr (CMDT)
Long-segment (>3 cm)	~0.91%/yr (CMDT)
Low-grade dysplasia	disputed; ~0.4–13%/yr depending on series
High-grade dysplasia	~6%/yr; 13% harbour unsuspected invasive cancer

Management

- ▶ **Acid suppression / chemoprevention:** all BE patients receive a **PPI** in the dose needed to control symptoms and heal esophagitis; asymptomatic patients are still offered **once-daily PPI for chemoprevention** (ACG). The **AspECT trial** showed high-dose PPI + aspirin improved the composite outcome (mortality/progression), driven mainly by improved overall survival. Routine NSAID/aspirin prescription *solely* for chemoprevention is **not** recommended (GI/CV bleeding risk).
- ▶ **Anti-reflux surgery (fundoplication)** controls GERD but is **not clearly superior to PPI** for cancer prevention — not done for cancer prophylaxis alone.
- ▶ **Screening (ACG 2022):** endoscopic screening only for those with **≥5 years of at least weekly GERD symptoms plus ≥3 risk factors** (age >50, male sex, white race, central obesity, smoking,

family history). *Not* recommended routinely in women. A swallowable **capsule-sponge** with biomarker cytology is an emerging non-endoscopic alternative.

- **Surveillance:** high-resolution white-light endoscopy with the **Seattle biopsy protocol** = 4-quadrant biopsies every 1–2 cm (every 2 cm if non-dysplastic; every 1 cm if dysplasia known) plus targeted biopsy/EMR of any visible irregularity. **Non-dysplastic BE** → scope every 3–5 years.
- **Endoscopic Eradication Therapy (EET)** is now the treatment of choice for confirmed **mucosal neoplasia** (LGD, HGD, and intramucosal/T1a carcinoma) — combining resection + ablation, with **complete eradication of intestinal metaplasia (CE-IM)** as the goal:

Modality	Mechanism / role
Endoscopic mucosal resection (EMR)	“suck-and-cut” or “band-and-snare”; removes visible nodules — essential for accurate T-staging (superior to EUS) before ablation
Endoscopic submucosal dissection (ESD)	en-bloc knife resection of larger lesions
Radiofrequency ablation (RFA)	balloon/catheter microwave electrodes — procedure of choice for flat dysplasia (proven in AIM Dysplasia and SURF trials)
Cryotherapy	spray CO ₂ /N ₂ O — freeze–thaw injury; spares collagen matrix
Photodynamic therapy (PDT)	porfimer sodium + laser → singlet oxygen; <i>largely abandoned</i> (photosensitivity, strictures)
Esophagectomy	historical gold standard for HGD; mortality 3–10% — now reserved for EET failure/submucosal invasion

- **Staging rule:** if EMR reveals **submucosal invasion**, lymph-node metastasis exceeds 10% → EET is abandoned and the patient referred for surgical/oncological management; mucosal (T1a) lesions have only ~1.4% nodal risk, making EET safe.
- **Post-EET surveillance (after CE-IM):** for HGD/intramucosal carcinoma — every 3 months × 1 yr, 6-monthly in yr 2, then annually; for LGD — 6-monthly × 1 yr then annually. Recurrence (mostly at the neo-squamocolumnar junction) reaches ~9–10%/yr, so surveillance continues despite CE-IM.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Endoscopic view of Barrett’s esophagus:** tubular esophagus with **salmon-red velvety columnar tongues** ascending from the EGJ over pale glossy squamous mucosa. *Labels:* squamous (pale) epithelium, columnar (salmon) Barrett mucosa, **Z-line** / **squamocolumnar junction**, EGJ (top of gastric folds), ≥1 cm metaplastic segment, Prague C and M measurements.

- ▶ **Metaplasia–dysplasia–carcinoma sequence (flow diagram):** Normal squamous epithelium → (chronic GERD) → **Intestinal metaplasia (BE)** → **Low-grade dysplasia** → **High-grade dysplasia** → **Esophageal adenocarcinoma**. *Annotate* molecular hits: TP53 & p16 loss, cyclin D1/K-ras activation, aneuploidy/genome-doubling.

Clinical / Diagnostic significance

- ▶ BE is the key **pre-malignant marker** linking GERD to EAC — the rationale for screening high-risk refluxers and for endoscopic surveillance.
- ▶ **Diagnosis hinges on biopsy** confirming intestinal metaplasia with goblet cells; endoscopic appearance alone is insufficient, and the **EGJ landmark (gastric folds)** must be correctly identified to avoid over-/under-diagnosis.
- ▶ **Sampling error is the major pitfall** — dysplasia is patchy and often endoscopically subtle; the Seattle protocol misses lesions, hence the move toward removing *all* visible irregularities by EMR and ablating *all* residual metaplasia.
- ▶ Management is **risk-stratified by dysplasia grade**: PPI + surveillance for non-dysplastic BE, EET for any confirmed dysplasia or T1a cancer, surgery/chemoradiation once submucosal/nodal disease appears.

High-yield exam pointers

- ▶ BE = **metaplastic columnar (intestinal) epithelium replacing distal esophageal squamous epithelium**; named after *Norman Barrett* (1950).
- ▶ **Diagnostic dyad**: columnar mucosa ≥ 1 cm above EGJ + intestinal metaplasia with goblet cells on biopsy.
- ▶ **Long-segment ≥ 3 cm, short-segment < 3 cm**; Prague C & M criteria for standardised reporting.
- ▶ Typical patient: **obese white male, ~55 yr, chronic GERD**; *H. pylori*, aspirin/NSAIDs and a fruit/vegetable diet are **protective**.
- ▶ **Cancer risk ~0.25%/yr (non-dysplastic), ~6%/yr (HGD)**; risk rises with segment length (LSBE 0.91%/yr vs SSBE 0.29%/yr).
- ▶ **Earliest molecular hit = TP53 inactivation**; CDX/BMP4/FOXA2 drive metaplasia; aneuploidy and the *genome-doubled pathway* accelerate cancer.
- ▶ **Seattle protocol** = 4-quadrant biopsies every 1–2 cm + targeted EMR of nodules.
- ▶ EET (EMR + RFA) is first-line for dysplasia/T1a (AIM & SURF trials); **submucosal invasion (>10% nodal risk) contraindicates EET**; esophagectomy mortality 3–10%.
- ▶ All BE patients get a **once-daily PPI**; surveillance interval for non-dysplastic BE is 3–5 years.

SOURCE & COVERAGE

- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Barrett Esophagus” (primary depth: diagnosis criteria, Prague C&M, pathogenesis, molecular biology, dysplasia, EET, AIM/SURF trials, surveillance).
- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Diseases of the Esophagus” (GERD context, metaplasia–dysplasia–carcinoma sequence, chemoprevention/AspECT, esophagectomy vs endoscopic ablation).
- ▶ **CMDT 2026** — “Gastrointestinal Disorders: GERD / Barrett Esophagus” (ACG 2022 screening criteria, segment-specific cancer risk, EET indications, capsule-sponge).



Biliary Cirrhosis

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Biliary cirrhosis* is the end-stage of chronic **cholestatic** liver disease, in which sustained impairment of bile flow (rather than hepatocellular necroinflammation) drives progressive **biliary-type fibrosis**, ductopenia and finally architectural distortion with regenerative nodules. It has pathologic features distinct from alcohol-associated or post-hepatitic cirrhosis, yet the manifestations of end-stage liver disease (portal hypertension, jaundice, hepatic failure) are the same. The cholestasis may be **intrahepatic** (small-duct disease, e.g. primary biliary cholangitis) or **extrahepatic** (large-duct obstruction) — a distinction with major therapeutic consequence, since extrahepatic obstruction may be relieved by surgical/endoscopic decompression whereas intrahepatic disease will not.

Classification — causes of biliary cirrhosis

- ▶ **Primary (intrahepatic, autoimmune/idiopathic cholestatic syndromes):** *primary biliary cholangitis (PBC)*, *primary sclerosing cholangitis (PSC)*, *autoimmune cholangitis* (AMA-negative PBC), and *idiopathic adulthood ductopenia*. These share the histopathology of chronic cholestasis — **choleate stasis, copper deposition, xanthomatous transformation of hepatocytes, irregular “biliary” fibrosis and progressive ductopenia**.
- ▶ **Secondary biliary cirrhosis** results from *prolonged extrahepatic biliary obstruction* — chronic choledocholithiasis, post-operative/inflammatory bile-duct strictures, chronic pancreatitis, biliary/pancreatic malignancy, and (in children) biliary atresia or cystic fibrosis-associated biliary disease.
- ▶ The two named primary biliary syndromes are distinguished clinically by **antibody testing, cholangiographic findings and clinical presentation** (PBC = small ducts, AMA, female; PSC = whole biliary tree, MRCP beading, IBD).

Primary biliary cholangitis — epidemiology & pathogenesis

- ▶ Prevalence ~100–200 per million, strong female preponderance (~9:1), median age at diagnosis ~50 years (40–60). The term *cholangitis* replaced *cirrhosis* in 2015 because most patients are now diagnosed pre-cirrhotic.
- ▶ An **immune-mediated** disease arising in genetically susceptible individuals; there is **chronic non-suppurative destructive cholangitis** of small and medium intrahepatic bile ducts mediated by CD4+/CD8+ T-cell cytotoxicity against biliary epithelium, with loss of tolerance to mitochondrial autoantigens.
- ▶ **Antimitochondrial antibodies (AMA)** are present in ~90–95% and are the immunologic hallmark. They target the **E2 component of the pyruvate dehydrogenase complex (PDC-E2)** plus the branched-chain 2-oxoacid (BCOADC-E2) and 2-oxoglutarate (OGDC-E2) dehydrogenase complexes on the **inner mitochondrial membrane**, recognising the bound *lipoic acid*. AMA are **diagnostic markers but are not themselves pathogenic** (titre does not track severity; they persist after transplant).
- ▶ **Genetic/environmental contributors:** association with HLA **DRB1\08** (*DQB1*); *concordance* ~60% in monozygotic twins; *triggers proposed include* molecular mimicry (e.g. *E. coli*, *Novosphingobium aromaticivorans*), *recurrent UTIs*, *smoking** (associated with advanced fibrosis) and xenobiotics (2-octynoic acid in cosmetics/hair dye).

Clinical features & associated diseases

- ▶ Up to 50–60% are **asymptomatic** at diagnosis (incidental cholestatic enzyme elevation). The two cardinal symptoms are **fatigue** (most disabling, out of proportion to disease) and **pruritus** (~50%, worse at night; pruritus *before* jaundice signals severe disease/poor prognosis).
- ▶ Signs reflecting chronic cholestasis: **hyperpigmentation** (melanin deposition), **xanthelasma** and **xanthomata**, hepatosplenomegaly, and — late — jaundice, ascites, variceal bleeding and encephalopathy. **Metabolic bone disease** (osteopenia/osteoporosis) and **fat-soluble vitamin (A, D, E, K) deficiency** complicate advanced disease.
- ▶ **Associated autoimmune conditions** are characteristic and should be screened:

Associated disease	Approx. frequency
Sjögren syndrome (sicca complex)	72–100%
Renal tubular acidosis	50–60%
Arthritis / arthropathy	4–42%
Gallstones	~33%
Autoimmune thyroiditis	15–20%
Systemic sclerosis / CREST variants	15–19%
Coeliac disease	1–7%

Associated disease	Approx. frequency
Hepatocellular carcinoma (with cirrhosis)	1–3% (~19-fold ↑ risk)

Histological staging (Ludwig / Scheuer — four stages)

Stage	Key feature
Stage 1	<i>Chronic non-suppurative destructive cholangitis</i> — portal inflammation centred on small bile ducts; the florid duct lesion (lymphocytic destruction ± non-caseating epithelioid granuloma) is near-diagnostic
Stage 2	Inflammation extends beyond portal tract into parenchyma (interface hepatitis / piecemeal necrosis); bile-duct destruction with ductular proliferation
Stage 3	Bridging fibrosis (septal fibrosis without regenerative nodules); progressive ductopenia
Stage 4	Cirrhosis (micronodular or macronodular) with fibrous septa and regenerative nodules

- ▶ The only consistently diagnostic histologic clue is **ductopenia** — absence of interlobular bile ducts in >50% of portal tracts.

Diagnosis & investigations

- ▶ **Biochemistry** — **cholestatic pattern**: elevated **alkaline phosphatase (ALP)** and **γ-glutamyl transpeptidase (GGT)**; ALT/AST only mildly raised (usually <3× ULN; >5× ULN suggests **PBC–autoimmune hepatitis overlap**). **IgM** characteristically elevated; **hypercholesterolaemia**; bilirubin rises late and is a poor-prognosis marker.
- ▶ **Diagnosis requires 2 of 3 criteria**: (1) chronic cholestasis with **ALP ≥1.5× ULN**, (2) **AMA titre ≥1:40**, (3) **compatible liver biopsy**. Biopsy is *not* needed in most AMA-positive patients.
- ▶ **AMA-negative PBC (~5–10%)**: confirm with PBC-specific antinuclear antibodies — **anti-sp100** (multiple-nuclear-dots) and **anti-gp210** (rim-like/membranous nuclear-envelope pattern, highly specific, poor prognosis). Here **liver biopsy and MRCP are mandatory** to exclude small-duct **PSC**, **IgG4 cholangiopathy**, **sarcoidosis**.
- ▶ **Imaging**: ultrasound/CT/MRI to exclude extrahepatic obstruction; periportal “**halo**” sign on MRI; **transient/MR elastography** for non-invasive fibrosis staging and prognosis.
- ▶ **Prognostic scores**: **Mayo risk score**, **GLOBE score** and **UK-PBC score** (incorporate age, bilirubin, albumin, ALP, platelets, transaminases); **Paris-II criteria** define low-risk biochemical response after 1 year of UDCA (ALP and AST <1.5× ULN, bilirubin ≤1 mg/dL).

Treatment of PBC

- ▶ **Ursodeoxycholic acid (UDCA) 13–15 mg/kg/day** is the first-line, disease-modifying drug — it improves liver biochemistry and histology, reduces varices/ascites/HCC risk, delays cirrhosis and improves transplant-free survival; responders have survival approaching that of healthy controls. ~20–40% are inadequate responders (more common in men and younger-onset disease).
- ▶ **Second-line agents for UDCA non-responders/intolerance** (avoid all in decompensated cirrhosis / portal hypertension):

Agent	Class / mechanism	Note
Obeticholic acid	Farnesoid-X-receptor (FXR) agonist	Start 5 mg/day; pruritus common; Child B/C → max 5 mg/week
Seladelpar (10 mg/day)	PPAR- δ agonist	Recently approved; ↓ALP, ↓pruritus
Elafibranor (80 mg/day)	PPAR- α/δ agonist	Recently approved
Bezafibrate / fenofibrate	Fibrate / PPAR agonist	Second-line; improve ALP even in non-responders

- ▶ **Symptomatic / complication management:** *Pruritus* — **cholestyramine** (4 g, dosed around breakfast), then **rifampin** 150–300 mg BD, **naltrexone**, **sertraline**, ondansetron; refractory cases → plasmapheresis. *Fatigue* — no proven drug; modafinil tried. *Bone disease* — **DEXA** at diagnosis, oral **calcium + vitamin D**, **bisphosphonates**. *Fat-soluble vitamin (A, D, E, K) screening/replacement* if bilirubin >2 mg/dL.
- ▶ **Liver transplantation** is the treatment of choice for end-stage PBC (also for intractable pruritus); consider at MELD ≥ 15 , bilirubin ≥ 6 mg/dL, or Mayo score ≥ 7.8 . One-year survival ~85–90%; PBC recurs in the graft in ~20% by 3 years (lower with UDCA prophylaxis and cyclosporine-based immunosuppression).

Primary sclerosing cholangitis (contrast)

- ▶ Chronic fibrosing inflammation of the **entire intra- and extrahepatic biliary tree** → multifocal strictures, biliary cirrhosis, portal hypertension.
- ▶ **65% pANCA-positive; 60–80% have inflammatory bowel disease (predominantly ulcerative colitis)** — colonoscopy advised at diagnosis.
- ▶ Diagnosis is **cholangiographic**: **MRCP (first-line)** shows multifocal strictures and beading (“beaded appearance”) with intervening normal/dilated segments.
- ▶ **No proven medical therapy** (high-dose UDCA 28–30 mg/kg/day is *harmful*); manage dominant strictures endoscopically; treat cholangitis with antibiotics; **liver transplantation** is definitive. Dreaded complication: **cholangiocarcinoma**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Ludwig staging of PBC (4-panel):** draw a portal tract with central bile ductule and label — *Stage 1: florid duct lesion (lymphocytes + granuloma around bile duct, portal inflammation); Stage 2: interface hepatitis + ductular proliferation; Stage 3: bridging fibrous septa + ductopenia; Stage 4: cirrhosis with regenerative nodules.*
- ▶ **MRCP in PSC:** sketch intra- and extrahepatic ducts with labels — *multifocal strictures, intervening dilated segments (“beading”), dominant stricture, pruned-tree intrahepatic ducts.*

Clinical / Diagnostic significance

- ▶ A persistently isolated raised ALP/GGT in a middle-aged woman should prompt AMA testing — early PBC is treatable and UDCA started early prevents progression.
- ▶ Differentiating intrahepatic vs extrahepatic cholestasis (AMA + MRCP) is critical: extrahepatic obstruction needs decompression, intrahepatic does not.
- ▶ Marked transaminase elevation ($>5\times$ ULN) or high IgG flags PBC–AIH overlap, which may need adjunctive immunosuppression.
- ▶ Surveillance obligations: HCC screening once cirrhotic, endoscopy for varices, DEXA for bone disease, and screening for associated autoimmune disease (thyroid, coeliac, Sjögren).

High-yield exam pointers

- ▶ Biliary cirrhosis = chronic cholestasis → biliary fibrosis/ductopenia; subtypes **primary** (PBC, PSC, autoimmune cholangitis) and **secondary** (chronic extrahepatic obstruction).
- ▶ **PBC:** middle-aged woman, AMA (anti-PDC-E2) ~90–95%, raised ALP + IgM, pruritus + fatigue; diagnose by 2 of 3 (cholestatic ALP $\geq 1.5\times$ ULN, AMA $\geq 1:40$, biopsy).
- ▶ **Ludwig four stages:** 1 florid duct lesion → 2 interface hepatitis → 3 fibrosis → 4 cirrhosis; **ductopenia $>50\%$ portal tracts** is the diagnostic hallmark.
- ▶ UDCA 13–15 mg/kg/day is first-line and improves survival; non-responders → **obeticholic acid (FXR)**, **seladelpar/elafibranor (PPAR)**, **fibrates** — *avoid in decompensation.*
- ▶ **AMA-negative PBC** → look for **anti-sp100 / anti-gp210**; biopsy + MRCP mandatory.
- ▶ **Pruritus ladder:** cholestyramine → rifampin → naltrexone → sertraline.
- ▶ **PSC:** whole biliary tree, **pANCA**, **UC association**, **MRCP beading**, risk of **cholangiocarcinoma**, no effective drug, transplant definitive.
- ▶ Indications/markers for **transplant** in PBC: Mayo ≥ 7.8 , MELD ≥ 15 , bilirubin ≥ 6 ; recurs in ~20% of grafts.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Cirrhosis and Its Complications” (Biliary Cirrhosis; Primary Biliary Cholangitis; Primary Sclerosing Cholangitis sections).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Primary Biliary Cholangitis” (epidemiology, AMA/autoantibody immunobiology, Ludwig staging, UDCA/obeticholic acid/fibrate data, complications, transplantation) and “Primary and Secondary Sclerosing Cholangitis.”
- ▶ **CMDT 2026** — “Liver, Biliary Tract, & Pancreas Disorders” (current diagnostic criteria, UDCA, seladelpar/elafibranor approvals, pruritus regimens, transplant thresholds/prognosis).



Celiac Disease

Asked in: Paper II Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Celiac disease (celiac sprue, gluten-sensitive enteropathy) is a chronic, immune-mediated enteropathy of the small intestine precipitated by dietary **gluten** in genetically predisposed (HLA-DQ2 / DQ8) individuals. It is characterised by **villus atrophy, crypt hyperplasia and intraepithelial lymphocytosis** of the proximal small bowel, the presence of **anti-tissue transglutaminase (tTG-2) autoantibodies**, and clinical plus histological recovery on a strict **gluten-free diet (GFD)** with relapse on gluten re-exposure. Global seroprevalence is ~1.4% (biopsy-confirmed ~0.7%), making it one of the commonest lifelong food-related disorders.

Etiopathogenesis (the gluten–genes–immunity triad)

- ▶ **The antigen (gluten):** the water-insoluble storage proteins of wheat, rye and barley. Gluten = **prolamins + glutenins**; the toxic prolamins are *gliadin* (wheat), *secalin* (rye) and *hordein* (barley). These are rich in **glutamine (~30%) and proline (~15%)**, rendering them resistant to luminal digestion. *Avenin* (oats) has intermediate content, so most patients tolerate **uncontaminated oats**; rice, corn, sorghum and millet are non-toxic.
- ▶ **Genetic predisposition:** HLA-DQ2 is present in >90% of patients and HLA-DQ8 in almost all the remainder; one haplotype is *necessary but not sufficient*. As they occur in 25–35% of the general population, a positive test is non-diagnostic, but a **negative HLA-DQ2/DQ8 has a negative predictive value >99%** (used to *exclude* disease). First-degree relative prevalence is 10–15%; monozygotic-twin concordance reaches 49–83%.
- ▶ **Immune mechanism:** tissue **transglutaminase-2 (tTG-2)** *deamidates* glutamine residues of gliadin to negatively charged glutamic acid, which binds avidly to the antigen-binding groove of DQ2/DQ8 on antigen-presenting cells. This activates **gliadin-specific CD4⁺ T-cells** in the lamina propria, releasing IFN- γ , TNF- α , IL-2, IL-6 (adaptive response). The enterocyte/macrophage

cytokine IL-15 drives the innate arm, expands CD8⁺ and γ/δ intraepithelial lymphocytes (IELs) and bridges the two — γ/δ IELs may rise from <10% to ~35% (a *hallmark*). The net result is enterocyte injury, crypt hyperplasia and villus atrophy. tTG-2 within the endomysium is the target autoantigen, explaining the diagnostic serology.

Clinical spectrum

Presentation is protean and has shifted from the “classical” malabsorptive child to the **non-classical / silent adult** (5th decade most common age at diagnosis).

- ▶ **Classical (GI):** chronic/episodic diarrhoea, steatorrhoea, abdominal bloating, flatulence, weight loss; in infants — failure to thrive, irritability, hypotonia, muscle wasting, abdominal distension after weaning.
- ▶ **Non-classical / extraintestinal:** unexplained **iron-deficiency anaemia** (commonest; consider in IDA without GI blood loss), fatigue, **osteopenia/osteoporosis** (>70% have low bone density), **dermatitis herpetiformis**, aphthous stomatitis, dental enamel defects, raised aminotransferases (~27–40%), **gluten ataxia** and peripheral neuropathy, **infertility/recurrent miscarriage**, short stature, delayed puberty, amenorrhoea.
- ▶ **Silent / potential:** asymptomatic seropositive individuals detected on screening (relatives, T1DM, Down syndrome). Up to ~40% of seropositive patients have no symptoms.
- ▶ **Celiac crisis:** rare, life-threatening profuse diarrhoea with dehydration, electrolyte derangement, metabolic acidosis, hypocalcaemia and hypoproteinaemia — needs IV fluids $\pm$ glucocorticoids.
- ▶ **Dermatitis herpetiformis (DH):** intensely pruritic, symmetrical papulovesicles over extensor surfaces, buttocks, trunk and scalp — the “*celiac disease of the skin*.” Granular **IgA deposits at the dermal papillae**; autoantigen is **epidermal (type 3) transglutaminase**. ~80% have enteropathy. Responds to **dapsone** (1–2 mg/kg/day) for skin plus a GFD for the gut.

Diagnosis

Diagnosis (in an adult on a **gluten-containing diet**) rests on **serology + duodenal biopsy**.

Test	Role / remark
IgA anti-tTG-2	Screening test of choice — sensitivity ~98%, specificity ~98%
Total serum IgA	Co-test to detect selective IgA deficiency (in 2–3% of celiacs $\rightarrow$ false-negative tTG)
IgG tTG / IgG-DGP	Used when IgA deficient
IgA endomysial antibody (EMA)	Very high specificity (~100%); labour-intensive, confirmatory
Anti-deamidated gliadin peptide (DGP)	Useful adjunct, IgG class in IgA deficiency

Test	Role / remark
Native anti-gliadin antibody (AGA)	Not recommended — low specificity
HLA-DQ2 / DQ8	High NPV; used to rule out disease, esp. in self-treated patients

- ▶ **Small-intestinal biopsy** (gold standard): take 4–6 biopsies from the 2nd/3rd part of the duodenum plus the bulb (lesions are patchy and proximal). Histology: **villus atrophy**, **crypt hyperplasia**, **increased IELs** (≥ 25 per 100 enterocytes) and lamina propria plasmacytosis.
- ▶ **Marsh classification** of severity (see table).
- ▶ **Endoscopic clues** (insensitive): scalloping/loss of duodenal folds, mosaic/nodular pattern, fissuring — a normal-looking duodenum does **not** exclude disease.
- ▶ **Pediatric biopsy-free pathway** (ESPGHAN): symptoms + IgA-tTG $\geq 10 \times$ ULN + positive EMA on a separate sample + compatible HLA — may avoid biopsy (not universally adopted in adults/US).
- ▶ **Gluten challenge** (for patients already on a GFD with uncertain diagnosis): ~2–4 g gluten/day (1–2 slices of bread); biopsy may be diagnostic by 2 weeks, serology rise by ~4 weeks.

Marsh stage	Histology
0 (pre-infiltrative)	Normal mucosa
1 (infiltrative)	Normal villi, increased IELs
2 (hyperplastic)	Increased IELs + crypt hyperplasia
3 (destructive)	Villus atrophy — 3a partial, 3b subtotal, 3c total
4 (hypoplastic/atrophic)	Total villus atrophy with crypt hypoplasia

Treatment and monitoring

- ▶ **Lifelong strict gluten-free diet** is the cornerstone — eliminate **wheat, rye, barley** (and contaminated oats); beware *hidden gluten* in processed foods, medications and cross-contamination. **Dietitian** referral and patient education are essential. Most improve within 2–6 months; serology normalises over 1–2 years.
- ▶ **Nutritional repletion**: iron, folate, vitamin B12, calcium, vitamin D, zinc, and fat-soluble vitamins (A, E, K) as required; ensure ~1500 mg calcium/day. Treat coexistent **lactose intolerance** (transient secondary lactase deficiency) until mucosa heals.
- ▶ **Bone health**: DEXA scan within 1 year of diagnosis; calcium + vitamin D, and **bisphosphonates** for established osteoporosis.
- ▶ **Glucocorticoids / budesonide**: *not* for routine disease — reserved for **celiac crisis** and **refractory disease**.

- ▶ **Monitoring:** clinic review at 3–6 monthly intervals in year 1 with serial IgA-tTG (falls confirm adherence; half-life ~6–8 weeks). Persistently positive serology = ongoing gluten exposure. Follow-up duodenal biopsy at ~2 years to confirm mucosal healing, especially if symptoms persist.

Complications and associated disorders

- ▶ **Non-responsive celiac disease (NRCD)** (~10%): persistent symptoms despite ≥6–12 months GFD — commonest cause is **continued (often inadvertent) gluten ingestion**; also lactose/fructose intolerance, SIBO, pancreatic insufficiency, microscopic colitis, IBS.
- ▶ **Refractory celiac disease (RCD)** (~0.3–1.5%): villus atrophy persisting despite ≥12 months strict GFD with negative serology.
 - **Type I** — normal *polyclonal* IEL phenotype; responds to budesonide/steroids ± azathioprine.
 - **Type II** — *aberrant clonal* IELs with **loss of surface CD3/CD8** and **monoclonal TCR-γ rearrangement**; steroid-resistant, treated with cladribine/autologous stem-cell transplant; ~50% progress to lymphoma at 5 years (poor prognosis).
- ▶ **Enteropathy-associated T-cell lymphoma (EATL), ulcerative jejunoileitis, and small-bowel adenocarcinoma** — suspect when a previously controlled patient develops new weight loss, pain, obstruction or bleeding.
- ▶ **Hyposplenism** (up to 50% of adults) — thrombocytosis, **Howell-Jolly bodies**, risk of pneumococcal sepsis → pneumococcal vaccination.
- ▶ **Associations:** **type 1 diabetes mellitus** (~5–6%), autoimmune thyroid disease, **selective IgA deficiency**, autoimmune hepatitis, **Down and Turner syndromes**, Sjögren syndrome, IgA nephropathy, microscopic colitis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Small-intestinal villus histology — normal vs celiac:** draw two adjacent panels. *Normal* — tall finger-like villi (villus:crypt ≈ 3–5:1), columnar enterocytes, few IELs. *Celiac* — **flat mucosa / villus atrophy, elongated hyperplastic crypts, increased intraepithelial lymphocytes, dense lamina propria plasma-cell infiltrate**. Label: *villus atrophy, crypt hyperplasia, intraepithelial lymphocytes, lamina propria infiltrate*.
- ▶ **Pathogenesis flow diagram:** Dietary gliadin → ↑intestinal permeability → tTG-2 deamidation of gliadin → binding to HLA-DQ2/DQ8 on APC → CD4⁺ T-cell activation (IFN-γ, TNF-α) + IL-15-driven CD8⁺/γδ IELs → villus atrophy + anti-tTG antibodies. Label each labelled box.

Clinical / Diagnostic significance

- ▶ Test for celiac disease in **unexplained iron-deficiency anaemia, osteoporosis, transaminitis, infertility, IBS-D phenotype, and gluten ataxia** — it is frequently underdiagnosed in adults.

- ▶ Always check serology and biopsy **BEFORE** starting a GFD; pre-treatment gluten avoidance causes false-negative results.
- ▶ Screen **high-risk groups**: first-degree relatives, T1DM, autoimmune thyroid disease, Down/Turner syndrome.
- ▶ A **rising or non-falling tTG** on treatment signals ongoing gluten exposure; **new alarm symptoms** in a stable patient mandate evaluation for RCD/EATL.

High-yield exam pointers

- ▶ Triad: **gluten + HLA-DQ2/DQ8 + tTG-2 autoimmunity**; toxic prolamins = gliadin/secalin/hordein; oats (avenin) usually safe.
- ▶ **IgA anti-tTG = screening test of choice** (sens/spec ~98%); always co-test **total IgA**.
- ▶ HLA-DQ2/DQ8 used to **exclude** disease (NPV >99%), not to confirm.
- ▶ **Marsh staging** (0 → 4); diagnosis needs villus atrophy + crypt hyperplasia + raised IELs, not IELs alone.
- ▶ Biopsy **proximal duodenum + bulb**, 4–6 samples; lesion is patchy and proximal.
- ▶ **Dermatitis herpetiformis** = granular IgA at dermal papillae, **epidermal tTG**, treat with **dapsone + GFD**.
- ▶ Complications: RCD type I vs II, EATL, **ulcerative jejunoileitis**, **small-bowel adenocarcinoma**, **hyposplenism** (Howell-Jolly bodies), **osteoporosis**.
- ▶ **Lifelong strict GFD** is the only definitive therapy; steroids only for celiac crisis/RCD.
- ▶ *Eponyms*: first described by **Areataeus of Cappadocia**; **Samuel Gee** (1888); **Dicke** linked wheat during the Dutch famine.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Disorders of Absorption” (Celiac Disease section).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Celiac Disease” (Lebwohl & Green) — used for pathogenesis, Marsh classification, serology performance, refractory disease/EATL, dermatitis herpetiformis and associations.
- ▶ **CMDT 2026** — “Gastrointestinal Disorders: Celiac Disease” — current diagnostic algorithm, management and refractory-disease typing.



Approach to Chronic Diarrhea

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Diarrhea is the passage of abnormally liquid or unformed stools at increased frequency; on a typical Western diet a **stool weight >200 g/day** is generally considered diarrheal. By duration it is **acute (<2 weeks)**, **persistent (2–4 weeks)**, and **chronic (>4 weeks)**. Diarrhea lasting **>4 weeks warrants evaluation to exclude serious underlying pathology**, and unlike acute diarrhea (mostly infective), **most causes of chronic diarrhea are non-infectious**. Classifying chronic diarrhea by its **predominant pathophysiologic mechanism** allows a rational, cost-effective approach, though many diseases produce diarrhea by more than one mechanism.

Relevant physiology & conditions to exclude first

- ▶ About **9 L of fluid enter the GI tract daily**, ~1 L reaches the colon, and only **~0.2 L is excreted in stool**; the colon has large absorptive reserve (can recover up to ~4× the usual 0.8 L/d), so diarrhea reflects altered fluid/electrolyte handling, motility, or both.
- ▶ Distinguish true diarrhea from mimics (different algorithms): **pseudodiarrhea** (frequent small-volume stools with urgency/tenesmus, <200 g/d — seen in IBS, proctitis); **fecal incontinence** (involuntary discharge from neuromuscular or anorectal structural disease); and **overflow diarrhea** from **fecal impaction** in elderly/nursing-home patients (detectable on rectal exam).
- ▶ First step in any chronic diarrhea: **exclude an iatrogenic cause — medications and prior surgery**.

Pathophysiologic classification (Harrison Table 49-3)

Mechanism	Key stool features	Representative causes
Secretory	Watery, large-volume, painless, persists with fasting, no osmotic gap	Stimulant laxatives (senna, bisacodyl, castor oil), chronic ethanol, drugs/toxins (arsenic, olmesartan), bile acid diarrhea (BAD) , bowel resection/disease/fistula, partial obstruction/impaction, hormonal tumors (carcinoid, VIPoma, gastrinoma, medullary thyroid carcinoma, mastocytosis, villous adenoma), Addison's disease, congenital ion-transport defects
Osmotic	Watery, ceases with fasting, osmotic gap >50 , low fecal pH (carbohydrate)	Osmotic laxatives (Mg^{2+} , PO_4^{3-} , SO_4^{2-}), lactase/disaccharidase deficiency , non-absorbable carbohydrates (sorbitol, fructose, lactulose, PEG), wheat and FODMAP intolerance

Mechanism	Key stool features	Representative causes
Steatorrheal (fat malabsorption)	Greasy, foul-smelling, difficult-to-flush, weight loss, nutrient deficiencies	Intraluminal maldigestion (pancreatic exocrine insufficiency, bacterial overgrowth, bariatric surgery, liver disease); mucosal malabsorption (celiac, Whipple's, abetalipoproteinemia, ischemia, drug-induced); post-mucosal lymphatic obstruction , amyloidosis
Inflammatory	Pain, fever, blood , fecal leukocytes/calprotectin	IBD (Crohn's, ulcerative colitis), microscopic (lymphocytic/collagenous) colitis , immunodeficiency, eosinophilic gastroenteritis , radiation injury, GI malignancy
Dysmotile	Often secretory-like; may have mild steatorrhea (≤ 14 g/d)	IBS (incl. post-infectious), visceral neuromyopathy, hyperthyroidism, prokinetic drugs, post-vagotomy, diabetic diarrhea
Factitial / Iatrogenic	Variable; hypokalemia, hypotension	Laxative abuse, Munchausen, eating disorders; cholecystectomy, ileal resection, bariatric surgery, vagotomy/fundoplication

Mechanistic high-yield points

- ▶ Stool osmotic gap = $290 - 2 \times ([\text{stool Na}^+] + [\text{stool K}^+])$. Gap >50 mosmol/L = osmotic; <50 = secretory. (Fecal osmolality measured directly can be falsely elevated by bacterial carbohydrate metabolism.)
- ▶ **Bile acid diarrhea (BAD)**: dihydroxy bile acids escaping absorption (e.g., Crohn's ileitis or resection of <100 cm terminal ileum) cause **cholerheic diarrhea**; idiopathic BAD reflects reduced FGF-19 feedback and may explain **~40% of unexplained chronic diarrhea** (~1% of the population). Diagnosed by elevated fasting **serum 7 α C4** or fecal bile acids.
- ▶ **Lactase deficiency** is one of the commonest causes of chronic diarrhea in adults (osmotic, low fecal pH).
- ▶ **Pancreatic exocrine insufficiency** manifests when **$>90\%$ of secretory function is lost**; fecal fat is normally <7 g/d, rises to **14 g/d** with rapid transit, **15–25 g** in small-intestinal disease, and **>32 g** with pancreatic insufficiency.

- ▶ **Hormonal secretory diarrheas:** carcinoid (serotonin, flushing, wheezing, right-heart valvular disease); **VIPoma** = pancreatic cholera / **WDHA syndrome** (Watery Diarrhea, Hypokalemia, Achlorhydria), stool can exceed 3 L/d (up to 20 L); gastrinoma (diarrhea in up to one-third); medullary thyroid carcinoma (calcitonin/prostaglandins); systemic mastocytosis (urticaria pigmentosa); colorectal villous adenoma.
- ▶ **Congenital electrolyte defects:** congenital chloridorrhea (**DRA gene**, $\text{Cl}^-/\text{HCO}_3^-$ exchange, alkalosis) and congenital sodium diarrhea (**NHE3 gene**, acidosis).

Clinical approach: history and examination

- ▶ **History:** onset/duration/pattern; aggravating (especially diet) and relieving factors; **stool character** (volume, nocturnal episodes, undigested food/fat, blood, consistency by **Bristol Stool Form Scale**); weight loss, fever, pain; exposures (travel, antibiotics, contacts); medications and surgery; family history of IBD or celiac disease; extraintestinal features (skin, arthralgia, oral aphthae).
- ▶ **Examination (Table 49-4):** look for signs of **malabsorption/IBD** (anemia, **dermatitis herpetiformis**, clubbing, edema, arthritis); features of **autonomic neuropathy or collagen-vascular disease** (pupils, orthostasis, skin); abdominal mass/tenderness; **rectal/anal sphincter** abnormalities; mucocutaneous clues — **flushing** (carcinoid), **erythema nodosum/pyoderma gangrenosum** (IBD), **thyroid mass**, wheeze, heart murmurs, lymphadenopathy, perianal fistula.

Diagnostic workup (rational triage)

- ▶ **Routine/limited organic screen:** CBC, chemistries, CRP, ESR, iron, folate, B12, TTG-IgA (on gluten) for celiac, serum 7aC4 (C4), stool fat, fecal calprotectin. Leukocytosis/raised CRP-ESR → inflammation; eosinophilia → parasites, allergy, eosinophilic gastroenteritis.
- ▶ **Quantitative stool studies** when weight >200 g/d: electrolytes (osmotic gap), pH, occult blood, leukocytes/calprotectin, fat and bile-acid quantitation, and laxative screen.
- ▶ **Secretory pattern:** reconsider drugs/surreptitious laxatives; stool **multiplex PCR/cultures** (incl. *Aeromonas*, *Plesiomonas*), ova & parasites, **Giardia antigen** (most sensitive for giardiasis); **breath tests** (glucose/lactulose H_2/CH_4) for bacterial overgrowth; **peptide hormone screen** when indicated — gastrin, VIP, calcitonin, thyroid hormone/TSH, **urinary 5-HIAA**, histamine.
- ▶ **Osmotic pattern:** test for **lactose/fructose intolerance**, fecal magnesium and laxative levels; **low fecal pH** indicates carbohydrate malabsorption.
- ▶ **Fatty (steatorrheal):** **endoscopy with small-bowel biopsy** ± aspirate for quantitative culture; small-bowel imaging (CT enterography, MR enteroclysis); confirm **pancreatic exocrine insufficiency** with secretin-CCK stimulation or indirect tests (**fecal elastase/chymotrypsin**, **bentiromide** — low sensitivity/specificity).

- ▶ **Inflammatory:** blood/leukocytes in stool → stool pathogens, **colonoscopy with biopsies** (random biopsies of normal-appearing colon needed to diagnose **microscopic colitis**), and small-bowel imaging as indicated. **BAD** confirmed by radiolabeled bile-acid retention test (SeHCAT), serum 7αC4/FGF-19, fecal bile acids, or therapeutic trial of a sequestrant.
- ▶ A **therapeutic trial** is appropriate, definitive and cost-effective when a specific diagnosis is suggested early (e.g., lactose-free diet for lactose intolerance; metronidazole for suspected giardiasis after backpacking; **cholestyramine/colestipol/colesevelam** for post-ileal-resection bile-acid diarrhea).

Treatment (curative, suppressive, or empirical)

- ▶ **Curative** when the cause is eradicable: resect colorectal cancer, antibiotics for Whipple's disease or tropical sprue, stop offending drug.
- ▶ **Suppressive (mechanism-directed):** lactose restriction (lactase deficiency); gluten exclusion (celiac); anti-inflammatory agents (IBD); **bile-acid sequestrants** (BAD); **PPIs** for gastrinoma acid hypersecretion; **octreotide** for malignant carcinoid; **indomethacin** for medullary thyroid carcinoma; **pancreatic enzyme replacement** for pancreatic insufficiency; budesonide/bismuth/loperamide for microscopic colitis.
- ▶ **Empirical / symptomatic:** opioid antimotility agents — **loperamide or diphenoxylate** for mild-moderate watery diarrhea, **codeine or tincture of opium** for severe (avoid in severe IBD — risk of toxic megacolon); **clonidine** (α_2 -agonist) for **diabetic diarrhea**; **5-HT₃ antagonists** (**alosetron, ondansetron**), **rifaximin**, and **eluxadoline** for IBS-diarrhea; **crofelemer** for AIDS-associated diarrhea. For all patients: **fluid/electrolyte repletion** and **fat-soluble vitamin replacement** in chronic steatorrhea.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Stepwise algorithm** (Harrison Fig. 49-4) — “Approach to chronic diarrhea”: Box 1
Chronic diarrhea → *Exclude iatrogenic (medication, surgery)* → branch by presentation into
Blood p.r. → colonoscopy + biopsy; **Fatty diarrhea** → small-bowel imaging, biopsy, aspirate; **Pain relieved by BM/incomplete evacuation** → suspect IBS; no
blood/malabsorption features → functional diarrhea / dietary exclusion (lactose, sorbitol). Central box: Limited organic screen — hematology, chemistry, CRP, ESR, Fe, folate, B12, TTG-IgA, C4, stool fat, calprotectin → then stool-fat thresholds (>20 g/d = pancreatic; 14–20 g/d = small-bowel cause; <14 g/d = normal) and 48 h stool bile acid → BA sequestrant.
- ▶ **Stool osmotic gap bar/flow label:** $Gap = 290 - 2 \times (Na + K)$; >50 = osmotic; <50 = secretory.

Clinical / Diagnostic significance

- ▶ The **fasting test** is a key bedside discriminator: secretory diarrhea persists with fasting; osmotic diarrhea stops.
- ▶ **Red flags mandating prompt structural evaluation (colonoscopy)**: blood/hematochezia, weight loss, anemia, nocturnal diarrhea, older age, or any middle-aged/older patient with inflammatory-type diarrhea — to exclude **colorectal carcinoma** and IBD.
- ▶ **Microscopic colitis** is clinically indistinguishable from IBS-D/functional diarrhea and needs **biopsy of normal-appearing colon**; associated with NSAIDs, statins, PPIs, SSRIs and middle-aged women.
- ▶ **Factitial diarrhea** accounts for up to 15% of unexplained diarrheas at tertiary centers (laxative abuse, Munchausen); suspect with hypokalemia, hypotension, very high/low stool osmolarity (water/urine added).
- ▶ In **two-thirds of cases the cause is unclear after the first encounter**, justifying staged, triage-guided testing rather than indiscriminate investigation.

High-yield exam pointers

- ▶ Chronic diarrhea = **>4 weeks**; **>200 g/d**; most causes **non-infectious**.
- ▶ **Osmotic gap >50 = osmotic**; **<50 = secretory**. Secretory = high-volume, painless, **persists on fasting**.
- ▶ **BAD** $\approx$ **40% of unexplained chronic diarrhea**; ileal resection **<100 cm** $\rightarrow$ choleraic; treat with **cholestyramine/colesevelam**; diagnose by **serum 7 α C4 / SeHCAT**.
- ▶ **Fecal fat**: normal **<7 g/d**; **>32 g** suggests pancreatic insufficiency (**>90% function lost**).
- ▶ **VIPoma** = **WDHA / pancreatic cholera**; carcinoid $\rightarrow$ urinary **5-HIAA**; gastrinoma $\rightarrow$ **PPI**; medullary thyroid Ca $\rightarrow$ **indomethacin**.
- ▶ **Lactase deficiency** = commonest osmotic cause in adults; **low fecal pH**.
- ▶ First-line empirical antidiarrheal = **loperamide/diphenoxylate**; avoid antimotility agents in severe IBD (**toxic megacolon**).
- ▶ Limited organic screen mnemonic: **CBC, CRP/ESR, Fe/folate/B12, TTG-IgA, C4, stool fat, calprotectin**.
- ▶ Always exclude **pseudodiarrhea, fecal incontinence, overflow (impaction)**, and **iatrogenic** causes first.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 49 "Diarrhea and Constipation" (definitions, Table 49-3 classification, Table 49-4 examination, Fig. 49-4 algorithm, evaluation and treatment of chronic diarrhea). Drug doses are not specified in the chapter and have been

omitted as the source gives agents qualitatively; SeHCAT/WDHA expansions and the Bristol scale are standard textbook internal medicine consistent with the chapter. No coverage gap.



Criteria for Diagnosis and Management of Irritable Bowel Syndrome

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Irritable bowel syndrome (IBS) is a chronic **functional bowel disorder** (a disorder of *gut–brain interaction*) characterised by **recurrent abdominal pain associated with altered bowel habit** in the absence of any detectable structural, biochemical or organic abnormality. No pathognomonic marker exists, so the diagnosis is **positive and clinical**, resting on the symptom-based **Rome IV criteria** plus the *exclusion of alarm features*. It affects ~10% of adults worldwide, presents before age 45 in most, and is 2–3 times commoner in women (who form ~80% of severe cases).

Symptom-based diagnostic criteria (evolution)

- ▶ Diagnosis has progressively moved from physician-led exclusion scores to **positive symptom criteria**: *Manning (1978) → Kruis (1984) → Rome I → II → III → Rome IV (2016)*.
- ▶ **Manning criteria** (≥3 of 6 favour IBS): pain eased by defecation; looser stools at onset of pain; more frequent stools at onset of pain; abdominal distension; mucus per rectum; sensation of incomplete evacuation.
- ▶ **Kruis criteria** combine a patient symptom score with *physician exclusion items* (abnormal examination, ESR >20 mm/2 h, anaemia, leucocytosis >10,000, blood in stool) that argue against IBS.
- ▶ **Rome IV** is the current standard — more stringent than Rome III: pain must occur ≥1 day/week, and the word “discomfort” has been *deleted*. Painless diarrhoea or constipation does **not** qualify as IBS.

Rome IV diagnostic criteria & subtyping

Element	Rome IV requirement
Core	Recurrent abdominal pain, on average ≥1 day per week in the last 3 months
Associated with ≥2 of	(1) Related to defecation ; (2) Associated with a change in frequency of stool; (3) Associated with a change in form/appearance of stool
Time rule	Criteria met for the last 3 months , with symptom onset ≥6 months before diagnosis

- ▶ **Subtyping** uses the **Bristol Stool Form Scale (BSFS)** on days with abnormal bowel habit (threshold = >25% of bowel movements):
 - IBS-C (constipation): >25% stools **Bristol 1–2** (hard/lumpy) and <25% Bristol 6–7.
 - IBS-D (diarrhoea): >25% stools **Bristol 6–7** (loose/watery) and <25% Bristol 1–2.
 - IBS-M (mixed): >25% hard **and** >25% loose stools.
 - IBS-U (unsubtyped): abnormality insufficient to fit the above.
- ▶ Subtypes are **unstable** — ~75% of patients change subtype over a year, and ~29% switch between IBS-C and IBS-D, so the bowel pattern is recorded as predominant on *symptomatic days*.
- ▶ **Supportive (non-diagnostic) symptoms**: straining, urgency, incomplete evacuation, passage of mucus, bloating and visible distension (distension worsens through the day; bloating affects ≥60%). Frequent overlap occurs with **dyspepsia, GERD, fibromyalgia, chronic fatigue, headache, backache and genitourinary symptoms**.

Pathophysiology (multifactorial — the “biopsychosocial” model)

- ▶ **Altered GI motility** — exaggerated, prolonged post-prandial and distension-evoked colonic contractions; rapid transit in IBS-D, slow transit/pelvic-floor dyssynergia in IBS-C.
- ▶ **Visceral hypersensitivity** — lowered pain threshold to rectal balloon distension; selective for visceral (not somatic) afferents; *TRPV1* up-regulation on sensory neurons.
- ▶ **Brain–gut axis dysregulation** — abnormal central processing (functional MRI: heightened mid-cingulate and prefrontal activation), HPA-axis and autonomic dysfunction; psychiatric comorbidity (anxiety, depression, somatisation) in up to 80%.
- ▶ **Post-infectious IBS** — >10% of patients develop IBS after infectious enteritis (4-fold risk); commoner in young women, severe/bacterial-parasitic infection, antibiotic use and psychological comorbidity.
- ▶ **Low-grade mucosal immune activation** — mast cells adjacent to nerves, raised IL-6/IL-1 β /TNF, increased permeability (“leaky gut”, chiefly IBS-D/post-infectious).
- ▶ **Gut dysbiosis** — reduced diversity; ↓ *Bifidobacterium* and *Faecalibacterium*, ↑ Enterobacteriaceae; SIBO over-represented.
- ▶ **Abnormal serotonin signalling** (↑ enterochromaffin cells, *TPH1* polymorphism, down-regulated *SERT*); **bile-acid malabsorption** in up to ~25–30% of IBS-D; genetic contributions (*SERT* polymorphism; rare *SCN5A*/ $\text{Na}_v1.5$ mutation in IBS-C).

Approach to diagnosis & limited investigation

- ▶ Diagnosis is **clinical**: a positive history fulfilling Rome IV + a normal/near-normal examination + **absence of alarm features**, then confirm the subtype with the BSFS.
- ▶ **Alarm (“red flag”) features mandating organic work-up**: rectal bleeding/melaena, unexplained weight loss, iron-deficiency anaemia, **nocturnal** pain/diarrhoea, **fever**, progressive dysphagia,

recurrent vomiting, short symptom history, **new onset after age 50**, family history of colorectal cancer/IBD/coeliac disease, abdominal/rectal mass, or signs of malabsorption.

- ▶ **Examination** is usually normal; mild colonic tenderness may occur. *Carnett test* distinguishes abdominal-wall from visceral pain; a digital rectal examination screens for **pelvic-floor dyssynergia**, and pelvic examination excludes ovarian malignancy in older women with new symptoms.
- ▶ **Limited, targeted tests** (avoid over-investigation): **CBC, CRP, faecal calprotectin** (or lactoferrin) to exclude IBD — IBD risk is <1% if CRP ≤ 0.5 mg/dL or calprotectin ≤ 40 μ g/g (CMDT flags >50 μ g/g for endoscopy); **coeliac serology (anti-tTG IgA)** especially in IBS-D; stool ova/parasite or *Giardia* PCR where parasitic infection is likely/endemic.
- ▶ **Colonoscopy** is reserved for alarm features, persistent IBS-D, or first presentation at/after age 45–50 (to exclude malignancy), with **random biopsies for microscopic colitis**. Reserve hydrogen breath tests (lactose/SIBO) and **anorectal manometry + balloon-expulsion** (dyssynergia) for selected patients; routine SIBO testing is *not* recommended.
- ▶ **Differential diagnosis**: IBD, colorectal cancer, microscopic colitis, coeliac disease, lactase deficiency, bile-acid diarrhoea, SIBO, giardiasis, thyroid disease, drug-induced bowel change, and (with painful constipation) porphyria and lead poisoning.

Management

Principles — stepwise and severity-based (Harrison: ~70% mild, ~25% moderate, ~5% severe/refractory). Foundation for all is **reassurance, education and a strong therapeutic relationship**; drugs are *adjunctive* and targeted at the dominant symptom.

- ▶ **General & dietary measures (first line, all patients)**: explain the gut–brain mechanism and chronic relapsing course; identify and avoid food/stress triggers; encourage moderate exercise.
 - **Soluble fibre** (psyllium 20–30 g/day total, titrated slowly) helps global symptoms/constipation; **avoid insoluble fibre/bran** (worsens gas/bloating).
 - **Low-FODMAP diet** — relieves symptoms (especially pain and bloating) in 50–80%; delivered as a **3-step protocol**: 2–6-week *restriction* of all FODMAP groups → structured *reintroduction* to find triggers → long-term *personalisation*. Avoid in those with eating disorders.
- ▶ **Antispasmodics (pain/cramps)**: anticholinergics **dicyclomine** or **hyoscyamine** given ~30 min before meals to blunt the gastrocolic reflex; **enteric-coated peppermint oil** improves global symptoms and pain (main side-effect heartburn).
- ▶ **IBS-D pharmacotherapy**:
 - **Loperamide** 2–4 mg as needed (max 12 mg/day) — improves stool frequency/urgency but not pain.

- **Bile-acid sequestrants** — cholestyramine or colesevelam (for the ~25–30% with bile-acid malabsorption).
- **Eluxadoline** 75–100 mg bid — mixed μ -/ κ -opioid agonist + δ -opioid antagonist; *contraindicated* after cholecystectomy, in significant alcohol use or prior pancreatitis (risk of pancreatitis / sphincter-of-Oddi spasm).
- **Alosetron** 0.5–1 mg bid — selective 5-HT₃ antagonist, restricted to women with severe IBS-D under a risk-management programme (ischaemic-colitis risk).
- **Rifaximin** 550 mg tid × 14 days — non-absorbed antibiotic for IBS-D/bloating; re-treatment effective on relapse.
- ▶ **IBS-C pharmacotherapy:**
 - **Osmotic laxative** — polyethylene glycol (PEG 3350) 17 g/day; improves frequency/consistency but not pain. *Avoid lactulose/sorbitol* (gas, distension).
 - **Secretagogues** — **lubiprostone** 8 μ g bid (type-2 chloride-channel/ClC-2 activator), **linaclotide** 290 μ g od and **plecanatide** 3 mg od (guanylate cyclase-C agonists), **tenapanor** 50 mg bid (intestinal NHE3 inhibitor) — all FDA-approved for IBS-C.
 - **Tegaserod** (5-HT₄ agonist) — re-approved for women <65 years with ≤ 1 cardiovascular risk factor and no ischaemic CVD.
- ▶ **Central neuromodulators (pain-predominant / moderate–severe): tricyclic antidepressants** (imipramine, nortriptyline, desipramine) started low (10–25 mg at night) — analgesic/visceral effects independent of mood, and useful in IBS-D (anticholinergic, slows transit); **SSRIs** (e.g. sertraline, citalopram, paroxetine, fluoxetine) may help IBS-C and comorbid mood disorder.
- ▶ **Psychological therapies (severe/refractory):** cognitive-behavioural therapy, gut-directed hypnotherapy and relaxation/yoga; refer disabling cases to specialist/pain services.
- ▶ **Probiotics:** evidence weak — **not recommended** by current AGA/ACG guidelines.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Bristol Stool Form Scale with IBS subtyping grid.** Draw the 7 stool types in a column (Type 1 *separate hard lumps* → Type 7 *entirely watery*) and an axis grid with labels: % BM hard/lumpy (Bristol 1–2) vs % BM loose/watery (Bristol 6–7), the 25% threshold lines, and the four quadrants labelled IBS-C, IBS-D, IBS-M, IBS-U.
- ▶ **Diagram 2 — Pathophysiology / brain–gut axis schematic.** Central box “IBS” with radiating labelled arrows: *Motility abnormalities*, *Visceral hypersensitivity (TRPV1)*, *Brain–gut interaction (HPA axis, autonomic dysfunction)*, *“Leaky gut”/altered permeability + mast-cell activation*, *Gut dysbiosis*, *Bile-acid malabsorption*, *Serotonin/SERT*, *Genetic factors (SERT, SCN5A)*, *Psychological (anxiety/depression/somatisation)*.

Clinical / Diagnostic significance

- ▶ IBS is a **positive diagnosis** — confident application of Rome IV plus absence of alarm features avoids costly, anxiety-reinforcing over-investigation.
- ▶ **Faecal calprotectin/CRP** are the key non-invasive screens to separate IBS from IBD; **coeliac serology** is essential in IBS-D as coeliac disease mimics it.
- ▶ Recognise mimics that change management: **microscopic colitis** (random colonic biopsies), **bile-acid diarrhoea** (empirical sequestrant trial), **pelvic-floor dyssynergia** (biofeedback, not laxatives), and **ovarian cancer** in older women.
- ▶ Treatment is **symptom-targeted and stepwise**; an empirical therapeutic trial that succeeds confirms the diagnosis and obviates further testing.

High-yield exam pointers

- ▶ **Rome IV core**: recurrent abdominal pain ≥ 1 day/week $\times$ 3 months + ≥ 2 of (defecation-related / change in stool frequency / change in stool form); onset ≥ 6 months prior.
- ▶ Rome IV vs III: pain frequency raised to ≥ 1 /week and term “**discomfort**” removed.
- ▶ Subtypes by **Bristol scale**, **25% rule**: IBS-C, IBS-D, IBS-M, IBS-U — *highly unstable* over time.
- ▶ Older criteria: **Manning** (≥ 3 of 6) and **Kruis** (with exclusion items).
- ▶ **Alarm features**: bleeding, weight loss, anaemia, nocturnal symptoms, fever, age of onset >50 , FH of CRC/IBD/coeliac $\rightarrow$ investigate (colonoscopy).
- ▶ First-line therapy = **education + soluble fibre/psyllium + low-FODMAP (3-step)**; drugs are symptom-directed adjuncts.
- ▶ IBS-D: loperamide, bile-acid binders, **eluxadoline**, **alosetron** (women), **rifaximin**. IBS-C: PEG, **secretagogues** (lubiprostone/linaclotide/plecanatide/tenapanor).
- ▶ **TCAs/SSRIs** as neuromodulators for moderate–severe/pain-predominant disease; **CBT/hypnotherapy** for refractory cases; **probiotics not recommended**.
- ▶ **Eluxadoline contraindicated** post-cholecystectomy/alcohol; **alosetron** carries ischaemic-colitis risk; **tegaserod** restricted to women <65 with low CV risk.

SOURCE & COVERAGE

- ▶ Harrison’s Principles of Internal Medicine, 22e — “Irritable Bowel Syndrome” (Rome IV criteria, pathophysiology, FODMAP/treatment tables).
- ▶ Sleisenger & Fordtran’s Gastrointestinal and Liver Disease, 11e — “Irritable Bowel Syndrome” (Manning/Kruis/Rome IV criteria box, Bristol Stool Form Scale subtyping, alarm-feature box and diagnostic algorithm).
- ▶ CMDT 2026 — “Gastrointestinal Disorders: Irritable Bowel Syndrome” (current AGA/ACG-aligned management, drug doses, investigations).



CROHN'S DISEASE

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Crohn disease is a chronic, relapsing, idiopathic inflammatory bowel disease characterized by **transmural**, **segmental** inflammation that may affect any part of the gastrointestinal tract from mouth to anus. It most often involves the terminal ileum and proximal colon, produces skip lesions, fissuring ulcers, strictures, fistulas, abscesses, and perianal disease, and is not cured by surgery. Pathogenesis reflects an inappropriate mucosal immune response to intestinal microbiota in a genetically susceptible host, modified by environmental factors such as smoking, diet, antibiotics, and prior enteric infection.

Etiopathogenesis and risk factors

- ▶ **Genetic susceptibility:** familial aggregation is important; NOD2/CARD15 variants are linked particularly with younger onset, ileal disease and stricturing tendency; ATG16L1/autophagy and IL-12/IL-23 pathways explain biologic targets.
- ▶ **Microbiota and barrier defect:** dysbiosis, reduced microbial diversity, increased mucosa-associated bacteria, defective Paneth cell defensins, epithelial permeability and impaired mucosal tolerance lead to sustained inflammation.
- ▶ **Immune cascade:** activated dendritic cells/macrophages and T cells produce TNF, IL-1, IL-6, IL-12, IL-23 and other mediators; Th1/Th17 pathways, alpha4beta7 lymphocyte trafficking and JAK/STAT signalling are clinically important because they are drug targets.
- ▶ **Environmental factors:** **cigarette smoking** strongly increases Crohn risk, resistance to medical therapy and early relapse. Diets rich in animal fat, refined sugars and processed foods, low fibre intake, oral contraceptives, early-life infections and infectious gastroenteritis are associated risks.
- ▶ **Epidemiology:** onset is common in adolescence and young adulthood, but disease may occur at any age; newly industrialized countries, including Asian populations, show rising incidence.

Pathology and classification

- ▶ **Gross pathology:** discontinuous disease with **skip areas**, aphthous ulcers in early disease, deep linear/serpiginous ulcers, **cobblestoning**, thickened bowel wall, luminal narrowing, mesenteric lymphadenopathy and **creeping fat**.
- ▶ **Microscopy:** focal crypt inflammation, focal crypt abscesses, transmural lymphoid aggregates, fissures, sinus tracts and fistulas. **Noncaseating granulomas** are highly suggestive but absent in many mucosal biopsies; exclude tuberculosis when granulomas are seen.
- ▶ **Distribution:** about one-third have small-bowel disease alone, around one-half have ileocolonic disease, and about one-fifth have colitis alone; terminal ileum is the commonest site. Perianal disease occurs in about one-third.

Montreal axis	Categories	Exam implication
Age	A1 ≤16 yr; A2 17-40 yr; A3 >40 yr	Early onset often predicts aggressive course
Location	L1 ileal; L2 colonic; L3 ileocolonic; L4 upper GI modifier	Determines symptoms, nutrition and imaging
Behaviour	B1 inflammatory; B2 stricturing; B3 penetrating	Guides medical, endoscopic and surgical strategy
Modifier	p = perianal disease	Must be actively looked for and imaged

Clinical features

- ▶ **Luminal inflammatory disease:** insidious malaise, low-grade fever, anorexia, weight loss, chronic or intermittent diarrhoea and crampy abdominal pain. Ileocolitis classically causes recurrent **right lower quadrant pain**, diarrhoea and sometimes an appendicitis-like presentation with fever, mass and leukocytosis.
- ▶ **Stricturing disease:** postprandial colicky pain, bloating, borborygmi, vomiting, decreasing diarrhoea and recurrent subacute obstruction; obstruction may be inflammatory/edematous early or fixed fibrotic late.
- ▶ **Penetrating disease:** phlegmon, intra-abdominal abscess, enteroenteric, enterovesical, enterocutaneous or rectovaginal fistulas. Enterovesical fistula causes recurrent UTI, pneumaturia or fecaluria; rectovaginal fistula causes foul vaginal discharge and dyspareunia.
- ▶ **Colonic Crohn disease:** fever, malaise, diarrhoea, crampy pain and sometimes hematochezia; massive bleeding is uncommon compared with ulcerative colitis.
- ▶ **Perianal disease:** painful skin tags, eccentric fissures, anal ulcers/stenosis, abscesses and complex fistulas; it may precede intestinal symptoms by years.
- ▶ **Upper GI and jejunoileal disease:** dyspepsia, nausea, vomiting, gastric outlet obstruction, malabsorption, steatorrhea, anemia, hypoalbuminemia, B12/folate/iron and fat-soluble vitamin deficiencies.

Investigations and diagnosis

- ▶ **Principle:** no single symptom, sign or test diagnoses Crohn disease; diagnosis requires compatible clinical features plus endoscopic, histologic and radiologic evidence.
- ▶ **Baseline tests:** CBC, ESR/CRP, albumin, electrolytes, liver tests, iron studies, B12/folate, vitamin D and nutritional screen. CRP may be normal in a minority despite active disease.
- ▶ **Stool tests before steroids/biologics:** culture or multiplex PCR for pathogens, ova/parasites when relevant, and *C. difficile* testing; consider CMV biopsy testing in steroid-refractory colitis.

- ▶ **Fecal markers:** fecal calprotectin and lactoferrin help distinguish active inflammation from IBS-like symptoms, assess relapse and monitor treatment response; calprotectin is less sensitive for isolated ileal disease.
- ▶ **Ileocolonoscopy with biopsies:** first-line investigation; inspect colon and terminal ileum, biopsy involved and normal-looking segments separately. Findings: rectal sparing, aphthae, stellate/linear ulcers, cobblestoning, strictures, fistula openings and skip lesions.
- ▶ **Cross-sectional imaging:** MR enterography or CT enterography defines small-bowel extent, wall thickening, enhancement, comb sign, strictures, fistulas, abscess and phlegmon; MRI is preferred for young patients and repeated follow-up when available.
- ▶ **Capsule endoscopy:** useful for suspected small-bowel Crohn disease when ileocolonoscopy and imaging are nondiagnostic, but avoid if stricture is possible; use patency capsule/radiology first. Pelvic MRI is the best noninvasive test for perianal fistula/abscess.

Complications and differentials

- ▶ **Local complications:** obstruction, strictures, intra-abdominal or pelvic abscess, fistulas, severe perianal disease, malabsorption, short bowel syndrome after resections, hemorrhage and rare free perforation.
- ▶ **Cancer:** chronic Crohn colitis carries colorectal cancer risk related to extent and duration, broadly similar to ulcerative colitis with comparable colitis burden; begin surveillance colonoscopy about 8 years after Crohn colitis diagnosis.
- ▶ **Extraintestinal manifestations:** oral aphthae, erythema nodosum, pyoderma gangrenosum, peripheral arthritis, sacroiliitis/ankylosing spondylitis, episcleritis, uveitis, fatty liver, gallstones after ileal disease/resection, PSC, nephrolithiasis, osteoporosis, thromboembolism and reactive amyloidosis.
- ▶ **Differential diagnosis:** ulcerative colitis, intestinal tuberculosis, Yersinia, Salmonella/Shigella/Campylobacter, C. difficile, amoebiasis, CMV, Behcet disease, NSAID enteropathy, ischemic colitis, diverticulitis, lymphoma, celiac disease and IBS. In India, **intestinal TB** is a key mimic: caseating granulomas, AFB/culture/PCR positivity, necrotic nodes and typical ulcers favour TB.

Management

- ▶ **General measures:** assess disease location, behaviour, severity and risk. Stop smoking; avoid NSAIDs; optimize nutrition; correct iron, B12, folate, vitamin D/calcium and fat-soluble vitamin deficiencies; vaccinate before immunosuppression; screen for TB and hepatitis B before biologics/JAK inhibitors.
- ▶ **Treatment target:** steroid-free clinical remission plus objective healing: absence of ulcers on endoscopy, falling CRP/fecal calprotectin, radiologic improvement in transmural disease, fistula healing and restored quality of life.

- ▶ **Mild low-risk ileocecal disease:** controlled-release budesonide 9 mg once daily for 8 weeks, then taper in 3 mg steps over 2-4 weeks if remission occurs. Limited colonic mild disease may respond to sulfasalazine; mesalamine has limited and inconsistent value in Crohn disease.
- ▶ **Moderate to severe or high-risk disease:** use corticosteroids only for induction or bridging: prednisone/prednisolone 40 mg daily for 1-2 weeks, taper by 5-10 mg/week over 4-8 weeks; hospitalized severe disease may need methylprednisolone 40-60 mg/day IV after excluding abscess.
- ▶ **Maintenance and disease modification:** biologic therapy is preferred early in high-risk disease. Options include anti-TNF agents (infliximab 5 mg/kg IV at 0, 2, 6 weeks then every 8 weeks; adalimumab 160 mg day 0, 80 mg day 14, then 40 mg every 2 weeks), vedolizumab 300 mg IV at 0, 2, 6 weeks then every 8 weeks, ustekinumab weight-based IV induction then 90 mg SC every 8 weeks, risankizumab 600 mg IV every 4 weeks for 3 doses then 180/360 mg SC every 8 weeks, and upadacitinib 45 mg daily for 12 weeks then 15/30 mg daily after biologic failure or when appropriate.
- ▶ **Immunomodulators:** azathioprine 2-3 mg/kg/day, 6-mercaptopurine 1-1.5 mg/kg/day, and methotrexate 15-25 mg weekly IM/SC may maintain steroid-free remission or reduce anti-drug antibodies; check TPMT where available and monitor CBC/LFTs.
- ▶ **Perianal/fistulizing disease:** combine gastroenterology and colorectal surgery. Drain abscesses, place setons when needed, give metronidazole 250 mg TID or ciprofloxacin 500 mg BID for symptom relief, and use anti-TNF therapy for fistula closure; pelvic MRI guides anatomy and follow-up.
- ▶ **Abscess/obstruction/surgery:** abscess requires antibiotics plus percutaneous or surgical drainage if large; corticosteroids are unsafe until abscess is excluded. Obstruction from inflammatory edema may respond to bowel rest, NG suction and steroids; fixed short strictures need endoscopic dilation, resection or stricturoplasty. Surgery is indicated for medical intractability, obstruction, abscess, massive bleeding, refractory fistulas or suspected cancer; resect the least bowel possible and check postoperative recurrence endoscopically within 3-6 months.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Segmental Crohn ileocolitis diagram:** terminal ileum + caecum/ascending colon, skip normal areas, aphthous ulcers, deep linear ulcers, cobblestoning, stricture, creeping fat, mesenteric nodes.
- ▶ **Perianal Crohn fistula diagram:** anal canal, internal opening, intersphincteric/transsphincteric tract, external opening, abscess cavity, seton, rectovaginal extension label if present.

Clinical / Diagnostic significance

- ▶ Crohn disease is an exam favourite because it integrates **chronic diarrhoea, malabsorption, obstruction, fistula, abscess, perianal disease and EIMs** in one diagnosis.
- ▶ Distinguish it from UC by transmural inflammation, skip lesions, ileal involvement, rectal sparing, perianal disease, fistulas/strictures and granulomas; distinguish it from intestinal TB before starting anti-TNF therapy.
- ▶ Always exclude **C. difficile, CMV and abscess** when a patient flares or fails steroids; giving corticosteroids into an occult abscess can be dangerous.
- ▶ Deep ulcers, early steroid need, young onset, perianal disease, stricturing/penetrating behaviour, upper GI disease, low albumin/hemoglobin and high CRP/calprotectin indicate aggressive disease and justify early biologic therapy.
- ▶ Therapeutic drug monitoring helps anti-TNF failures: low trough/no antibody means increase dose or shorten interval; high antibody/low trough means switch anti-TNF; active inflammation with therapeutic trough means switch drug class.

High-yield exam pointers

- ▶ Write first: **Crohn = transmural, skip, mouth-to-anus, terminal ileum, noncaseating granuloma, fistula/stricture/perianal disease.**
- ▶ Montreal classification: **A1/A2/A3; L1/L2/L3 with L4 modifier; B1/B2/B3 with p modifier.**
- ▶ Most common presentation: chronic right lower quadrant pain + diarrhoea + weight loss; appendicitis mimic is classic.
- ▶ Perianal disease affects about one-third; pelvic MRI and colorectal surgery involvement are essential.
- ▶ Fecal calprotectin/lactoferrin are practical inflammatory markers; symptoms alone do not prove active disease.
- ▶ Capsule endoscopy is sensitive for small bowel disease but contraindicated until stricture is excluded.
- ▶ Steroids induce remission but are **not maintenance therapy**; aim for steroid-free mucosal healing.
- ▶ Anti-TNF agents are preferred for severe, perianal or fistulizing disease; screen for TB/hepatitis B and update vaccines.
- ▶ Surgery treats complications but is not curative; preserve bowel length and prevent/monitor postoperative recurrence.

SOURCE & COVERAGE

Harrison 22e — “Inflammatory Bowel Disease”; Sleisenger & Fordtran’s GI & Liver 11e — “Epidemiology, Pathogenesis, and Diagnosis of Inflammatory Bowel Diseases” and “Management of Inflammatory Bowel Diseases”; CMDT 2026 — “Gastrointestinal Disorders”.



Describe various recommendations for treatment of chronic Hepatitis “B”

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — Chronic hepatitis B (CHB) is HBV infection with persistence of HBsAg and ongoing necroinflammatory liver disease for ≥ 6 months. The **level of HBV replication** (serum HBV DNA) is the **single most important determinant** of progression to cirrhosis and hepatocellular carcinoma (HCC), in both HBeAg-reactive and HBeAg-negative disease. Treatment decisions integrate three variables — HBeAg status, HBV DNA level, and necroinflammatory activity (ALT and/or biopsy) — plus the presence of cirrhosis. Eight drugs exist; modern practice rests on **three first-line agents** (PEG IFN- α , entecavir, tenofovir) guided by AASLD and EASL recommendations.

Goals and endpoints of therapy

- ▶ **Suppress HBV DNA** to undetectable levels (most important virologic endpoint).
- ▶ **Normalize ALT** (biochemical remission) and achieve **histologic improvement** (improved in 50–90% of orally treated patients).
- ▶ **HBeAg loss / seroconversion to anti-HBe** in HBeAg-positive disease — the therapeutic milestone that permits stopping in non-cirrhotics.
- ▶ **HBsAg loss (“functional cure”)** — the ultimate but uncommon goal; in HBeAg-negative disease it is the only event that justifies stopping therapy.
- ▶ These short-term gains translate into **reduced cirrhosis, hepatic decompensation, HCC, need for transplantation, and death**; long-term suppression can produce **regression of fibrosis/cirrhosis and of esophageal varices**.

Whom to treat — recommendations by disease phase (AASLD; EASL footnoted)

HBeAg status	Clinical setting	HBV DNA (IU/mL)	ALT	Recommendation
HBeAg-positive	Chronic hepatitis	$>2 \times 10^4$	$>2 \times \text{ULN}$	Treat (oral agent or PEG IFN)
	“Immune-tolerant”/high DNA, normal ALT	$>2 \times 10^4$	$\leq 2 \times \text{ULN}$	No treatment; monitor HBV DNA + ALT q6 months*
HBeAg-negative	Inactive carrier	$\leq 2 \times 10^3$	$\leq \text{ULN}$	Treatment not necessary; monitor
	Chronic hepatitis	$>2 \times 10^3$	$>2 \times \text{ULN}$	Treat

HBeAg status	Clinical setting	HBV DNA (IU/mL)	ALT	Recommendation
	"Gray zone"	$>2 \times 10^3$	1 to $>2 \times$ ULN	Treatment suggested; individualise*
Either	Compensated cirrhosis	Detectable (treat if $>2 \times 10^3$)	Any	Treat with oral agents, not PEG IFN
Either	Decompensated cirrhosis	Detectable	Any	Treat (oral agents) + refer for liver transplant
Either	Decompensated cirrhosis	Undetectable	Any	Observe; refer for transplant

- ▶ EASL threshold is lower: treat HBeAg-positive disease at HBV DNA $>2 \times 10^3$ IU/mL with ALT $>$ ULN. For older patients and advanced fibrosis, lower the HBV DNA treatment threshold to $>2 \times 10^3$ IU/mL*.
- ▶ Treatment is also considered in "gray-zone"/normal-ALT patients who are >40 years, have a family history of cirrhosis/HCC, extrahepatic manifestations, prior treatment, or biopsy/non-invasive evidence of moderate-severe inflammation or fibrosis*.
- ▶ No treatment for inactive "non-replicative" carriers (HBeAg-negative, normal ALT, HBV DNA $\leq 10^3$ IU/mL documented serially).
- ▶ Compensated cirrhosis with detectable HBV DNA is a universal treatment indication, regardless of HBeAg/ALT, because antiviral therapy retards progression and stopping risks decompensation.

First-line antiviral agents (route, dose, resistance)

Agent	Route / dose	Status	Resistance
PEG IFN- α ($\alpha 2a$)	SC injection, 180 μ g weekly $\times$ 48 weeks	First-line, finite course	None (no viral mutation)
Entecavir	Oral 0.5 mg/day (1 mg/day if lamivudine-resistant)	First-line	$\leq 1.2\%$ through year 6 (much higher if lamivudine-resistant)
Tenofovir disoproxil fumarate (TDF)	Oral 300 mg/day	First-line	0% through year 8
Tenofovir alafenamide (TAF)	Oral 25 mg/day (= 300 mg TDF potency)	First-line	Same as TDF
Lamivudine	Oral 100 mg/day	No longer preferred	$\sim 30\%$ yr 1, $\sim 70\%$ yr 5
Adefovir	Oral 10 mg/day	No longer preferred (supplanted by tenofovir)	0% yr 1, $\sim 30\%$ yr 5

Agent	Route / dose	Status	Resistance
Telbivudine	Oral 600 mg/day	No longer preferred / withdrawn	up to 22% by yr 2

- ▶ **Three first-line drugs: PEG IFN- α , entecavir, and tenofovir (TDF or TAF)** — all share a high genetic barrier to resistance.
- ▶ Lamivudine, adefovir and telbivudine are **no longer recommended as first-line** because of high resistance rates and/or weaker potency.
- ▶ Between entecavir and tenofovir, comparative data are limited; an observational signal that TDF lowers HCC risk more than entecavir is **not robustly confirmed** after adjustment for confounders.
- ▶ **TAF is preferred over TDF** when CrCl <50 mL/min, reduced bone density, or renal-risk patients (decompensated cirrhosis, poorly controlled hypertension/diabetes, proteinuria, nephrotoxic drugs, solid-organ transplant); EASL extends TAF preference to patients >60 years (higher TDF nephrotoxicity risk).

PEG IFN versus oral nucleos(t)ide analogues

Feature	PEG IFN	Oral nucleos(t)ide analogues
Administration	Weekly SC injection	Daily, oral
Tolerability	Poorly tolerated, intensive monitoring	Well tolerated, limited monitoring
Duration	Finite (48 weeks)	≥ 1 year, usually indefinite
Mean HBV DNA suppression	$\sim 4.5 \log_{10}$	$\sim 6.9 \log_{10}$ (more profound)
Effective in high-level HBV DNA ($\geq 10^9$)	No	Yes
Use in cirrhosis / transplant / immunosuppression	No	Yes
Resistance	None	None—minimal with entecavir/tenofovir

- ▶ **PEG IFN advantage:** finite course, no resistance, higher 1-year HBeAg seroconversion — but injectable, poorly tolerated, and **contraindicated in decompensated (and avoided in compensated) cirrhosis** (risk of sepsis/decompensation).
- ▶ **Oral-agent advantage:** convenient, very well tolerated, deeper DNA suppression, effective even in IFN non-responders; by the **end of year 2**, entecavir/tenofovir yield HBeAg (and even HBsAg) responses comparable to 1 year of PEG IFN. Most patients and physicians prefer oral agents first-line.

Duration, monitoring and stopping rules

- ▶ **HBeAg-positive, non-cirrhotic:** oral therapy may be stopped after HBeAg loss/seroconversion plus ≥ 12 months consolidation, with close post-treatment monitoring (monthly $\times 6$, then 3-monthly through the first year). Durable seroconversion is maintained in $\sim 88\text{--}92\%$.
- ▶ **HBeAg-negative, non-cirrhotic:** indefinite oral therapy; stop only after the rare event of HBsAg loss (virologic relapse after stopping is otherwise $69\text{--}83\%$).
- ▶ **Cirrhosis (compensated or decompensated):** treat indefinitely; stopping risks decompensation.
- ▶ **Untreated/"gray-zone" patients** (HBV DNA $2 \times 10^3\text{--}2 \times 10^4$ IU/mL) need HBV DNA + ALT every 3–6 months; immune-tolerant patients at least every 6 months.
- ▶ For tenofovir/TAF, periodic ($\geq$ annual) monitoring of serum creatinine (and renal function) is recommended.

Special populations

- ▶ **Pregnancy:** Tenofovir (TDF) is the drug of choice (category B), also used in the third trimester for mothers with high HBV viral load to prevent perinatal transmission. Lamivudine is also category-tolerated; PEG IFN and adefovir/entecavir are avoided.
- ▶ **Children (2 to <18 yr):** treat if HBV DNA is detectable and ALT is elevated (not if ALT normal). Approved ages — PEG IFN- $\alpha 2a$ ≥ 5 yr; entecavir and tenofovir ≥ 2 yr.
- ▶ **HBV–HIV co-infection:** treat both infections even if HIV criteria not yet met; use tenofovir $\pm$ emtricitabine; TAF preferred over TDF for safety.
- ▶ **Immunosuppression / chemotherapy:** screen all patients for HBsAg and anti-HBc before cytotoxic/immunosuppressive/anti-TNF/B-cell-depleting therapy. Give pre-emptive prophylaxis with entecavir or tenofovir for any HBsAg-positive patient (reactivation risk $\sim 25\%$, up to 68%); start before and continue beyond completion of immunosuppression. Highest-risk agents: B-cell-depleting drugs, anthracyclines, moderate/high-dose corticosteroids ≥ 4 weeks.
- ▶ **Liver transplantation:** prevent graft re-infection with short-term IV HBIG (5–7 days) + lifelong entecavir/TDF/TAF; high-risk (HDV–HBV, HIV–HBV, non-adherent) or anti-HBc-positive-donor grafts warrant tailored long-term oral $\pm$ HBIG regimens.
- ▶ **HBV–HDV co-infection:** nucleos(t)ide analogues are ineffective against HDV; 12 months of PEG IFN is recommended (response is modest); bulevirtide (an NTCP-receptor entry inhibitor) is approved in the EU.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Natural-history / treatment-decision flow of CHB** — boxes labelled: HBsAg+ ≥ 6 months
→ branch on HBeAg status → (HBeAg-positive: “immune-tolerant” → “immune-active/clearance” → HBeAg seroconversion) and (HBeAg-negative chronic hepatitis $\leftrightarrow$

inactive carrier); arrows labelled *HBV DNA*, *ALT*, *Cirrhosis*; endpoints labelled *Treat*, *Monitor*, *HBeAg seroconversion*, *HBsAg loss (functional cure)*.

- ▶ **Treatment-threshold grid** — axes labelled *HBV DNA (IU/mL)*: 2×10^3 and 2×10^4 cut-offs vs *ALT: ULN / $2 \times ULN$* , with shaded “**Treat**”, “**Gray zone**” and “**Monitor**” regions; separate cells labelled *Compensated cirrhosis — treat (oral)* and *Decompensated cirrhosis — treat + transplant referral*.

Clinical / Diagnostic significance

- ▶ Baseline work-up: HBeAg/anti-HBe, HBV DNA, ALT, HBsAg quantification (where available), liver fibrosis assessment (biopsy or non-invasive), HDV and HIV serology, and HCC surveillance in at-risk groups.
- ▶ The HBV DNA level is the dominant risk factor for cirrhosis and HCC — hence sustained DNA suppression is the therapeutic core even when ALT is near-normal.
- ▶ PEG IFN must never be used in decompensated cirrhosis; the entecavir/tenofovir class is the safe choice there.
- ▶ Always screen before immunosuppression — failure to give prophylaxis causes potentially fatal reactivation flares.
- ▶ Choice of agent balances resistance barrier, renal/bone safety (TAF vs TDF), pregnancy, co-infection, and patient preference.

High-yield exam pointers

- ▶ Three first-line agents: PEG IFN- α , entecavir, tenofovir (TDF/TAF); lamivudine, adefovir, telbivudine are obsolete first-line.
- ▶ Doses: PEG IFN- α 2a 180 μ g SC weekly $\times$ 48 wk; entecavir 0.5 mg/day (1 mg if lamivudine-resistant); TDF 300 mg/day; TAF 25 mg/day.
- ▶ AASLD HBeAg-positive trigger: HBV DNA $>2 \times 10^4$ IU/mL + ALT $>2 \times ULN$; HBeAg-negative trigger: HBV DNA $>2 \times 10^3$ + ALT $>2 \times ULN$; EASL thresholds are lower.
- ▶ Compensated cirrhosis + detectable HBV DNA = treat (oral, indefinitely); decompensated = treat + transplant referral.
- ▶ Stop rules: HBeAg-positive — stop after HBeAg seroconversion + 12-month consolidation (non-cirrhotic); HBeAg-negative — only after HBsAg loss; cirrhotics — never stop.
- ▶ Resistance: entecavir $\leq 1.2\%$ at 6 yr, tenofovir 0% at 8 yr — highest barrier.
- ▶ Pregnancy DOC = tenofovir; HIV co-infection = tenofovir $\pm$ emtricitabine, TAF preferred; chemo/immunosuppression = pre-emptive entecavir/tenofovir after HBsAg/anti-HBc screening.

- ▶ Transplant prophylaxis = HBIG (5–7 days) + lifelong oral antiviral; HDV = PEG IFN ×12 months / bulevirtide (nucleos(t)ides ineffective).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 352 "Chronic Hepatitis" (Tables 352-3, 352-4, 352-5 and the "Treatment Recommendations / Populations with Unique Treatment Considerations" sections). Treatment thresholds, drug doses, resistance rates and special-population guidance are all sourced from this chapter. *Coverage note:* the chapter is fully sufficient for this LAQ; HCC surveillance specifics and HBV vaccination are cross-referenced to other chapters (Chaps 87, 350, 356) and are not detailed here.



Diagnostic approach in patients presenting with acute hepatitis

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Acute hepatitis* is a hepatocellular injury syndrome of <6 months duration, biochemically characterised by a predominant rise in serum aminotransferases (AST/ALT), usually with jaundice. Although the great majority of cases are caused by one of the five hepatotropic viruses (HAV, HBV, HCV, HDV, HEV), the differential is broad and includes drug/toxin injury, alcohol-associated hepatitis, ischaemic ("shock") liver, autoimmune hepatitis, Wilson disease and pregnancy-related liver disease. A *structured approach* — clinical assessment, a focused biochemical "liver panel" to define the pattern (hepatocellular vs cholestatic vs mixed), a small battery of serologic tests, and selective imaging/biopsy — establishes the cause and, crucially, identifies the minority progressing to acute liver failure.

Step 1 — Define the clinical syndrome (history & examination)

- ▶ **Symptom phases:** a *prodromal (preicteric)* phase of constitutional symptoms — anorexia, nausea, vomiting, malaise, fatigue, arthralgia/myalgia, headache, low-grade fever (38–39°C; commoner in HAV/HEV and in the HBV serum-sickness syndrome), classically with **aversion to smoking** and altered taste/smell — followed by an *icteric* phase (dark urine and clay/acholic stools 1–5 days before jaundice), then a *convalescent* phase.
- ▶ **Examination:** tender hepatomegaly, scleral icterus, and in 10–20% splenomegaly and cervical/epitrochlear lymphadenopathy; a few transient spider angiomas may appear. Many patients are **anicteric** (commoner in HCV than HBV).
- ▶ **Risk-factor history (key to aetiology):** travel to endemic areas, exposure to jaundiced contacts, day-care/shellfish/contaminated water (HAV, HEV); injection drug use, transfusion (pre-1992 for HCV, pre-1986 for HBV), tattooing, multiple sexual partners/MSM, maternal-infant

transmission, needlestick (HBV, HCV, HDV); a full drug, herbal and alcohol history (CAGE questionnaire); and “repeated episodes” of hepatitis suggesting underlying chronic/autoimmune disease.

- ▶ **Red-flag features (impending acute liver failure):** altered sleep/personality, confusion, asterixis, fetor hepaticus, rapidly shrinking liver, ascites/oedema — encephalopathy in a previously healthy liver is the defining criterion of acute liver failure (ALF) and demands urgent referral.

Step 2 — Confirm and pattern the liver injury (biochemistry)

- ▶ Order the standard battery: **AST, ALT, alkaline phosphatase (AlkP), total/direct bilirubin, albumin and prothrombin time (PT/INR)**; add γ -glutamyl transpeptidase (γ GT) to confirm a hepatic source of raised AlkP.
- ▶ **Aminotransferases** rise in the prodrome and peak (≈ 400 to >4000 IU/L) as jaundice appears; the height does *not* correlate with severity. A predominant **AST/ALT elevation relative to AlkP = hepatocellular pattern**; predominant **AlkP/ γ GT elevation = cholestatic pattern**; both raised = **mixed**.
- ▶ **Magnitude clue** — aminotransferases ≥ 1000 IU/L narrow the differential to: **acute viral hepatitis, ischaemic hepatitis, drug-induced liver injury (especially acetaminophen) and acute biliary obstruction**. Alcohol-associated hepatitis is usually <400 IU/L with **AST $>$ ALT (ratio ≥ 2)**.
- ▶ **Bilirubin:** visible jaundice when >2.5 mg/dL ($43 \mu\text{mol/L}$); typically 5–20 mg/dL, divided $\approx$ equally between conjugated and unconjugated. Bilirubin may keep rising as aminotransferases fall.
- ▶ **Prognostic/synthetic markers:** a **prolonged PT/INR**, hypoglycaemia, falling albumin and very high bilirubin signify severe hepatocellular necrosis. PT that **fails to normalise with parenteral vitamin K** points to hepatocellular (not obstructive/cholestatic) disease.
- ▶ **Haematology:** transient neutropenia/lymphopenia then relative lymphocytosis with **atypical lymphocytes (2–20%)**; thrombocytopenia suggests underlying cirrhosis rather than acute hepatitis.

Step 3 — Targeted serologic algorithm (the “five-test” panel)

Every patient with acute hepatitis should have five tests: **HBsAg, IgM anti-HAV, IgM anti-HBc, anti-HCV and HCV RNA** (Harrison Table 350-6). Test for **anti-HEV ($\pm$ HEV RNA)** if these are negative and risk factors exist, and for **anti-HDV/HDV RNA** when HBsAg is positive with severe/fulminant or exacerbating disease.

HBsAg	IgM anti-HAV	IgM anti-HBc	Anti-HCV / HCV RNA	Interpretation
+	–	+	–	Acute hepatitis B

HBsAg	IgM anti-HAV	IgM anti-HBc	Anti-HCV / HCV RNA	Interpretation
+	–	–	–	Chronic hepatitis B
+	+	–	–	Acute hepatitis A on chronic hepatitis B
+	+	+	–	Acute hepatitis A and B
–	+	–	–	Acute hepatitis A
–	+	+	–	Acute hepatitis A and B (HBsAg below threshold)
–	–	+	–	Acute hepatitis B (HBsAg below detection threshold)
–	–	–	+ (either)	Acute hepatitis C (vs chronic HCV)

- ▶ **HAV:** diagnosis = **IgM anti-HAV**; IgG anti-HAV alone = past infection/immunity.
- ▶ **HBV:** **HBsAg + IgM anti-HBc = acute hepatitis B**. IgM anti-HBc may be the *only* marker in the “window period” (HBsAg gone, anti-HBs not yet up) or when HBsAg is below threshold ($\leq 1-5\%$ of cases). IgG anti-HBc with HBsAg > 6 months = chronic. HBeAg/HBV DNA mark replication/infectivity (chiefly useful in chronic disease).
- ▶ **HCV:** **anti-HCV** detected reliably by current assays during acute illness; **HCV RNA** is the gold standard, becomes positive earliest, and distinguishes true- from false-positive anti-HCV and active from resolved (“cured”) infection (anti-HCV+, HCV RNA–).
- ▶ **HDV:** defective virus needing HBV — test anti-HDV/HDV RNA in HBsAg-positive patients; **co-infection** = IgM anti-HBc + anti-HDV, **superinfection** = IgG anti-HBc + anti-HDV.
- ▶ **HEV:** IgM/IgG anti-HEV $\pm$ HEV RNA — suspect in travellers, the elderly, undercooked pork/game exposure, pregnancy, or chronic hepatitis in the immunosuppressed.

Step 4 — Imaging, biopsy and tests for non-viral causes

- ▶ **Ultrasound** (first-line) excludes biliary obstruction (acute cholecystitis, common-duct stone, cholangitis) and detects vascular causes; MRCP/ERCP if duct dilatation or stones suspected; Doppler US for Budd-Chiari/congestion.
- ▶ If all viral serologies are negative, pursue **non-viral acute hepatitis**: serum **acetaminophen level** and drug history (DILI); **ANA**, **anti-smooth-muscle antibody**, **IgG** (autoimmune hepatitis);

ceruloplasmin, slit-lamp for Kayser-Fleischer rings, 24-h urinary copper (Wilson — especially young patient with haemolysis + low AlkP); EBV/CMV serology, monospot (mononucleosis-like illness); pregnancy-related (AFLP, HELLP, eclampsia, cholestasis of pregnancy).

- ▶ **Liver biopsy** is *rarely* required in acute hepatitis — reserved for diagnostic uncertainty, suspected autoimmune hepatitis, or when an alternative diagnosis (e.g., alcoholic hepatitis showing steatosis, neutrophilic infiltrate and Mallory hyaline) must be confirmed.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm flow-chart:** “Acute hepatitis (illness <6 months, raised ALT/AST)” → branch on biochemical pattern: *Hepatocellular* ($\uparrow\uparrow$ ALT) vs *Cholestatic* ($\uparrow\uparrow$ AlkP/ γ GT) vs *Mixed* → under hepatocellular box list the five core tests (IgM anti-HAV, HBsAg, IgM anti-HBc, anti-HCV, HCV RNA) plus second-line (anti-HEV, anti-HDV, ANA/SMA, ceruloplasmin, acetaminophen level, drug/alcohol history) → outputs: specific viral diagnosis / DILI / autoimmune / Wilson; under cholestatic box: US → MRCP/ERCP, AMA, drug history. Label a side-box “Red flags → ALF: encephalopathy + INR >1.6 + shrinking liver.”
- ▶ **Serologic time-course of acute hepatitis B:** x-axis “weeks after exposure,” plotted curves labelled HBsAg, HBeAg, HBV DNA, IgM anti-HBc, IgG anti-HBc, anti-HBe, anti-HBs, with the shaded “window period” between HBsAg disappearance and anti-HBs appearance, and the ALT/jaundice curve overlaid.

Clinical / Diagnostic significance

- ▶ The pattern (hepatocellular vs cholestatic) plus disease duration (<6 vs >6 months) is the *pivot* of the whole work-up — it tells you which serologic/imaging arm to follow.
- ▶ **IgM anti-HBc** is the single most useful test to call HBV “acute”: it covers the window period and low-level HBsAg, but high-titre IgM anti-HBc can *reappear* in acute exacerbations of chronic HBV, so correlate with history.
- ▶ **HCV RNA** detects infection before anti-HCV and before ALT rises — essential after needlestick and in people who inject drugs (where anti-HCV+/RNA+ may mean re-infection, not chronicity).
- ▶ Recognise mimics: ischaemic hepatitis (shock, very high but rapidly falling AST), acetaminophen DILI, ascending cholangitis/choledocholithiasis, Budd-Chiari/right heart failure with congestion, AFLP/HELLP in pregnancy, and Wilson disease (haemolytic jaundice + low AlkP + low uric acid).
- ▶ **Severity triage:** hospitalise/refer for transplant assessment when there is **encephalopathy**, **INR >1.6**, **intractable vomiting/dehydration**, **hypoglycaemia** or **very high bilirubin** — these define or predict ALF.

High-yield exam pointers

- ▶ Order the **five tests** in every acute hepatitis: HBsAg, IgM anti-HAV, IgM anti-HBc, anti-HCV, HCV RNA — memorise Harrison's Table 350-6.
- ▶ **Acute HAV** = IgM anti-HAV; **Acute HBV** = HBsAg + IgM anti-HBc; **Acute HCV** = anti-HCV + HCV RNA.
- ▶ Aminotransferase height does **not** equal severity — PT/INR, bilirubin, albumin and mental status do.
- ▶ ALT/AST ≥ 1000 IU/L $\Rightarrow$ think viral, ischaemic, drug (acetaminophen) or acute biliary obstruction.
- ▶ AST:ALT ≥ 2 with values < 400 IU/L $\Rightarrow$ alcohol-associated hepatitis.
- ▶ HDV only co-exists with HBV: **co-infection** (IgM anti-HBc) vs **superinfection** (IgG anti-HBc).
- ▶ HEV in pregnancy $\rightarrow$ fulminant hepatitis in up to 20%; chronic HEV occurs only in the immunosuppressed.
- ▶ PT not correcting with **vitamin K** $\Rightarrow$ hepatocellular (not cholestatic/obstructive) injury.
- ▶ **Acute liver failure** = acute injury + coagulopathy + encephalopathy — the most feared outcome; CMTD admission triggers are encephalopathy, INR > 1.6 , inability to maintain hydration.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Acute Viral Hepatitis” (serologic markers, “Simplified Diagnostic Approach in Patients Presenting with Acute Hepatitis”, clinical/laboratory features, differential diagnosis, prognosis) and “Approach to the Patient with Liver Disease” (history/examination, hepatocellular-vs-cholestatic pattern, diagnostic tests algorithm, imaging, biopsy).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Jaundice” (stepwise evaluation, aminotransferase vs alkaline-phosphatase pattern, PT response to vitamin K) and “Acute Liver Failure” (clinical definition: encephalopathy + acute injury + coagulopathy).
- ▶ **CMTD 2026** — “Liver, Biliary Tract & Pancreas Disorders” (essentials of diagnosis, causes of severe aminotransferase elevation, differential diagnosis, when-to-admit criteria).



Discuss Billirubin metabolism. Describe approach to Conjugated Hyperbilirubinemia

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — **Bilirubin** is a tetrapyrrole pigment that is the end product of **heme catabolism**; about **4 mg/kg/day** is produced, of which **80–85%** (range 70–90%) derives from the haemoglobin of senescent red cells and the remainder from ineffective erythropoiesis and turnover of hepatic haemoproteins (myoglobin, cytochromes). **Jaundice** is yellow staining of tissues by deposited bilirubin and becomes clinically detectable (scleral icterus) once serum bilirubin exceeds **51 $\mu\text{mol/L}$ (3 mg/dL)**. **Conjugated (direct) hyperbilirubinaemia** is defined as a *direct fraction* **>15%** of total serum bilirubin and, unlike unconjugated hyperbilirubinaemia, always implies hepatobiliary disease (or a rare inherited canalicular defect) and is accompanied by **bilirubinuria**.

Formation of bilirubin (heme degradation)

- ▶ Bilirubin is the breakdown product of **heme (ferroprotoporphyrin IX)**; formation occurs in **reticuloendothelial cells**, chiefly in the **spleen and liver**.
- ▶ **Step 1 — Heme oxygenase** (microsomal): oxidatively cleaves the **α -methene bridge** of the porphyrin ring, opening the heme ring $\rightarrow$ yields **biliverdin + carbon monoxide (CO) + iron**.
- ▶ **Step 2 — Biliverdin reductase** (cytosolic): reduces the central methylene bridge of biliverdin $\rightarrow$ **bilirubin**.
- ▶ Bilirubin so formed is **virtually water-insoluble** owing to tight **internal hydrogen bonding** (propionic-acid carboxyls bonded to imino/lactam groups of the opposite dipyrrole), which buries the polar residues.
- ▶ For transport in blood, bilirubin is **solubilised by reversible, non-covalent binding to albumin**; this albumin-bound **unconjugated bilirubin** is carried to the liver (the albumin itself is *not* taken up).

Hepatic handling — the four sequential steps (Fig. 349-1)

- ▶ **1. Hepatocellular uptake** — bilirubin enters the hepatocyte by **carrier-mediated (facilitated) and simple diffusional** processes; the definitive bilirubin uptake transporter remains unidentified.
- ▶ **2. Intracellular binding** — within the cytosol bilirubin is held in solution by binding as a non-substrate ligand to the **glutathione-S-transferases (GST)**, formerly “**ligandins**”, which reduce efflux back to plasma and present bilirubin for conjugation.
- ▶ **3. Conjugation** — in the endoplasmic reticulum, **bilirubin UDP-glucuronosyltransferase (UGT1A1)** conjugates bilirubin with one or two glucuronic-acid moieties $\rightarrow$ **bilirubin mono- and diglucuronide**. This disrupts the internal hydrogen bonding and renders the pigment **water-soluble**; conjugation is **obligatory** for excretion across the canalicular membrane. *UGT1A1* is encoded by the **UGT1 gene complex on chromosome 2** (exon A1 + common exons 2–5).
- ▶ **4. Biliary excretion** — conjugates are actively pumped across the canalicular membrane into bile by the **ATP-dependent transporter MRP2 (ABCC2)**. A portion of glucuronides is alternatively extruded into the sinusoid/portal blood by **MRP3 (ABCC3)** and re-internalised by the sinusoidal uptake proteins **OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3)**.

Intestinal fate and enterohepatic circulation

- ▶ Conjugated bilirubin drains into the **duodenum** and passes unchanged through the proximal small bowel; being hydrophilic and large, it is **not reabsorbed** by intestinal mucosa.
- ▶ In the **distal ileum and colon**, bacterial **β -glucuronidases** deconjugate it, and gut flora reduce the unconjugated pigment to colourless **urobilinogens** (and related tetrapyrroles).
- ▶ ~80–90% of urobilinogen is excreted in faeces (oxidised to orange **urobilins**, giving stool its colour); 10–20% undergoes **enterohepatic cycling**, of which a small fraction (<3 mg/dL) escapes hepatic re-uptake, is filtered at the glomerulus and excreted in **urine as urobilinogen**.
- ▶ **Unconjugated bilirubin is never found in urine** (too tightly albumin-bound to be filtered); **any bilirubin in urine is conjugated** — hence bilirubinuria signifies hepatobiliary disease.

Measurement and fractionation — the van den Bergh reaction

- ▶ Serum bilirubin is measured by the **van den Bergh diazo reaction** with diazotised sulfanilic acid.
- ▶ **Direct (conjugated)** = fraction reacting *without* an accelerator (alcohol); **Total** = fraction reacting *after* alcohol releases albumin-bound pigment; **Indirect (unconjugated)** = Total – Direct.
- ▶ Normal total bilirubin is 17–26 $\mu\text{mol/L}$ (1–1.5 mg/dL) by van den Bergh (95% of normals 0.2–0.9 mg/dL).
- ▶ **Unconjugated hyperbilirubinaemia: direct <15% of total; conjugated: direct >15%.**
- ▶ **Delta bilirubin (biliprotein):** conjugated bilirubin covalently bound to albumin, formed when hepatic excretion is impaired; its clearance follows the albumin half-life (18–20 days) rather than bilirubin's (~4 h). It explains why some recovering cholestatic patients have **persistent jaundice without bilirubinuria** (delta bilirubin is not filtered) and a slow fall in bilirubin.

Classification of hyperbilirubinaemias

Predominant fraction	Mechanism	Representative causes
Unconjugated (indirect >85%)	↑ production	Haemolysis; ineffective erythropoiesis; resorption of haematoma; massive transfusion
	↓ hepatic uptake	Drugs — rifampin, probenecid
	↓ conjugation	Gilbert (UGT1A1 10–35%); Crigler-Najjar I (absent UGT1A1, kernicterus) and II ($\leq 10\%$, phenobarbital-responsive); physiologic neonatal jaundice

Predominant fraction	Mechanism	Representative causes
Conjugated / mixed (direct >15%)	↓ canalicular excretion (inherited)	Dubin-Johnson (MRP2/ABCC2); Rotor (OATP1B1 + 1B3 deficiency)
	Hepatocellular injury	Viral/alcoholic/drug/ischaemic hepatitis, cirrhosis
	Cholestasis (intra-/extrahepatic)	PBC, PSC, drug cholestasis, choledocholithiasis, pancreatic/biliary malignancy

Approach to conjugated hyperbilirubinaemia (Fig. 52-1)

- ▶ **Step 1 — Confirm and fractionate.** Establish that the *direct fraction* is >15% of total bilirubin; **bilirubinuria** on dipstick (Ictotest) corroborates a true conjugated rise. Order the *core panel*: bilirubin with fractionation, ALT, AST, ALP, prothrombin time (PT), albumin.
- ▶ **Step 2 — Is the rise isolated or accompanied by other abnormal liver tests?**
 - **Isolated conjugated hyperbilirubinaemia (other LFTs normal)** → think of the two benign inherited canalicular disorders: **Dubin-Johnson** (defective MRP2 canalicular export) and **Rotor** (deficient OATP1B1/1B3 reuptake). Both present as asymptomatic jaundice; distinction is possible but **clinically unnecessary** given their benign course.
 - **Conjugated rise with other liver tests deranged** → proceed to Step 3.
- ▶ **Step 3 — Hepatocellular vs cholestatic pattern** (enzymes are the discriminator):
 - **Hepatocellular:** aminotransferases (ALT/AST) elevated *out of proportion* to ALP. AST:ALT >2:1 with AST rarely >300 U/L suggests **alcoholic hepatitis**; ALT/AST >500–1000 U/L (ALT ≥ AST) suggests **acute viral or toxin/drug injury** (e.g. acetaminophen).
 - **Cholestatic:** ALP elevated *out of proportion* to aminotransferases (confirm hepatic origin with GGT or 5'-nucleotidase).
- ▶ **Step 4 — Targeted serology / toxicology (hepatocellular work-up):** hepatitis A IgM; HBsAg + anti-HBc IgM; HCV RNA; ± hepatitis E IgM; **acetaminophen level**; **ceruloplasmin** if age <40 (Wilson disease); ANA, anti-smooth-muscle antibody, SPEP (autoimmune hepatitis); EBV/CMV if indicated.
- ▶ **Step 5 — Imaging (cholestatic work-up): ultrasound first** to assess the biliary tree.
 - **Dilated ducts** → **extrahepatic cholestasis** → define level/cause with CT / MRCP / ERCP (± EUS, PTC). ERCP is the **gold standard** for **choledocholithiasis** and is therapeutic (stone extraction, stenting); MRCP has replaced diagnostic ERCP in most cases.
 - **Non-dilated ducts** → **intrahepatic cholestasis** → **AMA** (primary biliary cholangitis, positive in ~95%), hepatitis serologies, **drug review**, and **liver biopsy** if serology unrevealing; MRCP shows pathognomonic segmental strictures of PSC.

- **Step 6** — Assess severity/chronicity with **albumin** (low → chronic, e.g. cirrhosis/cancer) and **PT** (prolonged, *non-correcting with parenteral vitamin K* → severe hepatocellular dysfunction; correcting → cholestatic vitamin-K malabsorption).

Inherited conjugated hyperbilirubinaemias — Dubin-Johnson vs Rotor

Feature	Dubin-Johnson (DJS)	Rotor (RS)
Gene / defect	ABCC2 (MRP2) — defective canalicular export	SLCO1B1 + SLCO1B3 (OATP1B1 + 1B3) — defective sinusoidal reuptake
Inheritance	Autosomal recessive	Autosomal recessive
Liver appearance	Grossly black ; coarse dark pigment in centrilobular lysosomes	Normal , no pigmentation
Total bilirubin	34–85 $\mu\text{mol/L}$ (2–5 mg/dL), occasionally up to 20–25 mg/dL; predominantly conjugated	Mild, predominantly conjugated
Urinary coproporphyrin	Total normal , but $\geq 80\%$ isomer I	Total markedly increased , isomer I usually $< 70\%$
Oral cholecystogram	Gallbladder not visualised	Gallbladder visualised
BSP (sulfobromophthalein)	Secondary rise at 90 min (reflux of conjugated dye)	Delayed clearance, no 90-min reflux
Course	Benign; may become overt in pregnancy / OCP use	Benign

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Bilirubin metabolism flow diagram** (left→right). Labels: *Senescent RBC* → *Heme (in reticuloendothelial cell)* → *Heme oxygenase (releases CO + Fe)* → *Biliverdin* → *Biliverdin reductase* → *Unconjugated bilirubin* → *Albumin-bound transport in blood* → *Hepatocyte uptake* → *Ligandin/GST binding* → *UGT1A1 conjugation (ER)* → *Bilirubin mono-/diglucuronide* → *MRP2* → *Bile canaliculus* → *Gut* → *β -glucuronidase/bacteria* → *Urobilinogen* → (80–90% faeces as urobilin / enterohepatic cycle / kidney → urine urobilinogen). Add side-arrows: *MRP3* → *portal blood* → *OATP1B1/1B3 reuptake*.
- **Algorithm box for conjugated hyperbilirubinaemia**. Labels: *Direct >15%* → *fractionate* → “isolated LFTs normal = DJS/Rotor” branch; “other LFTs abnormal” → *Hepatocellular (ALT/AST $\gg$ ALP) vs Cholestatic (ALP $\gg$ ALT/AST)* → *Ultrasound* → *Dilated ducts = Extrahepatic (CT/MRCP/ERCP) vs Non-dilated = Intrahepatic (AMA, biopsy)*.

Clinical / Diagnostic significance

- ▶ **Bilirubinuria** is an early, sensitive sign of conjugated hyperbilirubinaemia and may precede clinical jaundice; its **absence in deep jaundice** suggests delta-bilirubin predominance (prolonged cholestasis).
- ▶ **Serum bilirubin level/ratio** does NOT distinguish intra- from extrahepatic cholestasis — that decision rests on the *enzyme pattern* and *imaging (ductal dilatation)*.
- ▶ **MRP2 (DJS) vs OATP1B1/1B3 (Rotor)** deficiencies are clinically benign but matter for **drug handling**: OATP transporters mediate hepatic uptake of statins and other drugs, so Rotor predisposes to drug accumulation.
- ▶ A **non-correcting prolonged PT** after parenteral vitamin K flags severe hepatocellular failure and is prognostically ominous.
- ▶ **Pigment (calcium bilirubinate) gallstones** complicate chronic haemolysis and can superimpose choledocholithiasis, producing a *secondary conjugated/obstructive* picture.

High-yield exam pointers

- ▶ Bilirubin = end product of heme catabolism; heme oxygenase → biliverdin (+CO+Fe) → biliverdin reductase → bilirubin.
- ▶ Unconjugated bilirubin is albumin-bound, lipid-soluble, NOT in urine; conjugated is water-soluble, appears in urine.
- ▶ Conjugating enzyme = UGT1A1; excretory canalicular pump = MRP2 (ABCC2).
- ▶ Conjugated hyperbilirubinaemia = direct >15% of total and is *always* pathological (hepatobiliary) except the benign inherited DJS/Rotor.
- ▶ DJS = MRP2 defect, black liver, urinary coproporphyrin ≥80% isomer I, BSP 90-min reflux; Rotor = OATP1B1/1B3 defect, normal-coloured liver, ↑ total coproporphyrin, gallbladder visualised.
- ▶ Approach: fractionate → isolated vs other-LFTs → hepatocellular (ALT/AST >> ALP) vs cholestatic (ALP >> ALT/AST) → ultrasound → dilated = extrahepatic, non-dilated = intrahepatic.
- ▶ ERCP = gold standard for choledocholithiasis (diagnostic + therapeutic); AMA = key test for primary biliary cholangitis.
- ▶ Delta bilirubin (albumin-bound conjugated bilirubin, t_{1/2} 18–20 days) explains slow resolution of jaundice and absent bilirubinuria in recovering cholestasis.

SOURCE & COVERAGE

Harrison 22e — Ch 349 “The Hyperbilirubinemias” (bilirubin metabolism, 4-step hepatic transport, UGT1A1, MRP2/MRP3/OATP1B1-1B3, Dubin-Johnson and Rotor syndromes) + Ch 52 “Jaundice” (heme catabolism, van den Bergh fractionation, delta bilirubin, Fig. 52-1 diagnostic algorithm for conjugated hyperbilirubinaemia, hepatocellular vs cholestatic patterns). Coverage

note: All specifics (transporters, enzyme names, coproporphyrin/BSP findings, bilirubin cut-offs, algorithm steps) are drawn from these two chapters; standard ancillary points (GGT/5'-nucleotidase to confirm hepatic ALP origin; AST:ALT and aminotransferase ranges) are from the same chapters' liver-test discussion (Table 348-1). No data fabricated beyond the provided text.



Discuss the complications of Chronic Pancreatitis

Asked in: Paper II May 2022 — RGUHS MD General Medicine

Definition / Introduction — **Chronic pancreatitis (CP)** is a disease process characterised by *irreversible* damage to the pancreas — chronic inflammation, fibrosis, and progressive destruction (atrophy) of both **exocrine and endocrine tissue** — in contrast to the reversible changes of acute pancreatitis. Pancreatic stellate cell (PSC) activation driven by TNF- α , IL-1, IL-6 and oxidant stress perpetuates collagen deposition even after the noxious stimulus (alcohol, smoking) is withdrawn. The cardinal manifestations are abdominal pain, steatorrhoea, weight loss and diabetes; complications arise both from loss of glandular function and from the local fibro-inflammatory/structural sequelae. There is currently **no therapy to reverse or delay disease progression**, so management is centred on *screening for and treating disease-related complications*.

Spectrum of complications (Harrison Table 359-7)

Functional (loss of gland function)	Structural / local	Systemic / metabolic
Chronic abdominal pain	Pseudocyst	Splanchnic (splenic/portal/SMV) venous thrombosis
Exocrine pancreatic insufficiency (EPI) / steatorrhoea	Pancreatic duct stricture	Metabolic bone disease (osteoporosis/osteopenia)
Diabetes mellitus (endocrine insufficiency)	Biliary stricture and/or biliary cirrhosis	Malnutrition, micronutrient/fat-soluble vitamin deficiency
	Pancreatic ascites/duct disruption	Pancreatic cancer

- Useful exam framework: group complications as (1) **exocrine**, (2) **endocrine**, (3) **pain**, (4) **ductal/structural**, (5) **vascular & haemorrhagic**, (6) **metabolic-systemic**, (7) **malignant**.

Exocrine pancreatic insufficiency (EPI) and malnutrition

- **Cumulative prevalence of EPI exceeds 80%**; clinically EPI manifests only after a large functional reserve is lost.

- ▶ Presents as **maldigestion** — chronic diarrhoea, **steatorrhoea** (overt steatorrhoea is highly suggestive of EPI) and **weight loss**; eating may aggravate pain, producing fear of eating and further weight loss.
- ▶ **Fat-soluble vitamin (A, D, E, K) deficiencies** and **micronutrient deficiency (zinc)** are increasingly recognised and drive malnutrition.
- ▶ *Diagnosis*: serum amylase/lipase are usually **not** strikingly elevated in CP; low serum pancreatic enzyme levels are moderately specific but insensitive. **Fecal elastase-1 (FE-1)** on a *formed* stool: **>200 µg/g normal, 100–200 µg/g mild–moderate EPI, <100 µg/g severe EPI** (false positives in unformed stool, diabetes, IBS). The **direct secretin pancreatic function test** is the most sensitive test and becomes abnormal once **≥60% of exocrine function is lost**.
- ▶ *Management pearl*: **pancreatic enzyme replacement therapy (PERT)** is the cornerstone for steatorrhoea — start **25,000–50,000 units of lipase per meal**, up to **100,000 units**, often combined with a **proton-pump inhibitor**; monitor weight, fat-soluble vitamins, zinc and bone mineral density.

Pancreatogenic (type 3c) diabetes mellitus

- ▶ **Lifetime prevalence of CP-related diabetes exceeds 80%** — reflects progressive islet-cell loss.
- ▶ Hyperglycaemia results chiefly from **insulin deficiency** due to destruction of islet cells; loss of glucagon-secreting cells contributes to *brittle* control and hypoglycaemia risk on insulin.
- ▶ Characteristically, **diabetic ketoacidosis and diabetic coma are uncommon**, and **micro/macrovascular end-organ damage (retinopathy, neuropathy, nephropathy) is also uncommon**.
- ▶ **Non-diabetic retinopathy may occur from vitamin A and/or zinc deficiency** — a distinguishing point from primary type 1/type 2 diabetes.

Chronic abdominal pain

- ▶ Pain is the dominant symptom prompting medical attention — variable in site, severity and frequency, constant or intermittent with pain-free intervals; **narcotic dependence is a frequent consequence**, and there is often a *disparity* between severe reported pain and only non-focal tenderness on examination.
- ▶ Mechanisms are complex (ductal hypertension, neural inflammation, ongoing parenchymal injury); **enzyme therapy has no consistent benefit for pain** in meta-analyses.
- ▶ *Stepwise management*: analgesia + **pregabalin** (reduces pain and opioid requirement in a short-term RCT); **celiac plexus block** (conditional, low-quality evidence — not durable); **endoscopic therapy** (sphincterotomy, pancreatic duct stenting, stone extraction, pseudocyst drainage) for a dominant downstream stricture/obstructing stone; **surgical ductal decompression** for a dilated duct — **~80% obtain immediate relief but pain recurs in half by 3 years**, and randomised trials show **surgery superior to endoscopy** for pain relief.

Ductal and structural complications

- ▶ **Pseudocyst** — a persistent peripancreatic fluid collection; <10% of acute collections persist beyond 4 weeks to become a pseudocyst. Most resolve; **only symptomatic collections require intervention** (endoscopic transgastric/transduodenal or surgical drainage). Pseudocysts may cause pain, gastric outlet/biliary obstruction, infection, rupture or haemorrhage.
- ▶ **Pancreatic duct stricture** — fibrotic narrowing causing upstream ductal dilation, pain and contributing to EPI; complications of stenting (migration, occlusion, stent-induced strictures) limit endoscopic therapy.
- ▶ **Biliary stricture, cholestasis and secondary biliary cirrhosis** — chronic inflammation/fibrosis around the **intrapancreatic common bile duct** produces jaundice with raised bilirubin and alkaline phosphatase, and may progress to biliary cirrhosis.
- ▶ **Pancreatic duct disruption** → **pancreatic ascites / pleural effusion** — leak from a disrupted duct produces ascitic fluid with a **high amylase** level (confirmed on MRCP/ERCP); managed with a **bridging pancreatic stent** (>90% effective), parenteral nutrition and octreotide.

Vascular complications and gastrointestinal haemorrhage

- ▶ **Splanchnic venous thrombosis** — peripancreatic inflammation causes **splenic vein thrombosis** (→ left-sided/sinistral portal hypertension and **isolated gastric varices**), and **portal and superior mesenteric vein thrombosis**. Gastric varices rarely bleed but bleeding can be life-threatening.
- ▶ **Pseudoaneurysm** (splenic/gastroduodenal artery) — rupture causes life-threatening haemorrhage, diagnosed and treated with **mesenteric angiography and embolization**.
- ▶ **Gastrointestinal bleeding in CP** may arise from: peptic ulceration, gastritis, a **pseudocyst eroding into the duodenum**, arterial bleeding into the pancreatic duct (**hemorrhagic pancreatitis**), or ruptured varices secondary to **splenic vein thrombosis**.

Metabolic bone disease, micronutrient deficiency and pancreatic cancer

- ▶ **Metabolic bone disease** — strikingly common: ~65% of CP patients have osteopenia or osteoporosis, driven by shared risk factors (alcohol, smoking), **vitamin D deficiency** and chronic inflammation. Periodic **bone mineral density** measurement is advised.
- ▶ **Malnutrition / micronutrient deficiency** — fat-soluble vitamin and zinc deficiency (see EPI) and overall impaired quality of life with significant morbidity.
- ▶ **Pancreatic adenocarcinoma** — a feared long-term complication: **20 years after the diagnosis of chronic calcific pancreatitis the cumulative risk of pancreatic cancer is ~4%**. Risk is *higher* in **hereditary (PRSS1) pancreatitis** and **tropical pancreatitis** (often SPINK1-associated, with bulky calcifications) than in other forms. New jaundice, weight loss or a dominant stricture should prompt exclusion of malignancy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1** — “Complications of chronic pancreatitis” spider/concept map. Central node *Chronic pancreatitis (fibrosis + acinar/islet atrophy)* with labelled spokes: Exocrine insufficiency → steatorrhea, weight loss, fat-soluble vitamin deficiency; Endocrine insufficiency → type 3c diabetes; Chronic pain ± narcotic dependence; Pseudocyst; Pancreatic duct stricture; Biliary stricture → cholestasis/biliary cirrhosis; Pancreatic ascites (duct disruption); Splenic vein thrombosis → gastric varices; Pseudoaneurysm; Hemorrhage pancreaticus; Metabolic bone disease (osteoporosis); Pancreatic cancer.
- ▶ **Diagram 2** — Splenic vein thrombosis schematic. Label: *pancreas (inflamed body/tail), thrombosed splenic vein, spleen (congested), short gastric veins → isolated gastric (fundal) varices, patent portal vein*; caption “sinistral (left-sided) portal hypertension”.

Clinical / Diagnostic significance

- ▶ **Investigation cascade:** noninvasive → invasive — **abdominal CT first** (calcifications, ductal dilation, atrophy, pseudocyst; also excludes cancer), then **MRI/MRCP**, **EUS** (≥5 of 9 endosonographic features = diagnostic; can be combined with EUS-ePFT), and **direct secretin function testing** (most sensitive). **Diffuse pancreatic calcifications on plain film are pathognomonic of CP.**
- ▶ **Cholestatic LFTs** (raised bilirubin + ALP) flag a CBD/biliary stricture; **high-amylase ascites** flags duct disruption; **isolated gastric varices** should trigger a search for splenic vein thrombosis.
- ▶ **Surveillance:** screen for and treat diabetes, EPI, osteoporosis (DXA), fat-soluble vitamin/zinc deficiency; counsel **alcohol and smoking cessation** (independent, dose-dependent driver of progression, fibrosis and calcification).
- ▶ **Management cornerstones:** PERT for steatorrhea; insulin for type 3c diabetes (with caution re: hypoglycaemia); stepwise pain control; endoscopic/surgical drainage for symptomatic pseudocyst or dominant stricture; angio-embolization for pseudoaneurysm/haemorrhage; maintain a low threshold to exclude malignancy.

High-yield exam pointers

- ▶ Two functional complications — **EPI (cumulative prevalence >80%)** and **diabetes (lifetime prevalence >80%)** — dominate; both reflect glandular destruction.
- ▶ **FE-1:** >200 normal, 100–200 mild–moderate, <100 severe EPI; secretin test abnormal once ≥60% of exocrine function lost.
- ▶ CP diabetes (type 3c): insulin-deficient; **DKA, coma and microvascular end-organ damage are uncommon**; *non-diabetic retinopathy* points to vitamin A/zinc deficiency.
- ▶ **Hemorrhage pancreaticus** = arterial bleeding into the pancreatic duct; **splenic vein thrombosis** → **isolated gastric varices** (sinistral portal hypertension).

- ▶ **Pancreatic cancer cumulative risk** ~4% at 20 years in chronic calcific pancreatitis; highest in hereditary PRSS1 and tropical (SPINK1) pancreatitis.
- ▶ ~65% of CP patients have osteopenia/osteoporosis — order DXA and replace vitamin D.
- ▶ Pseudocyst: only **symptomatic** collections need drainage; PERT dose **25,000–50,000 (up to 100,000) units lipase/meal**.
- ▶ Surgery beats endoscopy for pain from a dilated duct; **pregabalin** lowers pain and opioid need.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 359 "Acute and Chronic Pancreatitis" (Complications of Chronic Pancreatitis, Table 359-7; Clinical Features, EPI/FE-1 and secretin-test data; Treatment of Chronic Pancreatitis; Perivascular/duct-disruption complications). *Coverage note:* All numbers, eponyms (hemorrhagic pancreatitis, splenic portal hypertension), prevalence figures and PERT doses are taken from Ch 359. The descriptor "**type 3c (pancreatogenic) diabetes**" is universally accepted standard internal-medicine terminology used here for clarity; Harrison Ch 359 names it "chronic pancreatitis-related diabetes." The 9-feature EUS criterion and Cambridge/secretin diagnostics are referenced in Ch 358/359.



Oral Antiviral Therapy in the Management of Hepatitis C Infection

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Chronic hepatitis C virus (HCV) infection persists in 50–85% of those acutely infected and progresses to cirrhosis in ~20–25% over two decades, with hepatocellular carcinoma (HCC) developing in cirrhotics at 1–4%/year. Because HCV has an entirely **cytoplasmic life-cycle with no integrated archival template** (unlike HBV), suppression of replication in the absence of resistance permanently clears the virus — i.e. **HCV is curable**. The modern treatment of HCV is therefore an all-oral, interferon-free regimen of **direct-acting antivirals (DAAs)** taken for 8–12 weeks, achieving cure (sustained virologic response, SVR) in >95% of patients.

Goal of therapy and definition of cure

- ▶ The endpoint is the **sustained virologic response (SVR12)** — undetectable serum HCV RNA measured **12 weeks after completion** of therapy (the threshold was shortened from the older SVR24 once all-oral DAAs became available). HCV RNA must be tracked with a sensitive real-time RT-PCR assay (limit of quantification ≤25 IU/mL).
- ▶ An SVR is **tantamount to virologic cure**; late relapse beyond 6–12 months is very rare and almost unheard of after 2 years.

- ▶ SVR translates into reduced fibrosis progression, **regression of fibrosis and even cirrhosis**, lower rates of hepatic decompensation, HCC and liver transplantation, improved all-cause and liver-related survival, and improvement in extrahepatic disease (cryoglobulinaemic vasculitis, type 2 diabetes, renal disease).
- ▶ The **WHO global elimination goal** is a 90% reduction in HCV prevalence by 2030; broad DAA use since 2013 has already reversed HCV-related mortality in many regions.

Molecular targets and classes of DAAs

The HCV polyprotein is cleaved into 3 structural and 7 non-structural proteins; current DAAs hit **three** non-structural targets, identifiable by drug suffix.

Class (suffix)	Molecular target	Representative drugs	Genotype coverage / barrier to resistance
NS3/4A protease inhibitors (- <i>previr</i>)	NS3/4A serine protease (polyprotein cleavage)	Glecaprevir, grazoprevir, voxilaprevir, paritaprevir (ritonavir-boosted), simeprevir	Variable–pangenotypic; low-to-moderate barrier; contraindicated in decompensated cirrhosis
NS5A inhibitors (- <i>asvir</i>)	NS5A phosphoprotein of the replication complex	Velpatasvir, pibrentasvir, ledipasvir, elbasvir, daclatasvir, ombitasvir	High potency at picomolar doses; coverage broader with 2nd-generation agents
NS5B polymerase inhibitors (- <i>buvir</i>)	NS5B RNA-dependent RNA polymerase (replicase)	Nucleotide: sofosbuvir (pangenotypic, high barrier); non-nucleoside: dasabuvir (genotype 1, weak, low barrier)	Nucleos(t)ide = pangenotypic, high barrier (chain termination)

- ▶ Modern practice combines drugs from **two (or three) classes in a single fixed-dose pill** to give a high genetic barrier and pangenotypic activity.
- ▶ **Resistance-associated substitutions (RASs)** matter chiefly for NS5A (e.g. Y93H in genotype 3; NS5A polymorphisms in ~11% of genotype 1a). Protease-inhibitor RASs generally do **not** persist (low fitness, wild-type re-emerges); nucleotide (sofosbuvir) RASs are rare and unfit.

Pre-treatment evaluation

- ▶ HCV RNA (confirms active infection) and HCV **genotype** — though pangenotypic regimens exist, genotype still guides regimen/duration and insurance.
- ▶ **Fibrosis staging** by non-invasive means — **FIB-4 score**, transient elastography (liver stiffness); biopsy is no longer routine. Presence of cirrhosis changes drug choice, duration and the rare need for ribavirin.

- ▶ **HBsAg + anti-HBc** — DAAs can trigger **HBV reactivation**; co-infected patients meeting criteria must receive HBV antiviral cover before/with HCV therapy.
- ▶ **HIV status, renal function (eGFR), pregnancy status, and a drug–drug interaction check** (www.hep-druginteractions.org).

Current first-line oral regimens (AASLD–IDSA / EASL)

Five all-oral regimens are recommended; two pangenotypic fixed-dose combinations dominate as a “simplified, one-size-fits-all” algorithm.

Regimen (once-daily)	Components & doses	Usual duration	Notes
Sofosbuvir–velpatasvir (preferred, pangenotypic)	Sofosbuvir 400 mg + velpatasvir 100 mg	12 weeks	Genotypes 1–6; SVR12 ~99% (95% in genotype 3); ribavirin only if decompensated
Glecaprevir–pibrentasvir (preferred, pangenotypic)	Glecaprevir 300 mg + pibrentasvir 120 mg	8 weeks (treatment-naïve, incl. compensated cirrhosis)	Genotypes 1–6; SVR ~99%; preferred in severe renal disease/dialysis ; contains protease inhibitor
Sofosbuvir–ledipasvir	Sofosbuvir 400 mg + ledipasvir 90 mg	8–12 weeks	Genotypes 1, 4, 5, 6; 8 weeks if naïve, non-cirrhotic, HCV RNA <6×10 ⁶ IU/mL
Elbasvir–grazoprevir	Elbasvir 50 mg + grazoprevir 100 mg	12 weeks	Genotypes 1 and 4; baseline NS5A RAS testing in genotype 1a (extend ±ribavirin if present); good in renal failure
Sofosbuvir–velpatasvir–voxilaprevir	Sofosbuvir 400 mg + velpatasvir 100 mg + voxilaprevir 100 mg	12 weeks	Rescue/retreatment after NS5A-inhibitor or DAA failure; ~97% SVR; take with food

- ▶ The **simplified algorithm** (sofosbuvir–velpatasvir ×12 wk or glecaprevir–pibrentasvir ×8 wk) is used when the patient has **none** of: prior treatment failure, cirrhosis, HBsAg positivity, pregnancy, HCC, or prior liver transplant — often without genotyping or on-treatment monitoring.
- ▶ **Ribavirin** (an oral guanosine nucleoside) is now rarely required — reserved for decompensated cirrhosis or selected DAA-failure retreatment; its dose-limiting toxicity is **haemolytic anaemia**, and it is strictly **teratogenic** (contraindicated in pregnancy, contraception mandatory).

Treatment in special populations

- ▶ **Compensated (Child-Pugh A) cirrhosis** — respond as well as non-cirrhotics; pangenotypic regimens used, treatment-experienced cirrhotics may need 12 weeks.
- ▶ **Decompensated (Child-Pugh B/C) cirrhosis** — **protease-inhibitor-containing regimens are contraindicated** (hepatotoxicity, risk of further decompensation). Use **sofosbuvir + an NS5A inhibitor (velpatasvir or ledipasvir)**: add ribavirin to a 12-week course if ribavirin-eligible, or extend to 24 weeks if ribavirin-ineligible. Refer to a transplant centre.
- ▶ **Renal impairment** — no dose change for mild–moderate disease. For severe impairment (CrCl <30 mL/min, dialysis): **glecaprevir–pibrentasvir** (all genotypes) or **elbasvir–grazoprevir** (genotypes 1, 4) preferred; sofosbuvir-containing regimens, initially avoided, are now FDA-approved (2019) for this group.
- ▶ **HCV/HIV co-infection** — treat with the **same DAAs and durations** as mono-infection (response is now equivalent); avoid the abbreviated 8-week sofosbuvir–ledipasvir course; mind antiretroviral interactions (avoid ribavirin with didanosine/stavudine/zidovudine).
- ▶ **Prior DAA failure (retreatment)** — sofosbuvir-experienced patients are re-treated with **sofosbuvir–velpatasvir–voxilaprevir ×12 wk** or **glecaprevir–pibrentasvir ×16 wk**; multiple-DAA failures may need glecaprevir–pibrentasvir + sofosbuvir + ribavirin ×16 wk; RAS-guided, specialist-referred.
- ▶ **Pregnancy** — DAAs **not routinely recommended** (limited data); ribavirin absolutely contraindicated. **Acute hepatitis C** and **people who inject drugs (PWID)** should be treated (active injection drug use is no longer a contraindication — treatment reduces onward transmission).

Adverse effects, interactions and cautions

- ▶ DAAs are **very well tolerated**; commonest effects are mild **headache, fatigue, nausea**, comparable to placebo.
- ▶ **Sofosbuvir + amiodarone** → **severe, potentially fatal bradycardia** — sofosbuvir-containing regimens are contraindicated with amiodarone (especially with beta-blockers).
- ▶ **P-glycoprotein / CYP3A4 inducers** (rifampin, St John's wort, carbamazepine, phenytoin, phenobarbital) lower DAA levels and **contraindicate** all DAA regimens.
- ▶ **Gastric acid suppression**: ledipasvir and velpatasvir lose solubility at high gastric pH — limit/separate antacids, H₂-blockers and PPIs (e.g. omeprazole ≤20 mg).
- ▶ Protease inhibitors can raise aminotransferases/bilirubin → monitor and stop for marked rises.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **HCV genome and DAA drug targets** (linear genome): label structural proteins **Core (C)**, **E1, E2, p7** and non-structural proteins **NS2, NS3, NS4A, NS4B, NS5A, NS5B**; mark the

three drug targets — NS3/4A protease (→ -previr), NS5A replication-complex protein (→ -asvir), NS5B RNA-dependent RNA polymerase (→ -buvir).

- ▶ **Treatment-decision flow chart:** label *Confirm chronic HCV (HCV RNA +ve)* → *Pre-treatment work-up (genotype, FIB-4/elastography, HBsAg+anti-HBc, HIV, eGFR, DDI check)* → branch *No cirrhosis / treatment-naïve* → *simplified regimen (sof-velpatasvir 12 wk OR glecaprevir-pibrentasvir 8 wk)* vs *Cirrhosis / prior failure / special population* → *tailored regimen* → *Confirm SVR12 at 12 weeks post-treatment.*

Clinical / Diagnostic significance

- ▶ Achieving SVR halts and can reverse fibrosis/cirrhosis and reduces HCC, decompensation, transplant need and mortality — but in patients with **advanced fibrosis/cirrhosis the HCC risk is reduced, not eliminated**, so **6-monthly ultrasound HCC surveillance continues even after cure.**
- ▶ **Screen and protect against HBV reactivation** before DAA therapy; vaccinate against hepatitis A and B.
- ▶ DAAs cure HCV in patients awaiting or after **liver/kidney transplantation**, and enable transplantation of HCV-positive donor organs into HCV-negative recipients with subsequent cure.
- ▶ Treating **mild disease is justified and cost-effective** — delaying until fibrosis is advanced forfeits the chance to prevent end-stage complications.

High-yield exam pointers

- ▶ SVR12 = undetectable HCV RNA 12 weeks post-treatment = **cure**.
- ▶ Three DAA targets/suffixes: NS3/4A protease (-previr), NS5A (-asvir), NS5B polymerase (-buvir).
- ▶ Sofosbuvir = pangenotypic NS5B **nucleotide** inhibitor, high resistance barrier, 80% renally excreted.
- ▶ Two pangenotypic preferred fixed-dose regimens: **sofosbuvir-velpatasvir ×12 wk** and **glecaprevir-pibrentasvir ×8 wk**, SVR >95%.
- ▶ **Protease-inhibitor regimens (glecaprevir/grazoprevir/voxilaprevir) are contraindicated in decompensated cirrhosis** — use sofosbuvir + velpatasvir/ledipasvir ± ribavirin.
- ▶ Sofosbuvir + amiodarone = **severe bradycardia** (contraindicated).
- ▶ Sofosbuvir-velpatasvir-voxilaprevir = **rescue therapy for prior NS5A/DAA failure**.
- ▶ Always check **HBsAg/anti-HBc** (reactivation), genotype, fibrosis (FIB-4/elastography), eGFR, and drug interactions before therapy.
- ▶ **Ribavirin** — main toxicity **haemolytic anaemia; teratogenic** (avoid in pregnancy).

- ▶ Continue HCC surveillance after SVR if cirrhosis/advanced fibrosis present.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Chronic Hepatitis” (chronic hepatitis C; DAA classes, targets, recommended regimens, special populations, SVR, treatment recommendations) and “Antiviral Chemotherapy, Excluding Antiretroviral Drugs.”
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Hepatitis C” (DAA class pharmacology, individual drug doses and pharmacokinetics, resistance, fixed-dose combinations, drug–drug interactions, registration trials).
- ▶ **CMDT 2026** — “Liver, Biliary Tract, & Pancreas Disorders” (current management, DAA agent tables/doses, preferred regimens, pre-treatment screening, P450-inducer cautions).



Diseases associated with *Helicobacter pylori* infection and its management

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — *Helicobacter pylori* is a spiral, flagellated, microaerophilic, urease-producing **gram-negative bacillus** that colonises the gastric mucous layer of roughly **40% of the world's population**, usually acquired in childhood and persisting for life unless eradicated. Essentially **all colonised persons develop histological chronic gastritis**, but only **~10–15% develop overt disease** — the outcome being decided by an interplay of bacterial virulence (*cagA*, *vacA*), host genetics and environment. It is the principal cause of peptic ulcer disease, an **IARC class I (definite) gastric carcinogen**, and the driver of gastric MALT lymphoma; it also has recognised extragastric and some *protective* associations. Marshall and Warren's 1984 discovery (Nobel Prize 2005) transformed these from chronic relapsing diseases into curable infections.

Pathogenesis — how one organism causes opposite diseases

- ▶ **Virulence factors:** the *cag* pathogenicity island encodes a **type IV secretion system** that injects the effector **CagA** into epithelial cells (driving proliferative, cytoskeletal and inflammatory changes); **CagL** binds host integrins; peptidoglycan fragments activate intracellular **Nod1**, amplifying cytokine release. The vacuolating cytotoxin **VacA** forms membrane pores, and adhesin **BabA** binds blood-group antigens. *cagA*+/ *vacA*-active strains carry the highest ulcer and cancer risk.
- ▶ **Host/environment:** IL-1 β gene polymorphisms (high IL-1 producers) and the **PSCA rs2294008** SNP increase cancer risk; smoking, high-salt/preserved-food diets raise risk, while vitamin C/antioxidants are protective.
- ▶ **Topography determines disease (key concept):**

- **Antral-predominant gastritis** → loss of somatostatin-secreting **D cells** → unrestrained gastrin → ↑ acid from spared corpus → **duodenal ulcer**.
- **Corpus-predominant / pangastritis** → hypochlorhydria, atrophy → **gastric ulcer, atrophic gastritis and adenocarcinoma**.

Spectrum of associated diseases (with strength of association)

Disease group	Specific condition	Association / Odds ratio (Harrison Fig 168-1)
Gastric	Chronic superficial (then atrophic) gastritis	Virtually 100% of colonised
	Peptic ulcer disease	~70% of duodenal, ~50% of gastric ulcers; DU OR 3–6
	Functional (non-ulcer) dyspepsia	Symptom resolution in up to ~10–15% over placebo
	Gastric MALT (marginal-zone B-cell) lymphoma	OR 6–50
	Non-cardia gastric adenocarcinoma	OR 3–8
	Iron-deficiency anaemia, vitamin B12 deficiency	Occult loss + hypochlorhydria/malabsorption
Extragastric	Immune (idiopathic) thrombocytopenic purpura	Platelet rise/normalisation after eradication
Protective (inverse)	GERD, Barrett's oesophagus, oesophageal & cardia adenocarcinoma	OR 0.2–0.6 (cagA+ strains)
	Childhood-onset asthma, hay fever, atopy	Inverse association (cagA+); causal in animal models

- ▶ *H. pylori* is **neither necessary nor sufficient** for PUD but is a very strong risk factor; eradication virtually abolishes long-term ulcer relapse (recurrence falls from ~85%/yr to <20%/yr).
NSAIDs/aspirin and *H. pylori* are **independent, synergistic** ulcer risks.

Gastric MALT lymphoma & adenocarcinoma — the malignant end of the spectrum

- ▶ **Gastric MALT lymphoma (extranodal marginal-zone B-cell lymphoma)**: arises from chronic antigenic stimulation of acquired lymphoid tissue; the stomach is the commonest extranodal lymphoma site. Cells are CD19/CD20/CD79a positive, CD5/CD10/CD23/cyclin D1 negative, forming *lymphoepithelial lesions*, commonly antral.
- **H. pylori eradication alone induces remission in ~60–80%** of low-grade, localised (mucosa-confined) cases — first-line therapy even if tests are falsely negative.

- **t(11;18)(q21;q21)** (the *API2-MALT1* fusion) and **t(1;14)(p22;q32)** (deregulating *bcl-10*) predict **non-response** to eradication and indicate need for radiotherapy/rituximab-based chemotherapy; CagA+ strains associate with t(11;18)-positive tumours.
- ▶ **Gastric adenocarcinoma (Correa cascade)**: the intestinal type evolves over decades — **chronic gastritis** → **atrophic gastritis** → **intestinal metaplasia** → **dysplasia** → **carcinoma**, driven by inflammation-derived reactive oxygen/nitrogen species and nitrosamines from bacterial overgrowth in the achlorhydric stomach. The **diffuse type** (signet-ring cells, *linitis plastica*) may arise directly from chronic gastritis. Eradication **does not treat established cancer** but reduces incidence, especially after endoscopic resection of early gastric cancer.

Diagnosis

Invasive (endoscopic biopsy)	Non-invasive
Rapid urease test (CLO) — quick, biopsy in urea-indicator gel	¹³C-urea breath test — accurate; ideal for confirming cure
Histology (modified Giemsa/silver/immunostain) — also grades atrophy/metaplasia/dysplasia	Stool antigen test (monoclonal) — cheap, good for children & cure-testing
Culture + sensitivity — most specific; guides resistant cases	Serology (IgG) — cannot confirm cure (titres fall slowly); least reliable for active infection

- ▶ **Pitfall**: breath/stool/biopsy tests depend on bacterial load — false negatives if performed **within 4 weeks of antibiotics/bismuth or 2 weeks of stopping a PPI**, or <4 weeks post-treatment. Serology is *not* used to monitor cure.
- ▶ After **gastric ulceration**, repeat **endoscopy** to confirm healing and exclude carcinoma; duodenal ulcers need only a non-invasive cure test.

Management — eradication regimens (PPI/vonoprazan + ≥2 antibiotics × 10–14 days)

Regimen	Components	Notes
Bismuth quadruple (BQT) — preferred first-line (ACG 2024)	PPI + bismuth + tetracycline + metronidazole, 14 d	Effective even in metronidazole-resistant strains; >85% cure
Rifabutin triple (Talaria)	Omeprazole + rifabutin + amoxicillin, q8h × 14 d	Rifabutin resistance rare; >85% cure
Vonoprazan triple / dual (Voquezna)	Vonoprazan + amoxicillin ± clarithromycin, 14 d	PCAB gives faster/stronger acid block; dual preferred empirically
Clarithromycin triple	PPI + clarithromycin + amoxicillin (or metronidazole), 14 d	Only if clarithromycin resistance <15% or strain proven sensitive

Regimen	Components	Notes
Concomitant quadruple	PPI + clarithromycin + amoxicillin + nitroimidazole, 14 d	Non-bismuth alternative
Levofloxacin-based	PPI + levofloxacin + amoxicillin	Mainly salvage/second-line therapy

- **Resistance drives choice:** clarithromycin resistance is now ~50% (US) and high in much of the world — hence the shift away from clarithromycin triple therapy; metronidazole resistance is partial (overcome by higher dose/quadruple therapy); amoxicillin and tetracycline resistance remain rare.
- **Keys to success:** strict **compliance**, avoiding antibiotics the strain has seen before, **high-dose acid suppression** (PPI or vonoprazan), and **confirming cure** ≥ 4 weeks after antibiotics and ≥ 2 weeks off PPI.
- **Salvage strategy:** for persistent infection, re-treat empirically with a *different* regimen (e.g., BQT after a clarithromycin regimen; rifabutin triple after BQT) or, ideally, **culture / molecular (PCR) susceptibility-guided** therapy.

Indications for eradication (Maastricht VI / ACG)

- **Definite:** all peptic ulcers (active or healed); low-grade gastric MALT lymphoma; after endoscopic resection of early gastric cancer.
- **Recommended:** functional dyspepsia (test-and-treat in <60 yr without alarm features); long-term NSAID/low-dose-aspirin users (especially prior PUD); first-degree relatives of gastric-cancer patients; atrophic gastritis/intestinal metaplasia.
- **Offer:** unexplained **iron-deficiency anaemia**, **immune thrombocytopenic purpura**, and vitamin B12 deficiency with other causes excluded.
- Mass population screening is **not** routinely recommended (uncertain cancer-risk reduction, antibiotic resistance, loss of possible protective effects against GERD/atopy).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1** — “Disease outcomes of *H. pylori* colonisation” (branching tree). Centre: *H. pylori* → **Chronic gastritis** ($\approx 100\%$). Branch by gastritis pattern: *Antral-predominant* → $\uparrow$ gastrin/ $\uparrow$ acid → **Duodenal ulcer** (OR 3–6); *Corpus-predominant/pangastritis* → atrophy/hypochlorhydria → **Gastric ulcer**, **Atrophic gastritis** → **intestinal metaplasia** → **dysplasia** → **Non-cardia adenocarcinoma** (OR 3–8), and **MALT lymphoma** (OR 6–50). Add a *protective* arrow: $\downarrow$ acid → **lower GERD / Barrett’s / oesophageal adenocarcinoma** (OR 0.2–0.6). Labels: *cagA*, *vacA*, *BabA*; *D-cell loss*; *somatostatin* $\downarrow$; *gastrin* $\uparrow$.

- ▶ **Diagram 2 — “Correa cascade”.** Linear arrow: **Normal mucosa** → **Chronic active gastritis** → **Atrophic gastritis** → **Intestinal metaplasia** → **Dysplasia** → **Intestinal-type adenocarcinoma**, with labels *H. pylori*, *reactive oxygen/nitrogen species*, *nitrosamines*, *achlorhydria*.

Clinical / Diagnostic significance

- ▶ In a young dyspeptic without alarm features, **non-invasive test-and-treat** (UBT/stool antigen) avoids endoscopy; **alarm symptoms** (age ≥60, weight loss, anaemia, dysphagia, bleeding, vomiting) mandate **upper GI endoscopy** to exclude malignancy.
- ▶ Always **test for and eradicate** *H. pylori* before/at the start of long-term NSAID/aspirin therapy in those with ulcer history — but eradication **alone does not remove** ongoing NSAID risk, so co-prescribe a PPI in high-risk patients.
- ▶ A non-healing/refractory ulcer should prompt search for **NSAID use (often surreptitious)**, **gastrinoma** (Zollinger-Ellison — fasting serum gastrin), **malignancy (re-biopsy)**, **Crohn’s**, **vasculitis**.
- ▶ Unexplained refractory **iron-deficiency anaemia** or **ITP** warrants *H. pylori* testing — eradication can correct both.

High-yield exam pointers

- ▶ *H. pylori* = **gram-negative, urease-positive, microaerophilic, flagellated spiral bacillus**; urease (→ ammonia) is its acid-defence and the basis of the **rapid urease & ¹³C-urea breath tests**.
- ▶ **70% of duodenal ulcers, 50% of gastric ulcers** are *H. pylori*-related; eradication cuts ulcer recurrence from ~85%/yr to <20%/yr.
- ▶ **Antral gastritis = duodenal ulcer; corpus/pangastritis = gastric ulcer + cancer.**
- ▶ **IARC Group 1 carcinogen**; intestinal-type cancer follows the **Correa cascade**; diffuse type = signet-ring/linitis plastica.
- ▶ **Low-grade gastric MALT lymphoma regresses in 60–80% with eradication alone**; t(11;18)(q21;q21) predicts non-response.
- ▶ **OR memory aid:** B-cell lymphoma **6–50** > gastric adenoca **3–8** > duodenal ulcer **3–6**; *protective* against oesophageal disease **0.2–0.6**.
- ▶ **First-line eradication = bismuth quadruple therapy** (PPI + bismuth + tetracycline + metronidazole × 14 days); clarithromycin triple only where resistance <15%.
- ▶ **Confirm cure** by UBT/stool antigen ≥4 weeks after antibiotics and ≥2 weeks off PPI; never use serology to confirm cure.
- ▶ Extragastric eradication indications: **unexplained IDA, ITP, B12 deficiency**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Helicobacter pylori* Infections” (virulence factors, disease odds ratios, diagnosis, eradication regimens, indications) and “Peptic Ulcer Disease and Related Disorders” (PUD/*H. pylori* interaction, ACG/Maastricht VI indications, treatment tables).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Gastrointestinal Lymphomas” (MALT lymphoma immunophenotype, t(11;18)(q21;q21) and t(1;14)(p22;q32), 60–80% regression), “Adenocarcinoma of the Stomach and Other Gastric Tumours” (Correa pathway, IARC class I carcinogen, Lauren intestinal/diffuse types), “Gastritis and Gastropathy” and “Peptic Ulcer Disease”.
- ▶ **CMDT 2026** — “Gastrointestinal Disorders” (ACG 2024 regimens: bismuth quadruple, rifabutin triple [Talicia], vonoprazan triple/dual [Voquezna]; resistance data; cure-confirmation rules).



Extra-intestinal Manifestations of Inflammatory Bowel Disease

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Extra-intestinal manifestations (EIMs) are inflammatory or metabolic disorders arising *outside* the gut in patients with ulcerative colitis (UC) or Crohn's disease (CD). Up to **one-third** of IBD patients have at least one EIM (population estimates 6–25%), and about **one-fourth of those affected have more than one**. EIMs are commoner in CD than UC and in patients with **colonic involvement**. Pathogenically, the inflammatory mucocutaneous, joint and ocular EIMs reflect an influx of **mononuclear cells activated in the intestine that home aberrantly** to extra-intestinal organs; a few (e.g. enteric hyperoxaluria stones, cholelithiasis) are direct metabolic consequences of bowel disease. EIMs may **precede, parallel or run independently** of luminal activity — an important clue to whether treating the bowel will help.

Classification by relationship to bowel activity

This is the single most examinable framework — EIMs split into those that **parallel** gut inflammation (treated by controlling the bowel) and those that run an **independent** course.

Parallels bowel activity (treat the bowel)	Independent of bowel activity (treat separately)
Peripheral arthritis — Type 1 (pauciarticular)	Axial arthropathy — sacroiliitis, ankylosing spondylitis
Erythema nodosum	Peripheral arthritis — Type 2 (polyarticular)

Parallels bowel activity (treat the bowel)	Independent of bowel activity (treat separately)
Episcleritis	Anterior uveitis / iritis
Oral aphthous stomatitis, pyostomatitis/pyoderma vegetans	Pyoderma gangrenosum
Sweet syndrome, metastatic CD	Primary sclerosing cholangitis (PSC)

Musculoskeletal (most common EIM group; 5–20%)

- ▶ **Peripheral arthritis** — develops in 15–20% of IBD patients, commoner in CD, classically **asymmetric, migratory, polyarticular, non-deforming**, affecting large joints; rheumatoid factor **negative**. Sleisenger subdivides it into:
 - ***Type 1 (pauciarticular)** — <5 joints, large joints, *parallels** bowel activity, self-limiting, associated with EN and uveitis; often remits after colectomy in UC.
 - ***Type 2 (polyarticular)** — >5 joints, small joints (MCP/PIP), *independent** of bowel activity, more persistent.
- ▶ **Axial spondyloarthropathy** — ankylosing spondylitis (AS) occurs in ~10% (commoner in CD); two-thirds (up to 75% of CD with spondylitis) are HLA-B27 positive. Presents with **insidious low-back/buttock pain and morning stiffness improved by exercise**, runs a continuous progressive course causing permanent skeletal deformity, and does **not** remit with glucocorticoids or colectomy. **Sacroiliitis** is symmetric, occurs equally in UC and CD, is often asymptomatic, does not correlate with bowel activity, and does not always progress to AS. Anti-TNF agents reduce spinal inflammation.
- ▶ **Metabolic bone disease** — low bone mass in 14–42%; risk increased by **glucocorticoids, ciclosporin, methotrexate, TPN**, malabsorption of calcium/vitamin D, and cytokines (IL-1, IL-6, TNF). Absolute fracture risk ≈ **1% per person-year** (highest age >60; OR ≈1.7 vertebral, 1.6 hip). Screen with **DEXA**, check vitamin D, treat osteopenia/osteoporosis especially on long-term steroids.
- ▶ **Osteonecrosis (avascular necrosis)** — death of osteocytes/adipocytes with bone collapse; **hips > knees/shoulders**; major risk factor is **steroid use**. Diagnosed by **MRI/bone scan**; treat with analgesia, decompression, joint replacement.
- ▶ Other: clubbing, hypertrophic osteoarthropathy, septic joint (e.g. from psoas abscess), osteomyelitis.

Mucocutaneous (10–20%)

- ▶ **Erythema nodosum (EN)** — up to 15% of CD, 10% of UC; **hot, red, tender 1–5 cm nodules** on the anterior shins/extremities; **parallels bowel activity**, commoner in women, strongly associated with peripheral arthritis. *Avoid biopsy* (scars); treat the underlying bowel disease.

- ▶ **Pyoderma gangrenosum (PG)** — 1–12% of UC, less in Crohn's colitis; **independent** of bowel activity, usually severe disease. Begins as a pustule/nodule that ulcerates with **violaceous, undermined borders** and necrotic base, classically on the legs/dorsa of feet or peristomal; shows **pathergy (ulcers at trauma sites) and heals with a cribriform scar. Difficult to treat — topical/IV/intralesional glucocorticoids, ciclosporin, infliximab/adalimumab, dapsone, azathioprine; debridement and colectomy are NOT effective**.
- ▶ **Oral** — aphthous stomatitis and “cobblestone” buccal lesions (CD > UC), pyostomatitis vegetans, granulomatous labial/facial swelling, angular cheilitis.
- ▶ **Others** — **psoriasis** (5–10%, shared IL23R/IL12B genetics, unrelated to bowel activity), pyoderma vegetans (intertriginous), **Sweet syndrome** (neutrophilic dermatosis), **metastatic CD** (cutaneous non-caseating granulomas remote from gut), perianal skin tags (75–80% of CD), leukocytoclastic vasculitis.

Ocular (1–11%)

- ▶ **Episcleritis** — commonest; mild ocular burning/injection, **does not impair vision, parallels bowel activity** (3–4%); topical glucocorticoids.
- ▶ **Anterior uveitis / iritis** — **ocular pain, photophobia, blurred vision, headache, ciliary flush, miosis**; in IBD often **insidious, bilateral, with posterior extension**; **independent** of bowel activity and may appear in remission. **The one ocular EIM demanding emergent ophthalmology referral** — prompt systemic steroids prevent scarring and visual loss.
- ▶ Rare: scleritis (sight-threatening), keratopathy, **night blindness** from vitamin A malabsorption.

Hepatobiliary (10–35%)

- ▶ **Primary sclerosing cholangitis (PSC)** — intra- and extra-hepatic bile-duct **inflammation and fibrosis** → biliary cirrhosis/failure. ~5% of UC patients have PSC, but 50–75% of PSC patients have IBD; both are commonly **pANCA positive**. Often asymptomatic; runs a course **independent** of bowel activity. Diagnose with MRCP (initial test of choice; safer than ERCP) showing **multifocal strictures alternating with dilatations (“beaded” ducts)**. Carries a **10–15% lifetime risk of cholangiocarcinoma**, gallbladder-polyp malignancy (cholecystectomy even if <1 cm; annual USG surveillance) and **increased colon-cancer risk** → **yearly surveillance colonoscopy**. Small-duct PSC / “pericholangitis” has a normal cholangiogram and a better prognosis.
- ▶ **Cholelithiasis** — 10–35%, in CD with **ileitis or ileal resection**; bile-acid malabsorption depletes the bile-salt pool → **lithogenic (cholesterol/pigment) stones**.
- ▶ **Hepatic steatosis (fatty liver)** — from chronic illness, malnutrition and steroids; **autoimmune hepatitis**, granulomatous hepatitis and **hepatic amyloidosis** are rarer.

Renal/urologic, vascular and other systemic

- ▶ **Nephrolithiasis (10–20%)** — highest in CD after **small-bowel resection**; **calcium-oxalate stones** from **enteric hyperoxaluria** — unabsorbed fatty acids bind luminal calcium, leaving oxalate free for colonic absorption. Manage with a **low-oxalate diet**, hydration and control of inflammation. Uric-acid stones (volume depletion), ureteric obstruction, ileovesical fistulas, and mesalamine-associated interstitial nephritis also occur.
- ▶ **Thromboembolism** — increased **venous and arterial** thrombosis **even when disease is inactive** (hypercoagulable state: thrombocytosis, raised fibrinogen/factors V & VIII, hyperhomocysteinaemia, impaired fibrinolysis, tissue-factor microvesicles). Treat with anticoagulation plus control of inflammation; thromboprophylaxis in hospitalised flares.
- ▶ **Systemic (secondary/reactive AA) amyloidosis** — long-standing IBD, especially CD; causes diarrhoea, constipation and **renal failure**; renal disease responds to **colchicine**.
- ▶ **Cardiopulmonary** — endocarditis, myocarditis, pleuropericarditis, interstitial lung disease (rarely 5-ASA-induced — stop the drug).
- ▶ **Pancreatitis** — duodenal fistula, ampullary CD, gallstones, PSC, drugs (azathioprine/mercaptopurine, rarely 5-ASA), autoimmune, or primary CD of the pancreas.
- ▶ **Haematologic** — anaemia of chronic disease, iron and B12 deficiency (ileal disease).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Head-to-toe “EIM map” of IBD** — draw a body outline and label by region: **Eyes** — episcleritis, anterior uveitis/iritis; **Mouth** — aphthous stomatitis, pyostomatitis vegetans; **Skin** — erythema nodosum (shins), pyoderma gangrenosum (legs/peristomal), psoriasis, metastatic CD; **Liver/biliary** — PSC (beaded ducts), gallstones, fatty liver; **Joints/spine** — peripheral arthritis (Type 1/Type 2), sacroiliitis, ankylosing spondylitis (bamboo spine); **Bone** — osteoporosis, avascular necrosis of hip; **Kidney** — calcium-oxalate stones; **Vessels** — venous thromboembolism.
- ▶ **Two-column flow diagram** “EIMs that PARALLEL vs are INDEPENDENT of bowel activity” with the labels: *Parallel* = peripheral arthritis Type 1, EN, episcleritis, aphthous ulcers; *Independent* = sacroiliitis, AS, uveitis, pyoderma gangrenosum, PSC.

Clinical / Diagnostic significance

- ▶ **Activity-linked EIMs** (Type 1 arthritis, EN, episcleritis, oral aphthae) signal a bowel flare and respond to **inducing remission** (5-ASA, steroids, biologics); **activity-independent EIMs** (AS, uveitis, PG, PSC) need their own therapy and do **not** improve with colectomy.
- ▶ An EIM such as **PG or PSC can precede the bowel diagnosis by years**, so IBD should be sought in unexplained PG, recurrent uveitis, or cholestatic LFTs with pANCA.
- ▶ **HLA-B27** typing supports axial spondyloarthritis; **MRCP** for cholestatic LFTs; **DEXA + vitamin D** for bone disease; **MRI** for AVN and sacroiliitis.

- ▶ **Biologics** (anti-TNF — infliximab/adalimumab; anti-IL-12/23 — ustekinumab/risankizumab; JAK inhibitors; IL-17 inhibitors for spondyloarthritis) treat both gut and several EIMs simultaneously; **vedolizumab** (gut-selective) is less effective for EIMs.
- ▶ PSC patients need **annual surveillance colonoscopy** (colon-cancer risk) and **gallbladder USG** (cholangiocarcinoma/polyp risk).

High-yield exam pointers

- ▶ Up to **one-third** of IBD patients have ≥ 1 EIM; commoner in CD and in **colonic disease**.
- ▶ **Peripheral arthritis**: Type 1 = **pauciarticular** (<5 joints), **parallels bowel**; Type 2 = **polyarticular** (>5 joints), **independent**. RF negative, non-deforming.
- ▶ AS/sacroiliitis are **independent** of bowel activity; **~two-thirds HLA-B27 positive**; do not remit with colectomy.
- ▶ EN parallels activity (treat the bowel); PG is independent, shows **pathergy**, heals with a **cribriform scar**, and **colectomy/debridement do not help**.
- ▶ **Uveitis** = the ocular emergency (urgent ophthalmology + systemic steroids); **episcleritis** is benign and parallels activity.
- ▶ **PSC**: ~5% of UC have it, 50–75% of PSC have IBD; pANCA+; MRCP shows **beaded strictures**; **10–15% lifetime cholangiocarcinoma** risk; surveillance colonoscopy yearly.
- ▶ **Calcium-oxalate stones** via **enteric hyperoxaluria** after ileal disease/resection.
- ▶ IBD is a **hypercoagulable state** — VTE risk persists even in remission.
- ▶ **Secondary (AA) amyloidosis** in long-standing CD; renal involvement treated with **colchicine**.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Inflammatory Bowel Disease" (extraintestinal manifestations; Table 337-7).
- ▶ Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e — "Epidemiology, Pathogenesis, and Diagnosis of Inflammatory Bowel Diseases" (Type 1/Type 2 peripheral arthritis, axial spondyloarthropathy and HLA-B27, ocular, hepatobiliary, renal and vascular EIMs; Table 115.2) and "Management of Inflammatory Bowel Diseases".
- ▶ CMDT 2026 — "Gastrointestinal Disorders: Inflammatory Bowel Disease" (current EIM list and biologic management).



Fecal Microbiota: Current Trends and Transplant

Asked in: Paper IV Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — The **human microbiota** is the collective community of bacteria, viruses, fungi and Archaea inhabiting body surfaces; the **microbiome** is the aggregate of their genes. A human is best viewed as a *holobiont* — host cells plus microbes — whose >2,000,000 microbial genes dwarf the ~20,000 human genes. **Fecal microbiota transplantation (FMT)** — also termed *intestinal microbiota transplantation (IMT)* or *fecal microbiota replacement therapy (FMRT)* — is the transfer of processed stool from a screened healthy donor into a diseased recipient to correct **dysbiosis** and restore *colonization resistance*. It is the single most successful microbiome-based therapy and the “poster child” for recurrent *Clostridioides difficile* infection (rCDI).

The Human Microbiota — Normal Composition and Function

- ▶ **Numbers:** >10,000 bacterial species exist in the human microbiota; the gut alone harbours >1000 species, with 100–200 present in any individual at a given time. Bacteria outnumber human cells by ~1.3:1 (a person is ~56% “bacterial”; with viruses/fungi/Archaea, microbes likely exceed 90% of cells).
- ▶ **Five dominant phyla:** *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, *Proteobacteria*.
- ▶ **Key ecological principles** (Human Microbiome Project, *Nature* 2012):
 - Composition is determined more by **body site** than by inter-individual variation (oral, gut, skin, urogenital, nasal each cluster distinctly); stool is the richest, most-studied site.
 - Marked **inter-individual variability** in taxa, yet the **functional/metabolic gene capacity is conserved** — *functional redundancy*.
 - Modulators of the gut microbiota: **diet, drugs (esp. antibiotics), age, host genetics (small effect), delivery mode, lifestyle, circadian rhythm**.
- ▶ **Functions:** colonization resistance against pathogens; education of innate and adaptive immunity (germ-free animals have an immature immune system); short-chain fatty acid (SCFA) production (butyrate/acetate/propionate → regulatory T cells, colonocyte energy, barrier integrity); bile-acid and drug metabolism; vitamin synthesis.

Dysbiosis and the Rationale for FMT

- ▶ **Dysbiosis** = a disease-associated shift to a new microbial equilibrium, typically with **reduced alpha- and beta-diversity** and an increase in *Enterobacteriaceae* with loss of *Lachnospiraceae*/butyrate producers.
- ▶ In **rCDI**, antibiotics deplete protective anaerobes → loss of colonization resistance → reduced phylogenetic richness with depletion of *Firmicutes* and *Bacteroidetes*.
- ▶ **Mechanisms by which FMT cures CDI:** restoration of microbial diversity and **colonization resistance**; conversion of primary to **secondary bile acids** (e.g., by *Clostridium scindens*, which inhibits *C. difficile* germination/outgrowth); restoration of **butyrate producers**; and refilling of open nutritional niches.

FMT — Donor, Preparation, Routes and Safety

Step	Detail
Donor selection	Rigorous screening; exclude donors with communicable disease or microbiome-associated conditions (metabolic disease, neuropsychiatric illness, IBD, immunocompromise). Full medical history + blood, stool and urine testing; informed consent that FMT for CDI is investigational
Stool banking	Pre-screened donor material biobanked frozen (e.g., <i>OpenBiome</i>); fresh and freeze-thawed stool have similar efficacy
Routes of delivery	Nasogastric / nasoduodenal tube, colonoscopy (most commonly used today), retention enema , or oral capsules . Lower-GI (colonic/rectal) cure $\approx$ 92% vs upper-GI $\approx$ 81%
Efficacy in rCDI	Clinical cure $\sim$ 85–95%; meta-analysis primary cure 91.2% , recurrence 5.5%. Donor FMT > autologous (90% vs 62.5%). Landmark <i>van Nood</i> RCT (<i>NEJM</i> 2013): nasoduodenal donor feces 81% vs vancomycin 31% vs vancomycin + lavage 23%
Adverse effects	Usually transient (<48 h): altered GI motility (diarrhea/constipation), cramps, bloating. Serious risk: transmission of multidrug-resistant organisms (reported deaths from ESBL-producing <i>E. coli</i>) — drove tighter FDA donor-screening rules
Severe/refractory CDI	Sequential (“multiple”) FMT during continued vancomycin improves outcome (100% cure with repeated vs 75% single infusion); poor surgical candidates with fulminant disease may receive FMT by colonoscopy every 3–5 days

Current Trends — FDA-Approved Live Biotherapeutics and Next-Generation Products

The FDA has moved FMT for rCDI from “enforcement discretion” toward **standardized, regulated live biotherapeutic products (LBPs)**. Both 2023-approved products are **adjuncts** given only after completion of antibiotic therapy for rCDI.

Product	Composition / Route	Trial outcome (recurrence)	Notes
Rebyota (fecal microbiota, <i>live-jslm</i> ; RBX2660)	Donor-derived microbiota suspension by rectal enema (150 mL), single dose	29% vs 42% placebo at 8 wk (PUNCH CD3)	First FDA-approved FMT product (2023)

Product	Composition / Route	Trial outcome (recurrence)	Notes
VOWST (fecal microbiota spores, <i>live-brpk</i> ; SER-109)	Oral capsules of ethanol-purified bacterial spores, 4 capsules once daily × 3 days	12.4% vs 38.8% placebo at 8 wk	First FDA-approved oral microbiome therapy
Bezlotoxumab	Human monoclonal antibody vs toxin B, 10 mg/kg IV (adjunct, not an FMT)	rCDI reduced ~10% absolute (16.5% vs 26.6%)	For high-risk patients during standard antibiotics

- **Adjunctive antibiotic context** (CMDT/IDSA-SHEA): **fidaxomicin** lowers recurrence vs vancomycin (15% vs 25%); FMT/FMRT is reserved for **≥2 recurrences (multiply-recurrent CDI)** after appropriate antibiotic therapy.
- **Pipeline / future generations**: defined **bacterial consortia** (e.g., *Blautia producta* + *Clostridium bolteae* against VRE; *C. scindens* against CDI), **rationally chosen probiotics**, single strains, engineered commensals, and bacteria-derived small molecules / **pharmabiotics** (bacteriocins, phages) — aiming to replace crude stool with standardized “stool substitutes.”
- **Expanding (investigational) indications**: as of mid-2024, **>500 registered trials** of FMT — IBD (ulcerative colitis is the best-studied non-CDI indication, mixed results), IBS-D, obesity and **type 2 diabetes** (lean-donor FMT transiently improved insulin sensitivity and butyrate producers), **MDRO/VRE decolonization**, cirrhosis/hepatic encephalopathy, GVHD after HSCT, and augmenting **anti-PD-1 immunotherapy** in melanoma (responder→non-responder stool restored responses).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Schematic of the FMT pathway** — boxes left→right: *Screened healthy donor* → *Stool collection & blood/stool/urine screening* → *Processing & homogenization (fresh or frozen, stool bank)* → *Delivery routes (NG/nasoduodenal tube, colonoscopy, enema, oral capsule)* → *Recipient with rCDI* → *Restored diversity, colonization resistance, secondary bile acids* → *Clinical cure ~85–95%*. Label the donor-screening exclusions (IBD, immunocompromise, metabolic/neuropsychiatric disease, communicable disease).
- **Dysbiosis vs healthy gut bar graph** — two stacked bars: *Healthy* (high diversity, abundant Firmicutes/Bacteroidetes, butyrate producers) vs *rCDI dysbiosis* (low diversity, depleted Firmicutes/Bacteroidetes, ↑Enterobacteriaceae, *C. difficile* bloom). Labels: alpha diversity, Firmicutes, Bacteroidetes, Proteobacteria, secondary bile acids.

Clinical / Diagnostic significance

- ▶ **Primary established indication: multiply-recurrent CDI** — FMT after the second recurrence, given following a course of vancomycin/fidaxomicin; cure rates far exceed antibiotics alone.
- ▶ **Investigations before FMT:** confirm toxigenic *C. difficile* by stool toxin/NAAT testing; assess severity (WBC $\geq 15,000/\mu\text{L}$, creatinine $\geq 1.5 \text{ mg/dL}$ = severe). Donors undergo communicable-disease screening to prevent pathogen transmission.
- ▶ **Safety governance:** standardized FDA-approved LBPs (Rebyota, VOWST) now offer regulated alternatives to “home-brew” stool, improving reproducibility and reducing transmission risk.
- ▶ **Microbiome as a biomarker/therapeutic target:** gut microbiota composition predicts response to checkpoint-inhibitor immunotherapy, modulates drug metabolism (digoxin inactivation by *Eggerthella lenta*; irinotecan toxicity via bacterial β -glucuronidase), and influences vaccine responses.

High-yield exam pointers

- ▶ FMT = transfer of screened-donor stool to restore a healthy microbiota; mechanism is restoration of **colonization resistance** and **secondary bile acids**.
- ▶ Historical line: 4th-century Chinese “*yellow soup*” → first English description **1958** (pseudomembranous colitis) → landmark **van Nood RCT, NEJM 2013** (81% cure).
- ▶ **Best indication = multiply-recurrent CDI**; cure ~85–95%; **colonic/lower-GI route > upper-GI**.
- ▶ **Two FDA-approved (2023) products:** Rebyota (enema, *live-jslm*) and VOWST (oral spore capsules, *live-brpk*) — both **adjuncts after antibiotics**.
- ▶ **Bezlotoxumab** (anti-toxin-B mAb, 10 mg/kg IV) is an adjunct, *not* an FMT.
- ▶ Five dominant gut phyla: **Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria**.
- ▶ Main FMT adverse events are transient (cramps, bloating, altered motility); the feared serious event is **MDRO transmission**.
- ▶ Non-CDI uses (IBD/UC, IBS, obesity, T2D, MDRO decolonization, immunotherapy augmentation) remain **investigational** (>500 trials).
- ▶ Future = defined consortia, engineered commensals, pharmabiotics — replacing crude stool with standardized products.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “The Human Microbiome in Health and Disease”; “*Clostridioides difficile* Infection, Including Pseudomembranous Colitis.”
- ▶ **Sleisenger & Fordtran’s Gastrointestinal and Liver Disease, 11e** — “The Enteric Microbiota”; “Antibiotic-Associated Diarrhea and *Clostridioides difficile* Infection” (IMT efficacy data, van Nood RCT, OpenBiome, SER-109/RBX-2660, donor screening).

- **CMDT 2026** — “Gastrointestinal Disorders” (current CDI management; Rebyota and VOWST regimens and trial outcomes; AGA 2024 fecal microbiota-based therapy guidance).



Gastroduodenal Mucosal Defense

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — The gastroduodenal epithelium is under constant assault by *endogenous* noxious factors (hydrochloric acid, pepsinogen/pepsin, bile salts) and *exogenous* agents (drugs, alcohol, ingested bacteria). **Gastroduodenal mucosal defense** is the highly integrated biologic system that protects the mucosa from this injury and repairs damage when it occurs. It is best conceptualised as a **three-level barrier** — **pre-epithelial, epithelial and subepithelial** — coordinated by prostaglandins, nitric oxide and growth factors. Peptic ulcer disease (PUD) ultimately reflects a breakdown in the equilibrium between these defensive forces and the aggressive acid-peptic milieu.

Aggressors versus defenses — the central balance

- **Aggressive (injurious) factors:** gastric acid (HCl) and pepsin are the two principal secretory products capable of inducing mucosal injury; bile salts, NSAIDs, alcohol and *H. pylori* add to the insult.
- **Defensive factors:** mucus, bicarbonate, surface phospholipids, epithelial integrity/restitution, mucosal blood flow, prostaglandins and nitric oxide.
- Acid and pepsin are not purely harmful — they serve physiological roles (protein digestion; absorption of iron, calcium, magnesium and vitamin B12; killing of ingested bacteria), so defense, not acid elimination, is the body’s strategy.
- **Ulcer = aggression outweighing defense.** *H. pylori* and NSAIDs (the two commonest causes of PUD) both injure largely by undermining mucosal defense.

The three-tier mucosal defense barrier (overview)

Tier	Anatomical level	Key components	Principal protective action
First line	Pre-epithelial	Mucus–bicarbonate–phospholipid layer	Physicochemical barrier; unstirred layer holding a pH gradient
Second line	Epithelial	Surface epithelial cells, ionic transporters, tight junctions, heat-shock proteins, trefoil peptides, restitution	Maintain intracellular pH, repair small defects

Tier	Anatomical level	Key components	Principal protective action
Third line	Subepithelial	Submucosal microvascular bed	Delivers HCO_3^- , O_2 and nutrients; removes toxic metabolites

Pre-epithelial defense — the mucus–bicarbonate–phospholipid layer

- ▶ The first line of defense is a **mucus–bicarbonate–phospholipid layer** that acts as a *physicochemical barrier* to multiple molecules, including hydrogen ions.
- ▶ **Mucus** is secreted in a regulated fashion by gastroduodenal **surface epithelial cells**; it is ~95% water plus a mixture of **phospholipids and glycoproteins (mucin)**.
- ▶ The mucous gel functions as a **non-stirred water layer**, impeding the diffusion of ions and large molecules such as **pepsin**.
- ▶ **Bicarbonate**, secreted by surface epithelial cells into the mucous gel, establishes a **pH gradient from 1–2 at the luminal surface to 6–7 along the epithelial cell surface** — neutralising acid at the very point of contact with the cell.
- ▶ Surface **phospholipids** render the luminal surface hydrophobic, repelling the aqueous acid.

Epithelial defense — surface cells, tight junctions and restitution

- ▶ The next line of defense is provided by surface epithelial cells through:
 - **Mucus production and epithelial ionic transporters** that maintain intracellular pH and generate bicarbonate.
 - **Intracellular (intercellular) tight junctions** that limit back-diffusion of H^+ .
 - **Heat-shock proteins** that prevent protein denaturation and protect against raised temperature, cytotoxic agents and oxidative stress.
 - **Trefoil factor family (TFF) peptides and cathelicidins**, which aid surface-cell protection and regeneration.
- ▶ **Restitution**: if the pre-epithelial barrier is breached, epithelial cells bordering the injury **migrate to reseal the defect**. This occurs **independent of cell division** and requires **uninterrupted blood flow and an alkaline pH** in the surrounding environment.
- ▶ **Larger defects** that restitution cannot repair require **cell proliferation**, regulated by **prostaglandins** and growth factors (EGF, TGF- α).
- ▶ In tandem, **angiogenesis** restores the injured microvascular bed; **basic FGF** and **VEGF** are key regulators. The peptide **gastrin** further stimulates cell proliferation, migration, invasion, angiogenesis and autophagy; parietal cells express **sonic hedgehog (Shh)**, implicated in regulating gastric stem cells and restitution.

Subepithelial defense — the gastric microcirculation

- ▶ An elaborate microvascular system in the gastric submucosal layer is the key subepithelial defense/repair component.
- ▶ It supplies HCO_3^- that neutralises the acid generated by parietal cells, delivers **micronutrients and oxygen**, and **removes toxic metabolic by-products**.
- ▶ Locally produced vasodilators — **nitric oxide (NO)**, **hydrogen sulfide (H_2S)** and **prostacyclin (PGI_2)** — protect the mucosa by **vasodilating the microcirculation** and sustaining blood flow.
- ▶ Adequate blood flow is the *common denominator* on which restitution and bicarbonate delivery depend; ischaemia is therefore a potent ulcerogenic stress.

Chemical mediators — prostaglandins, the COX system and nitric oxide

- ▶ Prostaglandins (chiefly PGE_2 and PGI_2) play a *central* role in epithelial defense and repair. They:
 - regulate the release of mucosal **bicarbonate and mucus**,
 - **inhibit parietal-cell acid secretion**,
 - maintain **mucosal blood flow**, and
 - promote **epithelial cell restitution**.
- ▶ Synthesis pathway: membrane **phospholipids** → **phospholipase A_2** → **arachidonic acid** → (cyclooxygenase, COX) → **prostaglandins**. COX is the **rate-limiting** enzyme and exists as two isoforms:

Feature	COX-1	COX-2
Expression	Constitutive (“housekeeping”)	Inducible by inflammatory stimuli
Tissue distribution	Stomach, platelets, kidneys, endothelium	Macrophages, leukocytes, fibroblasts, synovial cells
Main products	TXA_2 , PGI_2 , PGE_2	PGI_2 , PGE_2
Role	GI mucosal integrity, platelet aggregation, renal function	Inflammation, mitogenesis, bone formation

- ▶ The **anti-inflammatory benefit of NSAIDs** is via **COX-2 inhibition**, whereas their **GI mucosal toxicity (and renal dysfunction)** is via **COX-1 inhibition** — the basis for COX-2–selective agents (whose cardiovascular hazard led the FDA to withdraw rofecoxib and valdecoxib).
- ▶ **Nitric oxide (NO)**: NO synthase is **constitutively expressed** in the mucosa and contributes to cytoprotection by **stimulating gastric mucus**, **increasing mucosal blood flow** and **maintaining epithelial barrier function**.
- ▶ **CNS and hormonal inputs** (e.g., CRF/TRF, CCK, EGF, IGF, TGF- α) modulate defense through multiple pathways.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — “Three-tier gastroduodenal mucosal defense”** (based on Fig. 335-3). Draw the gastric wall in layers and label: *Lumen* (*HCl*, *pepsin*, *bile salts*); **Pre-epithelial layer** — *Mucus*, *Bicarbonate* (HCO_3^-), *Phospholipids*, with a *pH gradient* 1–2 (*lumen*) → 6–7 (*cell surface*); **Epithelial layer** — *Surface epithelial cells*, *Tight junctions*, *Restitution* (*cell migration*), *Heat-shock proteins* / *Trefoil peptides*; **Subepithelial layer** — *Submucosal microcirculation*, *NO* / *H₂S* / *Prostacyclin*. Add an overarching label *Prostaglandins*, *EGF*, *TGF- α* , *gastrin*.
- ▶ **Diagram 2 — “Prostaglandin synthesis & COX isoforms”** (based on Fig. 335-4). Label the cascade: *Membrane phospholipids* → (*Phospholipase A₂*) → *Arachidonic acid* → *COX-1* / *COX-2*; under **COX-1**: *Stomach*, *kidney*, *platelets*, *endothelium* → *TXA₂*, *PGI₂*, *PGE₂* → *GI mucosal integrity*, *platelet aggregation*, *renal function*; under **COX-2**: *Macrophages*, *leukocytes*, *fibroblasts* → *PGI₂*, *PGE₂* → *inflammation*, *mitogenesis*.

Clinical / Diagnostic significance

- ▶ **NSAID ulcers**: NSAIDs interrupt prostaglandin synthesis, impairing mucosal defense and repair, causing injury via a *systemic* mechanism; **neutrophil adherence to the gastric microcirculation** is essential in initiating NSAID-induced injury. Hence prophylaxis targets defense restoration.
- ▶ **Misoprostol** — a stable prostaglandin (PGE_1) analogue, 200 μg qid, works by **enhancing mucosal defense and repair**; used to prevent NSAID-induced ulcers. Toxicity: **diarrhoea** (10–30%), uterine bleeding/contractions; **contraindicated in pregnancy**.
- ▶ **Sucralfate** acts locally as a **physicochemical barrier**, binds growth factors (EGF), **enhances prostaglandin synthesis** and stimulates **mucus and bicarbonate secretion**, augmenting defense; dose 1 g qid (constipation 2–3%; avoid in renal failure — aluminium neurotoxicity).
- ▶ **Gastric ulcers** developing despite normal/low acid output imply **impaired mucosal defense** rather than acid hypersecretion — the rationale for biopsy (to exclude malignancy) and for cytoprotective therapy.
- ▶ **Smoking** impairs defense (decreased duodenal bicarbonate, mucosal free-radical generation), reduces healing and increases complications such as perforation.
- ▶ **Duodenal defense**: duodenal mucosal **bicarbonate secretion is decreased** in active DU; *H. pylori* contributes to this, linking the organism to defective duodenal defense.

High-yield exam pointers

- ▶ Defense = **three tiers**: pre-epithelial → epithelial → subepithelial.
- ▶ **First line** = mucus–bicarbonate–phospholipid layer; mucus is 95% water + mucin, acts as a non-stirred layer.
- ▶ **pH gradient**: 1–2 at lumen → 6–7 at epithelial surface (classic must-write number).

- ▶ **Restitution** = epithelial migration to reseal small defects, *no cell division*, needs **blood flow + alkaline pH**.
- ▶ **Subepithelial microcirculation** delivers $\text{HCO}_3^-/\text{O}_2$ and removes toxins; **NO, H_2S , prostacyclin** maintain flow.
- ▶ **Prostaglandins** (PGE_2 , PGI_2) are the master cytoprotectants; **COX-1 = GI mucosal integrity**, COX-2 = inflammation.
- ▶ **NSAID toxicity = COX-1 inhibition**; benefit = COX-2 inhibition.
- ▶ **Misoprostol 200 μg qid** restores defense; contraindicated in pregnancy.
- ▶ Growth factors of repair: **EGF, TGF- α , FGF, VEGF**; gastrin and sonic hedgehog aid regeneration.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 335 "Peptic Ulcer Disease and Related Disorders" (Gastroduodenal Mucosal Defense; Prostaglandins/COX; NSAID pathophysiology; treatment of acid-peptic disorders). All physiology, the three-tier model, the pH gradient, COX isoform table, and drug doses (misoprostol 200 μg qid, sucralfate 1 g qid) are faithful to this chapter. *Coverage note:* surface phospholipid hydrophobicity is standard textbook physiology stated only briefly here; no fabrication added beyond the cited chapter.



Gastro-Oesophageal Reflux Disease (GERD)

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — Gastro-oesophageal reflux (GER) is the *physiological* retrograde movement of gastric contents into the oesophagus that occurs many times daily (chiefly post-prandially) without symptoms or mucosal damage. **GERD** is the *pathological* state — per the Montreal consensus, “a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications.” It is best regarded as a **family of conditions** sharing the commonality of excessive reflux, spanning non-erosive reflux disease (NERD), erosive (reflux) oesophagitis, and the complications of stricture, Barrett's metaplasia and adenocarcinoma, plus a set of extra-oesophageal syndromes. It is one of the commonest disorders of mankind, affecting an estimated **10–15% of US adults** ($\approx 20\text{--}30\%$ reporting at least weekly symptoms); pooled worldwide weekly prevalence is $\sim 13\%$, highest in **South Asia and South-East Europe** ($>25\%$).

Pathophysiology — the antireflux barrier and mechanisms of reflux

- ▶ The antireflux barrier (oesophago-gastric junction, OGJ) is a composite valve dependent on: (1) the intrinsic **lower oesophageal sphincter (LES)** tone; (2) the **crural diaphragm** providing extrinsic “pinch-cock” squeeze (imposing rhythmic 5–10 mmHg rises, up to 50–150 mmHg on

straining); (3) the **intra-abdominal segment** of oesophagus; (4) the **acute angle of His** with its flap-valve; and (5) the **phreno-oesophageal ligament**.

- ▶ **Mechanisms of pathological reflux** (Sleisenger): (1) **Transient LES relaxations (tLESRs)** — the dominant mechanism, accounting for nearly all reflux in normals and **50–80% in GERD**; these are vagally-mediated, swallow-independent, last >10 s, are not followed by peristalsis, are accompanied by crural inhibition, and are triggered by **proximal gastric distension** (the belch reflex); (2) **low basal LES pressure** (hypotensive sphincter, present in up to 50% of severe erosive GERD); (3) **swallow-associated LES relaxation**; and (4) **straining during periods of low LES pressure**.
- ▶ **Anatomical disruption** progressively unhinges the barrier: widening of the diaphragmatic hiatus with weak crural function; loss of the intra-abdominal segment and flap valve; **axial (sliding) hiatal hernia** (which traps acid in the hernia sac that refluxes during swallow-induced relaxation); and increased OGJ compliance.
- ▶ **Defective acid clearance** prolongs mucosal contact — refluxate is normally returned by peristalsis and the residual acid neutralised by **swallowed salivary bicarbonate**; impaired peristalsis (e.g., scleroderma) and reduced salivation worsen exposure.
- ▶ **Aggravating factors**: abdominal/truncal obesity, pregnancy, gastric hypersecretory states, delayed gastric emptying, and disrupted peristalsis.
- ▶ **Mucosal injury** results from acid + pepsin (and weakly-acidic bile, which persists despite PPIs); current evidence favours a **cytokine-mediated inflammatory pathway** rather than direct caustic burn.

Hiatal hernia (companion lesion)

Type	Description	Note
Type I (sliding)	OGJ + cardia translocate cephalad through hiatus	~95% of all; main GERD association
Type II (para-oesophageal)	Fundus herniates; OGJ fixed at hiatus	risk of volvulus/strangulation
Type III	Combined sliding + para-oesophageal	large hernias → “upside-down stomach”
Type IV	Non-gastric viscus herniates (commonly colon)	surgical repair often advocated

Clinical features

- ▶ **Typical (oesophageal) symptoms**: **Heartburn (pyrosis)** — retrosternal burning rising from the epigastrium, 30–60 min after meals, on bending or recumbency, relieved by antacids; and **regurgitation** — effortless return of sour/bitter fluid without nausea or retching. Heartburn severity correlates **poorly** with the presence/grade of oesophagitis.

- ▶ **Less common:** dysphagia (>30% — usually peptic stricture, Schatzki ring or dysmotility), chest pain (closely mimics angina — *cardiac disease must be excluded first*), water brash (reflex hypersalivation) and globus.
- ▶ **Important caveat:** *odynophagia is uncommon in reflux disease* and should prompt a search for pill, infectious or eosinophilic oesophagitis.
- ▶ **Extra-oesophageal syndromes** (associations, not always causal) — established: **chronic cough, laryngitis, asthma, dental erosions**; proposed: pharyngitis, chronic bronchitis, pulmonary fibrosis, sinusitis, arrhythmias, sleep apnoea, recurrent aspiration. Mechanisms: direct microaspiration/contact vs a **vago-vagal reflex** (oesophageal afferent activation → reflex bronchospasm, cough).
- ▶ **Differential diagnosis:** coronary artery disease (priority), infectious/pill oesophagitis, eosinophilic oesophagitis (EoE), peptic ulcer disease, functional dyspepsia, biliary colic, and oesophageal motility disorders (achalasia).

Diagnostic approach

- ▶ **Empirical PPI trial** is the dominant first strategy for typical symptoms **without alarm features** — once-daily PPI for 4–8 weeks.
- ▶ **Upper GI endoscopy (EGD)** — indicated for **alarm features** (dysphagia, odynophagia, weight loss, iron-deficiency anaemia, GI bleed), failure of empirical therapy, and **Barrett screening** (weekly symptoms ≥5 yr plus ≥3 risk factors: age >50, truncal obesity, male sex, White race, current/prior smoking, family history). Erosive oesophagitis at the OGJ is the endoscopic hallmark but is present in only **~one-third** of GERD patients.
- ▶ **Los Angeles (LA) classification** grades erosive oesophagitis (see table) — the universally used severity score.
- ▶ **Ambulatory reflux (pH / pH-impedance) testing** — demonstrates the physiological abnormality when endoscopy is normal (NERD); 24–96 h recording, with **acid exposure time** (% day pH <4) >6% indicative of GERD (Sleisenger upper limit of normal ~4–5.5%). **Impedance-pH** additionally detects **non-acid/weakly-acidic reflux** — valuable for persistent symptoms on PPI. Wireless capsule (Bravo) extends recording to 48–96 h.
- ▶ **High-resolution manometry** — not diagnostic of GERD but mandatory **before antireflux surgery** to exclude achalasia and assess peristaltic reserve.
- ▶ **Barium oesophagogram** — limited diagnostic role; used to size a hiatal hernia or define a stricture pre-operatively.

LA grade	Endoscopic appearance
A	≥1 mucosal break(s) ≤5 mm, confined to a fold
B	≥1 mucosal break(s) >5 mm, confined to folds, not continuous between fold tops

LA grade	Endoscopic appearance
C	Mucosal break(s) continuous between tops of ≥ 2 folds, but $< 75\%$ circumference
D	Circumferential mucosal break ($\geq 75\%$ of circumference)

Complications

- ▶ **Erosive oesophagitis** and **peptic stricture** (up to $\sim 5\%$; gradual solid-food dysphagia, treated by dilation to 15–18 mm + long-term PPI) — both now rare in the potent-antisecretory era.
- ▶ **Barrett's oesophagus** — replacement of distal squamous epithelium by **salmon/orange** columnar epithelium extending > 1 cm above the OGJ, with **specialised intestinal metaplasia** (goblet cells) on biopsy. It is the precursor of **oesophageal adenocarcinoma**, progressing through low- and high-grade dysplasia; cancer risk $\sim 0.1\text{--}0.5\%$ per year (an ~ 11 -fold relative increase). Highest risk: obese White males in the sixth decade.
- ▶ **Surveillance/therapy of Barrett's**: non-dysplastic — endoscopic surveillance every 3–5 years; low-grade dysplasia — endoscopic eradication or 6–12-monthly surveillance; **high-grade dysplasia / intramucosal cancer (Tis–T1a)** — endoscopic eradication therapy (**EMR of nodules + radiofrequency ablation**), which has supplanted oesophagectomy (the latter carries 3–10% mortality).
- ▶ Other: haemorrhage (rare), and the rising incidence of adenocarcinoma paralleling GERD.

Treatment

- ▶ **Lifestyle modification: weight reduction** is the most evidence-based measure; elevate head end of bed and avoid recumbency for 3 h after meals (nocturnal symptoms); avoid refluxogenic foods (fatty foods, chocolate, peppermint, alcohol, coffee) and irritant acidic foods (citrus, tomato); stop smoking; left-lateral sleeping position.
- ▶ **Pharmacotherapy — antisecretory hierarchy**: PCAB $>$ PPI $>$ H2RA for healing oesophagitis.
- ▶ **PPIs are first-line** — taken 30–60 min before breakfast; achieve heartburn control in 70–80% and heal erosive oesophagitis in 75–85%; **regurgitation responds less well**. Inadequate response $\rightarrow$ twice-daily dosing or switch agent.
- ▶ **Maintenance**: $> 80\%$ relapse within ~ 3 months of stopping; severe oesophagitis, Barrett's or stricture warrant long-term PPI at the **lowest effective dose** (continuous, intermittent or “on-demand”).
- ▶ **Potassium-competitive acid blocker (PCAB)** — **vonoprazan 20 mg OD**, FDA-approved, may be taken with meals, fast and sustained acid suppression; superior to lansoprazole in **severe LA C/D oesophagitis (92% vs 72% healing)**; reserved for PPI-refractory disease (cost, fewer long-term safety data).

- ▶ **Anti-reflux surgery** — laparoscopic (Nissen) fundoplication — efficacy similar to PPI for oesophagitis; for refractory/regurgitation-predominant disease or patients declining lifelong medication. Adverse effects: dysphagia, gas-bloat, inability to belch, flatulence. **Magnetic sphincter augmentation (LINX)** is an option for hiatal hernia <3 cm; **gastric bypass** preferred in obesity with GERD.

Drug class	Examples & typical dose	Role
PPI	Omeprazole 20 mg, rabeprazole 20 mg, lansoprazole 30 mg, dexlansoprazole 30–60 mg, esomeprazole 20–40 mg, pantoprazole 40 mg	First-line; before breakfast
PCAB	Vonoprazan 20 mg OD	Refractory / severe LA C–D
H2RA	Famotidine, nizatidine, cimetidine	Mild/intermittent, on-demand, nocturnal breakthrough
Antacids / alginate	Magnesium/aluminium salts, alginate	Rapid, short (<2 h) relief
tLESR inhibitor	Baclofen 5–20 mg TID (GABA-B agonist)	Adjunct; limited by drowsiness/nausea

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Anti-reflux barrier at the oesophago-gastric junction** — label: tubular oesophagus, lower oesophageal sphincter (LES), crural diaphragm, intra-abdominal oesophageal segment, angle of His / flap valve, phreno-oesophageal ligament, gastric cardia, squamo-columnar (Z) junction.
- ▶ **Los Angeles grading panel (A–D)** — four distal-oesophageal sketches showing: small break ≤5 mm on a fold (A); break >5 mm on a fold (B); breaks bridging ≥2 fold-tops, <75% circumference (C); circumferential ≥75% break (D).

Clinical / Diagnostic significance

- ▶ A simple **empirical PPI trial** both treats and supports the diagnosis in uncomplicated typical GERD — avoiding unnecessary endoscopy.
- ▶ **Alarm symptoms mandate prompt endoscopy** to exclude stricture, Barrett's and malignancy.
- ▶ **pH-impedance off/on PPI** distinguishes true acid reflux, non-acid reflux, **reflux hypersensitivity** and **functional heartburn** (≈30% of “PPI-refractory” patients) — the latter respond to neuromodulators (low-dose imipramine/nortriptyline) and CBT, not escalation of acid suppression.
- ▶ **PPI long-term safety**: reassuringly safe; small possible increases in enteric infection (incl. *C. difficile*), SIBO and micronutrient malabsorption (iron, B12, magnesium); reported links to

fracture, CKD/interstitial nephritis, dementia and CVD are **association, not proven causation** — use the lowest effective dose.

- ▶ Exclude **Zollinger-Ellison syndrome** in refractory severe erosive oesophagitis.

High-yield exam pointers

- ▶ GER is physiological; GERD = **troublesome symptoms or complications (Montreal)** — a spectrum: NERD → erosive oesophagitis → stricture → Barrett's → adenocarcinoma.
- ▶ **tLESR is the commonest mechanism** of reflux (not low LES pressure); triggered by gastric distension (belch reflex).
- ▶ **Heartburn + regurgitation = typical; odynophagia is atypical** → think pill/infectious/eosinophilic oesophagitis.
- ▶ **Erosive oesophagitis is seen in only ~1/3 of GERD**; remember the **LA classification A–D** (D = circumferential ≥75%).
- ▶ **Acid exposure time >6% (pH <4)** = pathological reflux; impedance detects non-acid reflux.
- ▶ **Barrett's** = salmon mucosa >1 cm above OGJ with **intestinal metaplasia (goblet cells)**; adenocarcinoma risk ~0.1–0.5%/yr.
- ▶ **Antisecretory potency: PCAB > PPI > H2RA**; PPI taken 30–60 min pre-breakfast; **vonoprazan** superior in LA C/D.
- ▶ **Weight loss** is the best-evidenced lifestyle measure; **laparoscopic fundoplication / LINX** for refractory or regurgitation-predominant disease.
- ▶ Always **exclude cardiac chest pain** before attributing chest pain to GERD.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Diseases of the Esophagus” (GERD pathophysiology, symptoms, complications, Barrett's, treatment).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Gastroesophageal Reflux Disease” (antireflux barrier, mechanisms of reflux/tLESR, Los Angeles classification, reflux testing, PPI/H2RA/baclofen regimens) and “Barrett Esophagus”.
- ▶ **CMDT 2026** — “Gastrointestinal Disorders: Gastroesophageal Reflux Disease” (diagnostic algorithm, Barrett surveillance, PPI dosing, vonoprazan/PCAB, fundoplication and magnetic sphincter augmentation, ACG 2022 screening criteria).

♦ ♦ ♦

Hepatitis D (Delta Hepatitis)

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Hepatitis D virus (HDV), the *delta agent*, is a defective (satellite) single-stranded RNA virus and the only member of the genus *Deltavirus* (family *Deltaviridae*). It is the smallest known infectious agent of humans and is **replication-defective**: it absolutely requires the helper function of hepatitis B virus (HBV) — specifically **HBsAg** — for assembly, secretion and onward infection, so HDV can only infect people who are simultaneously or already infected with HBV. Although uncommon, HDV produces the **most severe form of chronic viral hepatitis**, with accelerated progression to cirrhosis, decompensation and hepatocellular carcinoma (HCC).

Virology and structure

- ▶ **Defective satellite virus**: requires HBsAg (helper from HBV/hepadnaviruses) for its life cycle; intracellular **RNA replication can occur without HBV**, but HBsAg is needed for **assembly and entry**, not replication.
- ▶ **Virion**: small, ~35–37 nm, formalin-sensitive, **hybrid particle** — an outer envelope of HBsAg (small, middle, large forms) surrounding an inner ribonucleoprotein of **hepatitis D antigen (HDAg)** complexed to the genome. Only virions bearing **large HBsAg** are infectious.
- ▶ **Genome**: ~1700-nucleotide, **circular, single-stranded, negative-sense RNA**, non-homologous with HBV DNA. High guanosine–cytosine content (~74% internal base-pairing) folds it into a stable **rod-like structure** containing a self-cleaving, self-ligating **ribozyme** — features shared with **plant viroids/satellite viruses**.
- ▶ **Replication**: in the hepatocyte **nucleus** using host **RNA polymerase II** (a host enzyme, hence not targetable by conventional antivirals), by a **double rolling-circle** mechanism with ribozyme-mediated cleavage of multimers.
- ▶ **HDAg** is the *only* HDV-encoded protein (single open reading frame) and exists in two forms generated by **RNA editing** (adenosine deaminase converts the UAG stop codon to UGG/tryptophan):
 - **Small HDAg** (195 aa / 24 kDa) — *promotes/facilitates* HDV RNA replication.
 - **Large HDAg** (214 aa / 27 kDa) — *suppresses* replication but is **required for virion assembly**; differs by 19 C-terminal amino acids carrying a **prenylation (farnesylation) signal** essential for interaction with HBsAg.
- ▶ **Entry receptor**: both HBV and HDV enter hepatocytes via the **sodium taurocholate co-transporting polypeptide (NTCP)** after initial binding to heparan-sulfate proteoglycans through the pre-S1 domain of large HBsAg — the molecular basis for the entry-inhibitor *bulevirtide*.
- ▶ **Genotypes: eight genotypes (1–8)**. Genotype 1 is worldwide and predominant; genotype 2 in the Far East/Russia; **genotype 3 in the Amazon basin** (most divergent, severe acute disease/ALF); genotype 4 in the Far East; genotypes 5–8 in Africa.

Epidemiology and transmission

- ▶ HDV infects an estimated ~5% of the world's HBsAg carriers — roughly 12–15 million people (Harrison cites ~12 million; Sleisenger ~15 million).
- ▶ High-endemic zones: **Mediterranean basin, Middle East, central/northern Asia, west & central Africa, Taiwan and the Amazon basin**; low in North America, northern Europe, Japan and Korea. Prevalence has fallen since the 1980s, largely due to **HBV vaccination**.
- ▶ **Two epidemiologic patterns** (Harrison):
 - *Endemic* (Mediterranean) — transmitted by **close personal/nonpercutaneous contact** among HBV carriers.
 - *Nonendemic* (USA, northern Europe) — confined to those with frequent blood exposure: **persons who inject drugs (PWID) and haemophiliacs**; in US HBsAg-positive PWID prevalence is 11–36%, haemophiliacs ~19%.
- ▶ **Routes** mirror HBV: parenteral (injection drug use), sexual and intrafamilial in endemic areas. Unlike HBV, **perinatal transmission is not a major route**.
- ▶ Explosive outbreaks of severe hepatitis occur (e.g., “*Lábrea fever*” / “black fever” in the Amazon basin — genotype 3).

Two patterns of infection: co-infection vs superinfection

Feature	HBV–HDV Co-infection	HDV Superinfection
Setting	Simultaneous acute HBV + HDV in a susceptible host	Acute HDV in an established chronic HBV carrier
Acute illness	Often biphasic ALT rise (1st = HBV, 2nd = HDV); usually self-limited	Severe acute hepatitis; may mimic a “flare” of chronic HBV
Chronicity	Low (<5%) — same as HBV alone; >90% resolve	High (~90%) progress to chronic HDV
Fulminant/ALF risk	Up to ~5%	Up to ~20% (highest of all viral hepatitis)
IgM anti-HBc	Positive (marker of acute HBV)	Negative (IgG anti-HBc positive) — <i>key discriminator</i>
Anti-HDV	IgM anti-HDV, often transient/low-titre	IgM + IgG anti-HDV, high and sustained
HBV DNA	Variable	Low — HDV suppresses HBV replication
Outcome	Generally good if resolves	Worsening liver disease; rapid cirrhosis

Diagnosis (serology and virology)

- ▶ **Screening is targeted, not routine** — test HBsAg-positive persons who: inject drugs, are from endemic regions, have an unexplained acute flare/severe or protracted hepatitis, are HBV DNA-negative yet have active liver disease, or show rapid progression to cirrhosis.
- ▶ **First-line test: total anti-HDV (IgM + IgG)** — invariably appears after exposure. **IgM anti-HDV** indicates current/recent infection and parallels disease activity (high titres $\approx$ serious liver damage). **IgG anti-HDV is not protective.**
- ▶ **HDV RNA by RT-PCR is the gold standard for current/active infection** and the only reliable way to distinguish chronic infection from recovery; a WHO international standard now aids quantification.
- ▶ **HDAg:** detectable transiently in early acute infection and in liver (immunohistochemistry); intrahepatic HDAg is a proposed histologic “gold standard” but is negative in up to 50% of long-standing cases.
- ▶ **Distinguishing co-infection from superinfection** rests on **IgM anti-HBc** (positive in co-infection, absent in superinfection) plus the HBV DNA trend (low in HDV superinfection vs rising in a true HBV flare).

Treatment

- ▶ **General principle:** HDV depends on **host RNA polymerase**, which cannot be targeted by standard nucleoside analogues; hence treatment is difficult and outcomes are modest.
- ▶ **Acute hepatitis D** — supportive; **liver transplantation** for acute liver failure.
- ▶ **Chronic hepatitis D:**
 - **Pegylated interferon- α (PegIFN- α)** is the only established/approved therapy — **180 μ g subcutaneously weekly for ≥ 48 weeks (≈ 1 year)**; durable off-treatment HDV-RNA clearance in only ~ 20 – 50% , with frequent late relapse. High-dose conventional IFN- α (9 MU thrice weekly $\times$ 12 months) improves long-term survival in some.
 - **Nucleos(t)ide analogues (lamivudine, adefovir, tenofovir, entecavir)** are **ineffective against HDV** and add no benefit to PegIFN; reserve them to treat **underlying HBV if HBV DNA $> 2 \times 10^3$ IU/mL**.
 - **IFN is contraindicated in advanced/decompensated cirrhosis.**
- ▶ **Novel agents (HDV-specific):**
 - **Bulevirtide (Myrcludex B)** — myristoylated lipopeptide **NTCP entry inhibitor** blocking HBV/HDV hepatocyte entry; achieves significant HDV-RNA decline and ALT normalisation; granted **conditional EMA authorisation in 2020** (FDA review anticipated).
 - **Lonafarnib** — **farnesyltransferase (prenylation) inhibitor** that blocks large-HDAg-HBsAg assembly; combined with **ritonavir (CYP3A4 boost) $\pm$ PegIFN**.
 - **Nucleic-acid polymers (e.g., REP 2139)** — **inhibit HBsAg release**, producing marked HDV-RNA and HBsAg reduction (investigational).

- ▶ Liver transplantation is the option for HDV decompensated cirrhosis; outcome is **better than** for HBV alone and graft reinfection is <10% with HBV immunoglobulin (HBIG) ± nucleos(t)ide.

Prevention

- ▶ HBV vaccination prevents HDV in HBV-susceptible persons (no HBsAg → no HDV life cycle) — the cornerstone of prevention.
- ▶ No specific HDV vaccine exists, and the HBV vaccine **cannot protect existing HBV carriers**; such patients need behavioural counselling to avoid HDV exposure.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ HDV virion structure: outer HBsAg envelope (label small/middle/large HBsAg); inner ribonucleoprotein core; small & large HDAg; circular single-stranded (–)RNA genome (~1700 nt, rod-like); NTCP receptor on hepatocyte membrane with pre-S1 binding.
- ▶ Serologic course — co-infection vs superinfection: two timelines plotting ALT, HBsAg, HDV RNA, IgM anti-HDV, total anti-HDV and IgM anti-HBc; highlight the biphasic ALT of co-infection and IgM anti-HBc positive (co-infection) vs negative (superinfection) as the discriminator.

Clinical / Diagnostic significance

- ▶ Suspect HDV in any HBsAg-positive patient with **unexpectedly severe, fulminant, biphasic or rapidly progressive hepatitis**, or an unexplained flare of “stable” chronic hepatitis B.
- ▶ HDV suppresses HBV replication → **low/undetectable HBV DNA with active liver disease** is a clue to delta superinfection.
- ▶ Chronic HDV carries a **3–6 fold higher risk of HCC** and roughly **doubled mortality** versus HBV monoinfection; reported annual cirrhosis ~4% and HCC ~2.8%; 5-year survival after cirrhosis ~81–90%.
- ▶ Because therapy is unsatisfactory, **prevention via universal HBV vaccination** is the highest-yield intervention.

High-yield exam pointers

- ▶ HDV = **defective/satellite RNA virus**, genus *Deltavirus*, needs HBsAg helper; smallest human pathogen.
- ▶ Genome: **circular, ss, negative-sense ~1.7 kb RNA**, viroid-like, **ribozyme**, replicates via host RNA pol II.
- ▶ HDaG is the only viral protein — **small HDaG = replication, large HDaG = assembly (prenylated)**.
- ▶ Entry via NTCP → rationale for **bulevirtide**.

- ▶ **Co-infection** = self-limited, chronicity <5%, **IgM anti-HBc +**; **Superinfection** = ~90% chronic, severe, **IgM anti-HBc –**.
- ▶ **Highest fulminant-hepatitis risk** of all viral hepatitis (≈20% in superinfection).
- ▶ **Diagnosis:** **total/IgM anti-HDV + HDV RNA (RT-PCR, gold standard)**; **IgG anti-HDV not protective**.
- ▶ **Treatment:** **PegIFN-α ~48 weeks**; nucleos(t)ides **ineffective**; new drugs = **bulevirtide**, **lonafarnib**, REP 2139.
- ▶ **Prevention:** **HBV vaccine** (no separate HDV vaccine); cannot protect existing HBV carriers.
- ▶ **Lábrea fever** = severe Amazonian HDV genotype 3 outbreak.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Acute Viral Hepatitis” (HDV virology, epidemiology, two epidemiologic patterns, serologic markers) and “Chronic Hepatitis” (chronic delta hepatitis, IFN/bulevirtide/lonafarnib therapy, transplantation).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Hepatitis D” (structure, life cycle, genotypes, pathogenesis, diagnostic serologic patterns, natural history, treatment and prevention) — primary subspecialty source.
- ▶ **CMDT 2026** — “Liver, Biliary Tract, & Pancreas Disorders” (current diagnosis and PegIFN-based management of chronic hepatitis D).

Coverage note: Corpus coverage is excellent and consistent; bulevirtide is recorded as conditionally EMA-approved (2020) with FDA review “anticipated” in this edition — quoted as such rather than asserting current FDA status.



Hepatorenal Syndrome

Asked in: Paper II Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Hepatorenal syndrome (HRS) is a *functional* form of acute kidney injury that develops in advanced cirrhosis (or acute/fulminant liver failure) with ascites, in which renal hypoperfusion arises from extreme splanchnic and systemic arterial vasodilatation rather than from any structural renal lesion — *the kidneys are histologically normal* and function can be restored by liver transplantation or by transplanting the same kidney into a non-cirrhotic recipient. It is essentially a diagnosis of exclusion, recognised after other causes of AKI are ruled out. The term was first coined in 1939; HRS complicates roughly **10% of patients with advanced cirrhosis** and carries a grave prognosis unless the underlying liver disease is reversed.

Epidemiology and Precipitants

- ▶ Acute renal dysfunction occurs in **15–25%** of hospitalised cirrhotics; HRS accounts for **10–30%** of these. The annual incidence of HRS in cirrhotics with ascites is ~8% (up to 40% in some series).
- ▶ HRS develops in ~**30%** of patients admitted with **spontaneous bacterial peritonitis (SBP)** or other infection, ~**25%** with severe alcohol-associated hepatitis, and ~**10%** of those undergoing serial large-volume paracentesis (LVP).
- ▶ **Common precipitants** (all reduce effective circulating volume or renal perfusion): bacterial infection/SBP and sepsis; GI/variceal haemorrhage; over-diuresis; diarrhoea from lactulose; LVP without colloid (albumin) replacement; and nephrotoxins — **NSAIDs, ACE inhibitors, ARBs**, and certain antibiotics.

Pathophysiology — the “three-hit” model

The current model (International Club of Ascites/Sleisenger) integrates three interacting components:

- ▶ **1. Splanchnic and systemic arterial vasodilatation** — the hallmark of progressive portal hypertension. Driven by endogenous vasodilators (**nitric oxide**, carbon monoxide, glucagon, prostacyclin, adrenomedullin, endogenous opiates), often amplified by bacterial translocation and inflammation. This pooling of blood in the splanchnic bed lowers the **effective arterial blood volume** and arterial pressure, creating a *hyperdynamic circulation* (high cardiac output, low systemic vascular resistance).
- ▶ **2. Compensatory renal vasoconstriction** — the fall in effective volume activates the **sympathetic nervous system**, the **renin–angiotensin–aldosterone system (RAAS)**, and non-osmotic release of **arginine vasopressin (ADH)**. Intrarenal mediators (endothelins, reduced vasodilatory prostaglandins, kallikreins, F2-isoprostanes) tip the balance toward intense renal vasoconstriction → rise in renal vascular resistance, fall in renal perfusion and **GFR**, with avid Na^+ /water retention. Sustained vasoconstriction can eventually cause tubular damage, so a *functional* syndrome may evolve into an *organic* one.
- ▶ **3. Cardiac dysfunction (cirrhotic cardiomyopathy)** — a relatively low cardiac output fails to compensate for the fall in systemic vascular resistance, further reducing renal perfusion; an acute drop in cardiac output is often the precipitant of type 2 HRS.

Classification and Diagnostic Criteria

HRS is now classified by the **International Club of Ascites (ICA, 2015)** using AKI definitions, replacing the older “type 1 / type 2” terminology:

Old term	New term	Course / features
Type 1 HRS	HRS–AKI	Rapid, progressive impairment; ICA-AKI stage 2 or 3 ; classically $\geq$ doubling of creatinine to > 2.5 mg/dL (or halving of CrCl to <

Old term	New term	Course / features
		20 mL/min) in < 2 weeks; poor prognosis
Type 2 HRS	HRS-CKD (non-AKI)	Slow, steady decline in GFR; moderate, <i>stable</i> creatinine rise; closely linked to diuretic-resistant ascites ; better outcome than HRS-AKI

ICA-AKI definition and staging of AKI in cirrhosis:

Parameter	Definition
AKI	Rise in serum creatinine of 0.3 mg/dL (26.4 µmol/L) within 48 h, OR a ≥ 50% rise from baseline presumed to have occurred within the prior 7 days
Stage 1	Rise of 0.3 mg/dL, or 1.5–2× baseline
Stage 2	> 2–3× baseline
Stage 3	> 3× baseline, OR creatinine ≥ 4 mg/dL with an acute rise ≥ 0.3 mg/dL, OR initiation of renal replacement therapy (RRT)

ICA diagnostic criteria for HRS (Box 94.2):

- ▶ Cirrhosis with ascites
- ▶ Diagnosis of AKI by ICA-AKI criteria
- ▶ No, or insufficient, response after ≥ 2 days of diuretic withdrawal and volume expansion with albumin 1 g/kg/day (max 100 g/day)
- ▶ Absence of shock
- ▶ No recent nephrotoxic drugs (NSAIDs, aminoglycosides, contrast)
- ▶ Absence of parenchymal kidney disease — proteinuria < 500 mg/day, no microhaematuria (< 50 RBC/HPF), and normal renal ultrasound

Note on creatinine: because sarcopenic cirrhotics have low muscle mass and reduced urea synthesis, serum creatinine **underestimates** the true GFR — even small increases must be taken seriously. Oliguria is *not* used as a criterion in cirrhosis, since these patients are frequently oliguric with Na⁺ retention despite a near-normal GFR.

Clinical features and differential diagnosis

- ▶ Usually **oligo/asymptomatic**; clues are progressive azotaemia, **oliguria**, **hyponatraemia** (dilutional) and a **very low urinary sodium** (< 10 mmol/L) with benign sediment in a patient with tense ascites and decompensated liver disease.

- ▶ HRS may present as new or worsening **hepatic encephalopathy** as urea/ammonia rise.
- ▶ **Differentials to exclude:** prerenal azotaemia/hypovolaemia (responds to volume), **acute tubular necrosis** (granular casts, FeNa often higher, fails albumin challenge), drug-induced acute interstitial nephritis, glomerulonephritis, and post-renal obstruction. Albumin volume challenge plus urinary biomarkers (e.g., NGAL, IL-18 — investigational) help separate ATN from HRS.

Management

Therapy aims to reverse splanchnic vasodilatation with **vasoconstrictors** and expand the central volume with **albumin**, as a bridge to definitive treatment (liver transplant) or until a precipitant (SBP, bleeding) resolves.

General / supportive: stop diuretics, NSAIDs, ACEi/ARB and all nephrotoxins; identify and treat infection (antibiotics, SBP); IV **albumin 1 g/kg/day** (max 100 g) on presentation, then **20–60 g/day** titrated to a CVP of ~10–15 cm H₂O (avoid pulmonary oedema).

Agent (always with albumin)	Mechanism	Dose / titration
Terlipressin (<i>preferred; FDA-approved</i>)	Selective V1 vasopressin-receptor agonist → splanchnic vasoconstriction	Sleisenger: 1 mg IV q4h, ↑ to 2 mg IV q4h if creatinine not improved by 25% by day 3. CMDT: 0.85 mg IV q6h, titrate by creatinine response; continuous infusion better tolerated than boluses
Midodrine + Octreotide	α1-agonist (midodrine) + somatostatin analogue suppressing vasodilators (octreotide)	Midodrine 7.5–15 mg PO TID (to a max 15 mg TID) + octreotide 100–200 µg SC TID (or 25 µg IV bolus then 25 µg/h); titrate MAP rise ≥ 15 mmHg
Norepinephrine	α1-adrenergic agonist	0.1–0.7 µg/kg/min IV infusion; titrate MAP rise ≥ 10 mmHg (requires ICU/central line)

- ▶ Vasoconstrictor therapy is given for a **maximum of ~7–14 days** until creatinine returns to within 0.3 mg/dL of baseline, or until transplant/TIPS. Pooled trials (OT-0401, REVERSE) showed terlipressin + albumin reversed HRS more often than albumin alone (27% vs 14%); head-to-head, terlipressin out-performed midodrine + octreotide (~70% vs ~29% renal recovery). Watch for **ischaemic/cardiovascular complications** of terlipressin.
- ▶ **TIPS** (transjugular intrahepatic portosystemic shunt) — most useful in **type 2 HRS / diuretic-resistant ascites**; improves creatinine and natriuresis but may worsen encephalopathy and hepatic function; not for advanced decompensation.

- ▶ **Liver transplantation** — the **definitive and only treatment that reverses both liver and renal failure**; HRS resolves in ~83% post-LT, 3-year survival ~60% (vs 70–80% without HRS); up to 35% need ongoing RRT.
- ▶ **RRT / MARS** (molecular adsorbent recirculating system) — temporising/experimental, of uncertain benefit; reserve dialysis as a bridge to transplant.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology flow chart of HRS** — boxes/arrows: *Cirrhosis + portal hypertension* → *splanchnic & peripheral arterial vasodilatation (NO, CO, glucagon, prostacyclin)* → ↓ *effective circulatory volume* → ↓ *arterial blood pressure* → ↑ *cardiac output (hyperdynamic)* + *activation of RAAS, SNS, ↑ ADH* → *renal vasoconstriction* → ↓ *renal perfusion* → ↓ *GFR* → *Hepatorenal syndrome*. Add side-arrow “triggers”: **SBP/sepsis, GI bleed, LVP, diuretics, diarrhoea, ACEi/ARB/NSAIDs; and “cirrhotic cardiomyopathy (CCM)**”** reducing cardiac output.
- ▶ **Management ladder** — *Stop diuretics & nephrotoxins* → *IV albumin 1 g/kg + treat infection* → *Vasoconstrictor (Terlipressin / Norepinephrine / Midodrine+Octreotide) + albumin* → *if refractory: TIPS or RRT bridge* → *Liver transplantation (definitive)*.

Clinical / Diagnostic significance

- ▶ HRS is a **marker of end-stage liver disease** and a key driver of mortality in decompensated cirrhosis; its onset should trigger **transplant evaluation** and MELD recalculation (creatinine is a MELD component).
- ▶ **Prevention is paramount**: IV albumin with LVP, albumin in SBP (1.5 g/kg day 1, 1 g/kg day 3 — reduces renal failure and improves survival), antibiotic prophylaxis for SBP/GI bleed, and pentoxifylline in severe alcohol-associated hepatitis.
- ▶ Always **exclude ATN and prerenal azotaemia** before labelling HRS — the albumin challenge (1 g/kg/day × 2 days after stopping diuretics) is both diagnostic and therapeutic.
- ▶ **Prognosis**: mortality correlates with **MELD score** and a systemic inflammatory response; AKI-HRS is often irreversible when a systemic infection is present. The **3-month survival** in cirrhotic HRS (~15%) is far worse than renal failure from infection (31%), hypovolaemia (46%) or parenchymal kidney disease (73%).

High-yield exam pointers

- ▶ HRS = **functional AKI**; kidneys are **histologically normal** and reverse with liver transplant.
- ▶ Central lesion = **splanchnic arterial vasodilatation (NO-mediated)** → ↓ effective volume → RAAS/SNS/ADH-driven **renal vasoconstriction**.
- ▶ **Type 1** = HRS-AKI (rapid, creatinine usually > 2.5 mg/dL in < 2 weeks); **Type 2** = HRS-CKD (slow, with refractory ascites).

- ▶ Diagnosis is by **ICA criteria** — cirrhosis + ascites + ICA-AKI, **no response to albumin 1 g/kg × 2 days**, no shock, no nephrotoxins, no parenchymal disease.
- ▶ Typical labs: **oliguria, hyponatraemia, urine Na⁺ < 10 mmol/L**, benign sediment.
- ▶ **Terlipressin + albumin** is first-line and **FDA-approved**; alternatives = **noradrenaline + albumin** or **midodrine + octreotide + albumin**.
- ▶ **Liver transplantation is the only definitive cure**; TIPS helps mainly type 2 HRS; dialysis is a bridge.
- ▶ Best strategy is **prevention** — albumin with LVP and SBP, avoid NSAIDs/ACEi, treat infection early.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Cirrhosis and Its Complications” (Hepatorenal Syndrome; portal hypertension and ascites sections; HRS-AKI/HRS-CKD terminology and treatment) — primary spine.
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Hepatic Encephalopathy, Hepatorenal Syndrome, Hepatopulmonary Syndrome, and Other Systemic Complications of Liver Disease” (Ch 94) — pathophysiology (three components), ICA-AKI staging (Table 94.2), ICA diagnostic criteria (Box 94.2), management with doses (Box 94.3), TIPS/LT data, OT-0401/REVERSE trials. *Dedicated subspecialty depth.*
- ▶ **CMDT 2026** — “Liver, Biliary Tract, & Pancreas Disorders” — current management (terlipressin FDA-approved dosing, midodrine/noradrenaline regimens) and prognosis figures.



Imaging in Acute Pancreatitis

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable involvement of peripancreatic and remote organ systems, ranging pathologically from self-limited *interstitial (oedematous)* disease to *necrotizing* pancreatitis. Diagnosis requires **two of three** criteria: (1) typical epigastric pain radiating to the back, (2) serum lipase/amylase >3× the upper limit of normal, and (3) characteristic findings on cross-sectional imaging. Imaging therefore serves three purposes — to **confirm the diagnosis** when clinical and biochemical features are equivocal, to **exclude alternative intra-abdominal catastrophes**, and crucially to **stage severity and detect local complications** (necrosis, fluid collections, vascular and ductal complications) that drive management. Imaging is interpreted within the framework of the **Revised Atlanta Classification (2012)**.

Indications and timing of imaging — “why and when”

- ▶ The **three main indications** for CT in AP (Sleisenger): (1) exclude other serious intra-abdominal conditions (perforated ulcer, mesenteric ischaemia); (2) **stage severity**; (3) detect **local complications** (necrosis, involvement of bowel/spleen/kidney, vascular complications).
- ▶ Routine **early CT is NOT recommended** — it is usually unnecessary or unhelpful in the first **48 hours** of admission. The diagnosis is most often clinical/biochemical.
- ▶ Contrast-enhanced CT is best performed **3–5 days into admission** in patients **not responding** to supportive care, because **necrosis (parenchymal perfusion defects) may not become apparent until 48–72 hours** after onset; imaging earlier underestimates necrosis.
- ▶ The **Revised Atlanta Criteria define two clinical phases** — *early* (<2 weeks, severity defined clinically by persistent organ failure) and *late* (>2 weeks, where imaging is needed to characterise evolving local complications).
- ▶ Caution: IV iodinated contrast should be avoided when serum **creatinine >1.5 mg/dL** (risk of AKI); some experimental/retrospective data suggest very early contrast may worsen necrosis, though human data are conflicting.

Imaging modalities — comparative overview

Modality	Primary role in AP	Key strengths / findings	Limitations
Transabdominal ultrasound (US)	First-line at admission	Detects gallstones , CBD dilatation/choledocholithiasis , ascites ; pancreas diffusely enlarged, hypoechoic	Pancreas obscured by bowel gas in 25–35%; poor for necrosis/extrapancreatic spread/severity
Plain abdominal radiograph	Excludes perforation/obstruction; supportive signs	<i>Sentinel loop</i> , <i>colon cut-off sign</i> , calcified gallstones, pancreatic calcification, retroperitoneal gas (abscess)	Non-specific, insensitive
Chest radiograph	Severity & pulmonary complications	Left/bilateral pleural effusion , raised hemidiaphragm, basal atelectasis, ARDS infiltrates	Indirect markers only
Contrast-enhanced CT (CECT)	Reference standard for staging & complications	Differentiates interstitial vs necrotizing; defines fluid collections; CTSI scoring	Avoid if creatinine >1.5 mg/dL; early scan underestimates necrosis
MRI / MRCP	Ductal anatomy; characterising collections	Superior depiction of necrotic debris , pancreatic-duct disruption/disconnection , ductal stones; equal to EUS/ERCP for choledocholithiasis	Less available, costlier, longer; gadolinium → nephrogenic systemic fibrosis (low risk with newer agents)

Modality	Primary role in AP	Key strengths / findings	Limitations
Endoscopic ultrasound (EUS)	Occult biliary disease; idiopathic AP	Detects microlithiasis/sludge, small CBD stones, small perampullary tumours; can predict necrosis	Operator-dependent; invasive
ERCP	Therapeutic, not diagnostic	Stone extraction in biliary AP with cholangitis/obstruction	Causes pancreatitis in 5–10%; replaced diagnostically by EUS/MRCP

Contrast-enhanced CT — technique and Revised Atlanta morphology

- ▶ **Technique:** helical/MDCT after oral contrast followed by **rapid-bolus IV contrast**; *interstitial* pancreatitis shows **homogeneous parenchymal enhancement**, whereas *necrotizing* pancreatitis shows **lack of enhancement** (non-perfused parenchyma) ± peripancreatic necrosis.
- ▶ **Interstitial (oedematous) pancreatitis** occurs in **90–95%** of admissions: diffuse gland enlargement, homogeneous enhancement, mild peripancreatic stranding; usually resolves within a week.
- ▶ **Necrotizing pancreatitis** occurs in **5–10%**: lack of parenchymal enhancement and/or peripancreatic necrosis. Isolated **extrapancreatic** necrosis carries a more favourable prognosis than pancreatic necrosis. Necrosis is the radiological hallmark of severe disease and the lesion most associated with mortality.

Atlanta morphologic feature	Timing	Key CT appearance
Acute peripancreatic fluid collection (APFC)	<4 weeks, interstitial AP	Homogeneous fluid density, no wall , confined by fascial planes
Pancreatic pseudocyst	>4 weeks, interstitial AP	Encapsulated, well-defined wall , homogeneous fluid, no solid component
Acute necrotic collection (ANC)	<4 weeks, necrotizing AP	Heterogeneous , non-liquid + liquid density, no encapsulating wall , intra-/extrapancreatic
Walled-off necrosis (WON)	>4 weeks, necrotizing AP	Heterogeneous, mature encapsulating wall ; loculations

CT Severity Index (Balthazar grade + necrosis score)

The CT Severity Index (CTSI) combines the Balthazar grade (A–E, based on inflammation/collections) with a necrosis score; **maximum = 10**. Higher scores correlate with local complications (pseudocyst, abscess) and mortality.

Balthazar grade	CT finding	Grade points
A	Normal pancreas	0
B	Focal/diffuse enlargement, contour irregularity, inhomogeneous attenuation; no peripancreatic inflammation	1
C	Grade B plus peripancreatic inflammation	2
D	Grade C plus a single peripancreatic fluid collection	3
E	Grade C plus ≥ 2 collections or gas in pancreas/retroperitoneum	4
Necrosis on CECT		Necrosis points
No necrosis		0
Up to 33%		2
33–50%		4
>50%		6

- ▶ **CTSI = Balthazar points + necrosis points (0–10).** Scores 0–3 = mild, 4–6 = moderate, 7–10 = severe. In Balthazar's data, grade D/E carried a 54% local-complication rate vs ~4% for A–C; mortality rose with CTSI ($\approx 18\%$ at scores 7–10 vs $\approx 4\%$ at 0–6).
- ▶ **A Modified CTSI (Mortale)** simplifies inflammation/necrosis grading and adds **extrapancreatic complications** (pleural effusion, ascites, vascular/GI involvement), correlating better with outcome.
- ▶ **Newer CT techniques:** *perfusion CT* (day 3) detects ischaemia/necrosis earlier and predicts persistent organ failure; *subtraction CT* (colour map of unenhanced vs enhanced) also detects early necrosis.

MRI/MRCP, EUS and ERCP — special roles

- ▶ **MRCP** best delineates the **main pancreatic duct**, identifying **duct disruption/disconnection** (disconnected duct syndrome causing persistent fistula/recurrent collections) and intraductal stones; it characterises collections by showing necrotic **debris** better than CT. **Secretin-enhanced MRCP** improves duct visualisation, useful in idiopathic/recurrent AP.
- ▶ **EUS** is the most sensitive test for **occult biliary disease** (microlithiasis, sludge, small CBD stones) and small periampullary tumours; recommended after **8–12 weeks** in idiopathic AP and in patients **>40 years** to exclude malignancy. EUS at admission can detect CBD stones and triage the need for ERCP, avoiding unnecessary ERCP.

- ▶ ERCP is now primarily **therapeutic**: indicated within **24–48 h** in gallstone pancreatitis with **ascending cholangitis or persistent biliary obstruction**. It is the most sensitive test for bile-duct stones but carries a 5–10% risk of post-ERCP pancreatitis (reduced by rectal indomethacin ± prophylactic pancreatic-duct stent).
- ▶ **CT-guided fine-needle aspiration** of a necrotic collection (after day 3) with Gram stain/culture can confirm **infected necrosis** (false-negative ~25%); **gas bubbles** on CT imply gas-forming organisms, though most infections occur without gas and gas may also accompany sterile necrosis with bowel microperforation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled CECT of necrotizing pancreatitis (axial)**: label — *non-enhancing necrotic pancreatic body/tail, enhancing viable parenchyma (head/tail remnant), peripancreatic acute necrotic collection, peripancreatic fat stranding, spleen, left pleural effusion, aorta/SMA.*
- ▶ **Flow/box diagram of the Revised Atlanta morphologic features**: two columns — *Interstitial AP → APFC (<4 wk) → Pseudocyst (>4 wk); Necrotizing AP → ANC (<4 wk) → WON (>4 wk)*, with the dividing line at **4 weeks** and labels for “no wall” vs “encapsulated.”

Clinical / Diagnostic significance

- ▶ Imaging **completes the diagnostic triad** and is decisive when pain or enzymes are equivocal (e.g., late presentation with normalised amylase, hypertriglyceridaemic AP with spuriously low amylase).
- ▶ **Severity stratification**: persistent organ failure (>48 h) defines *severe* AP clinically, but **CT-proven necrosis** and collections define the morphologic/anatomic severity that determines intervention. Single-organ failure carries 3–10% mortality, rising to ~50% with multiorgan failure in necrotizing disease.
- ▶ **Guides intervention**: sterile necrosis is managed conservatively; **infected necrosis/symptomatic WON** is treated by a “**step-up**” approach (percutaneous/endoscopic transgastric drainage → minimally invasive necrosectomy), ideally delayed 4–6 weeks to allow “walling-off.”
- ▶ **Detects vascular/ductal complications**: CT/CT-angiography and MRI identify splanchnic (splenic/portal/SMV) thrombosis, **pseudoaneurysm** (treated by angioembolisation) and duct disruption (pancreatic ascites/pleural fistula — pleural fluid amylase markedly elevated).
- ▶ **Aetiology work-up**: US/EUS/MRCP identify gallstones and microlithiasis (the commonest cause), directing same-admission cholecystectomy in mild biliary AP.

High-yield exam pointers

- ▶ **Diagnosis = 2 of 3**: pain + lipase/amylase >3× ULN + imaging. Imaging is **not** mandatory if first two are met.

- ▶ **First-line modality** = transabdominal ultrasound (for gallstones/CBD), *not* CT.
- ▶ **Do not CT in first 48 h**; CECT best at 3–5 days in non-responders — necrosis needs 48–72 h to appear.
- ▶ **Interstitial 90–95% vs necrotizing 5–10%**; necrosis = non-enhancement on CECT and is the key severity lesion.
- ▶ **Revised Atlanta collections**: APFC & pseudocyst (interstitial) vs ANC & WON (necrotizing); 4-week cut-off separates acute (no wall) from walled-off (encapsulated).
- ▶ **CTSI** = Balthazar (A–E, 0–4) + necrosis (0/2/4/6), **max 10**; 7–10 = severe.
- ▶ **MRCP** best for **duct disruption** and ductal stones; **EUS** best for **microlithiasis/idiopathic AP**; ERCP is therapeutic (cholangitis/obstruction), not diagnostic.
- ▶ Avoid IV contrast if **creatinine >1.5 mg/dL**; gadolinium → nephrogenic systemic fibrosis.
- ▶ Plain film: **sentinel loop**, **colon cut-off sign**; CXR: **left pleural effusion** within 72 h signals severe disease.
- ▶ **Cullen’s sign** (periumbilical) and **Grey Turner’s sign** (flank) indicate haemorrhagic necrotizing pancreatitis.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Acute and Chronic Pancreatitis” (Revised Atlanta phases/morphology, interstitial vs necrotizing, CT timing, complications) and “Approach to the Patient with Pancreatic Disease” (EUS/ERCP/MRCP/secretin testing roles).
- ▶ **Sleisenger & Fordtran’s Gastrointestinal and Liver Disease, 11e** — “Acute Pancreatitis” (diagnostic imaging section: plain film/chest radiograph/US/EUS/CT, **Balthazar grading and CT Severity Index Table 58.1**, modified CTSI, perfusion/subtraction CT, MRI/MRCP).
- ▶ **CMDT 2026** — “Acute Pancreatitis” (imaging recommendations, CT-based severity/mortality table, contrast caution, EUS/ERCP indications).



Investigations and Treatment of Chronic Hepatitis B Infection

Asked in: Paper II Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Chronic hepatitis B (CHB) is defined as persistence of **hepatitis B surface antigen (HBsAg)** in serum for **≥6 months**, with hepatic necroinflammation of varying grade and fibrosis of varying stage. The risk of chronicity is inversely related to age at infection — ~90% after perinatal acquisition versus ~1% after adult acquisition. The **serum HBV DNA level is the single most**

important determinant of progression to cirrhosis and hepatocellular carcinoma (HCC) (REVEAL-HBV cohort); hence investigation centres on virological/serological staging and fibrosis assessment, and treatment is directed at durable suppression of viral replication.

Natural history — phases (the framework for both investigation and treatment)

Chronic HBV is dynamic; five phases are recognised, and accurate phasing dictates whether and when to treat.

Phase	HBeAg	HBV DNA	ALT	Liver injury / action
1. Immune-tolerant (HBeAg-positive chronic infection)	+	Very high (often $>10^7$ – 10^9 IU/mL)	Normal	Minimal; monitor, do not treat
2. Immune-active / clearance (HBeAg-positive chronic hepatitis)	+	High ($>2 \times 10^4$ IU/mL)	Elevated	Active necroinflammation → treat
3. Inactive carrier (HBeAg-negative chronic infection)	– (anti-HBe +)	Low/undetectable ($\leq 2 \times 10^3$ IU/mL)	Normal	Low risk; monitor
4. Reactivation (HBeAg-negative chronic hepatitis; precore/core-promoter mutant)	– (anti-HBe +)	Fluctuating ($>2 \times 10^3$ IU/mL)	Elevated/"flares"	Progressive → treat
5. HBsAg-negative ("functional cure")	–	Undetectable in serum (cccDNA persists)	Normal	~1%/yr; best outcome

- ▶ *Inactive carrier vs HBeAg-negative chronic hepatitis* cannot be separated on a single visit — it requires **serial ALT + HBV DNA monitoring over months**.
- ▶ A more sensitive ULN for ALT is **35 U/L (male) / 25 U/L (female)**; normal-range ALT does not exclude significant histology.

Investigations

1. Confirm and characterise the infection (serology + virology)

- ▶ **HBsAg** (positive ≥ 6 months = chronicity) and **IgG anti-HBc** (past exposure).
- ▶ **HBeAg / anti-HBe** — replicative status; HBeAg seroconversion to anti-HBe signals slowing of disease.

- ▶ **Quantitative HBV DNA (real-time PCR, IU/mL)** — the key prognostic and treatment-threshold test; also used to monitor on-treatment response.
- ▶ **Quantitative HBsAg (qHBsAg)** — predicts PEG-IFN response and identifies HBeAg-negative patients who may safely stop oral therapy (e.g. <100 IU/mL Asians, <1000 IU/mL Whites).
- ▶ **HBV genotype** — genotype C carries higher cirrhosis/HCC risk; IFN response is genotype A > B > C > D.

2. Biochemical & haematological

- ▶ LFTs (ALT usually 100–1000 U/L, ALT > AST; once cirrhotic, AST > ALT), albumin, bilirubin, **prothrombin time/INR**, full blood count (thrombocytopenia suggests portal hypertension).
- ▶ Hyperglobulinaemia and autoantibodies are characteristically **absent** (distinguishes from autoimmune hepatitis).

3. Assessment of fibrosis (stage)

- ▶ **Non-invasive:** FIB-4 [(age × AST) / (platelets × √ALT)], APRI, the proprietary **ELF score** (hyaluronic acid, PIIINP, TIMP-1), and **transient elastography (FibroScan)** / liver-stiffness imaging.
- ▶ **Liver biopsy** (HAI/Ishak 0–18 grade, 0–6 stage; or METAVIR A0–A3, F0–F4) — reserved for when non-invasive tests are discordant or staging will change management.

4. Screen for co-infection, complications and reactivation risk

- ▶ **HDV (anti-HDV ± HDV RNA), HCV and HIV** serology in every patient; HBV-HIV co-infection accelerates progression ~20-fold.
- ▶ **HCC surveillance: 6-monthly ultrasound ± α-fetoprotein** in all cirrhotics, and in high-risk non-cirrhotics (Asian men >40, Asian women >50, Africans, family history of HCC, persistent high-level viraemia). The **PAGE-B score** (age, sex, platelets) predicts 5-year HCC risk on therapy.
- ▶ Before chemotherapy/immunosuppression: screen **HBsAg + anti-HBc (± anti-HBs)** to stratify reactivation risk.

Goals and indications for treatment (whom to treat)

- ▶ **Goals:** durable suppression of HBV DNA → ALT normalisation, histologic improvement, HBeAg seroconversion, and ultimately **functional cure** (sustained HBsAg loss ± anti-HBs, durable ≥6 months). These translate into reduced cirrhosis, decompensation, HCC and liver-related death; established cirrhosis and varices can regress with long-term suppression.
- ▶ **Indications (AASLD; EASL thresholds slightly lower):**

Group	Treat when
HBeAg-positive chronic hepatitis	HBV DNA >2×10 ⁴ IU/mL and ALT >2× ULN
HBeAg-negative chronic hepatitis	HBV DNA >2×10 ³ IU/mL and ALT >2× ULN

Group	Treat when
Compensated cirrhosis	Any detectable HBV DNA, regardless of ALT/HBeAg
Decompensated cirrhosis	Any detectable HBV DNA — oral agents only; refer for transplant
“Grey-zone” / borderline ALT	Consider if age >40, family history of cirrhosis/HCC, extrahepatic disease, prior treatment, or moderate–severe fibrosis/inflammation on biopsy/non-invasive testing

- **Not treated (monitor 3–6 monthly):** immune-tolerant (HBeAg-positive, normal ALT) and inactive carriers.

Antiviral agents and treatment

Eight drugs are approved; only PEG-IFN- α , entecavir, and tenofovir (TDF or TAF) are recommended first-line. Oral agents are generally preferred — better tolerated, more profound DNA suppression, usable in cirrhosis/immunosuppression.

First-line agent	Dose	Key points
Entecavir	0.5 mg PO daily (1 mg if lamivudine-resistant)	High potency, high barrier to resistance ($\leq 1.2\%$ at 6 yr); reduce dose in renal impairment; weak anti-HIV activity $\rightarrow$ not as monotherapy in HIV co-infection
Tenofovir disoproxil fumarate (TDF)	300 mg PO daily	Potent; 0% resistance through 8 yr; monitor renal function/phosphate (Fanconi-like tubulopathy), reduced bone density
Tenofovir alafenamide (TAF)	25 mg PO daily	Equipotent to TDF; less renal/bone toxicity $\rightarrow$ preferred if CrCl < 50 mL/min, low bone density, or risk factors for renal injury
PEG-IFN- $\alpha 2a$	180 μ g SC weekly $\times$ 48 wk	Finite course, highest 1-yr HBeAg seroconversion ($\sim 30\%$), no resistance; contraindicated in decompensated cirrhosis, pregnancy, autoimmune disease, cytopenias

- ▶ *No longer first-line*: **lamivudine** (YMDD mutation — M204V/I — in ~70% at 5 yr), **adefovir**, **telbivudine** (low barrier to resistance). **Combination oral therapy gives no benefit over potent monotherapy** in treatment-naïve patients; for resistance, *switching* to a non-cross-resistant high-barrier agent (e.g. tenofovir for lamivudine resistance) is now preferred over add-on.

Endpoints and stopping rules

- ▶ **HBeAg-positive**: oral therapy may be stopped after HBeAg seroconversion plus **≥12 months consolidation** in non-cirrhotics, with close post-treatment monitoring for relapse; otherwise continue.
- ▶ **HBeAg-negative**: relapse is the rule on stopping → **indefinite therapy**, ideally until HBsAg loss (rare).
- ▶ **Cirrhosis**: treat **indefinitely** — stopping risks decompensation.
- ▶ **PEG-IFN futility**: if qHBsAg fails to fall to <20,000 IU/mL by week 24, discontinue.

Special populations

- ▶ **Pregnancy**: Tenofovir (TDF) is the **drug of choice**; start in the **third trimester** when maternal HBV DNA $\geq 200,000$ IU/mL to reduce perinatal transmission (plus neonatal HBIG + vaccine). Avoid IFN.
- ▶ **Immunosuppression / chemotherapy**: screen HBsAg + anti-HBc; give **pre-emptive entecavir/tenofovir prophylaxis** to all HBsAg-positive patients, and to anti-HBc-positive/HBsAg-negative patients receiving **B-cell-depleting agents (rituximab)** or stem-cell transplant. Continue 6 months after chemotherapy (12 months for B-cell depletion).
- ▶ **HIV co-infection**: use ART containing two anti-HBV drugs (e.g. **tenofovir + emtricitabine/lamivudine**); never lamivudine or entecavir monotherapy.
- ▶ **Liver transplantation**: prevent graft re-infection with short-course IV HBIG (5–7 days) + **lifelong entecavir/TDF/TAF**.
- ▶ **HDV co/super-infection**: treat with PEG-IFN- α (limited efficacy); the NTCP entry inhibitor **bulevirtide** is the major advance (EMA-approved); treat underlying HBV if DNA $> 2 \times 10^3$ IU/mL.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Phases of chronic HBV infection (time-course graph)**: x-axis = time/years; plot HBV DNA, ALT and qHBsAg curves across the five phases, with bands labelled *Immune-tolerant* → *Immune-active* → *Inactive carrier* → *Reactivation (HBeAg-negative)* → *HBsAg-negative*; mark HBeAg → anti-HBe seroconversion and HBsAg → anti-HBs (functional cure).
- ▶ **Treatment-decision algorithm**: boxes labelled *HBsAg+ ≥6 months* → branch on HBeAg status → thresholds (HBeAg+: DNA $> 2 \times 10^4$ & ALT $> 2 \times \text{ULN}$; HBeAg-: DNA $> 2 \times 10^3$ &

ALT >2×ULN; Cirrhosis: any detectable DNA) → *First-line: Entecavir / TDF / TAF / PEG-IFN* → *HCC surveillance 6-monthly US ± AFP.*

Clinical / Diagnostic significance

- ▶ HBV DNA is the master variable — both for diagnosis/phasing and as the therapeutic target; suppression below the level of detection lowers (but does not abolish) HCC risk.
- ▶ Extrahepatic immune-complex disease — **polyarteritis nodosa**, **membranous/membranoproliferative glomerulonephritis**, **leukocytoclastic vasculitis**, **arthralgias** — is itself an indication to treat.
- ▶ ALT “flares” may herald HBeAg seroconversion but can precipitate decompensation in cirrhotics — monitor closely, especially after stopping therapy.
- ▶ Antiviral therapy regresses fibrosis/cirrhosis and reduces transplant referral, but **HCC surveillance must continue even after HBsAg loss/seroconversion.**

High-yield exam pointers

- ▶ HBsAg >6 months = chronic; **IgM anti-HBc** distinguishes acute from chronic.
- ▶ First-line antivirals = **entecavir**, **tenofovir (TDF/TAF)**, **PEG-IFN**; doses **entecavir 0.5 mg/d**, **TDF 300 mg/d**, **TAF 25 mg/d**, **PEG-IFN-α2a 180 µg/week**.
- ▶ **Treat any cirrhotic with detectable HBV DNA**, irrespective of ALT/HBeAg — treat indefinitely.
- ▶ **Tenofovir = drug of choice in pregnancy**; start 3rd trimester if maternal DNA ≥200,000 IU/mL.
- ▶ **Screen HBsAg + anti-HBc before chemo/biologics**; prophylax with entecavir/tenofovir (mandatory with rituximab).
- ▶ **Functional cure = sustained HBsAg loss + undetectable DNA**; cccDNA persistence prevents sterilising cure.
- ▶ Resistance: **lamivudine** — YMDD (M204V/I); tenofovir/entecavir have the highest barrier.
- ▶ **HCC surveillance: 6-monthly ultrasound ± AFP**; PAGE-B predicts on-treatment HCC risk; genotype C = worst prognosis.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Chronic Hepatitis” (chronic hepatitis B grading/staging, HBV DNA phases, full antiviral pharmacology and AASLD/EASL treatment-recommendation tables, special populations).
- ▶ **CMDT 2026** — “Liver, Biliary Tract, & Pancreas Disorders” (five-phase classification, current drug doses, treatment thresholds, PAGE-B, prognosis).

- Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e — "Hepatitis B" (natural history, REVEAL-HBV data linking HBV DNA to cirrhosis/HCC, ALT ULN 35/25 U/L, genotype effects).



Irritable Bowel Syndrome

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Irritable bowel syndrome (IBS) is a chronic **functional bowel disorder** (a disorder of **gut–brain interaction**) characterised by **recurrent abdominal pain associated with altered bowel habits**, in the *absence of any detectable structural or biochemical abnormality*. No pathognomonic marker exists, so diagnosis is **symptom-based** (Rome IV criteria) after judicious exclusion of organic disease. It affects ~10% of adults and adolescents worldwide, is **2–3 times commoner in women** (who form ~80% of severe cases), and usually begins **before age 45**. Though benign, it markedly impairs quality of life and incurs high direct and indirect health-care costs.

Diagnostic criteria & classification

- **Rome IV criteria (2016):** *Recurrent abdominal pain, on average at least 1 day per week in the last 3 months, associated with ≥ 2 of:*
 - (1) related to **defecation**, (2) associated with a change in **frequency of stool**, (3) associated with a change in **form/appearance of stool**.
 - Criteria fulfilled for the last 3 months with **symptom onset ≥ 6 months** before diagnosis.
- **More stringent than Rome III** — pain must occur $\geq$ once/week and the term "*discomfort*" has been dropped. *Painless* diarrhoea or constipation does **not** qualify as IBS.
- **Supportive (non-diagnostic) symptoms:** straining, urgency, feeling of incomplete evacuation, passage of mucus, and bloating/distension.
- **Subtyping** by predominant stool form on the **Bristol Stool Form Scale** ($\geq 25\%$ of bowel movements rule):

Subtype	Stool pattern ($\geq 25\%$ of BMs)
IBS-C (constipation)	Hard/lumpy (Bristol 1–2) $\geq 25\%$; loose $< 25\%$
IBS-D (diarrhoea)	Loose/watery (Bristol 6–7) $\geq 25\%$; hard $< 25\%$
IBS-M (mixed)	Both hard and loose $\geq 25\%$
IBS-U (unsubtyped)	Insufficient abnormality to subtype

- Subtypes are **unstable** — over 1 year ~75% of patients switch subtype and ~29% switch between IBS-C and IBS-D.

Pathophysiology (multifactorial — disordered brain–gut axis)

- ▶ **Altered GI motility:** exaggerated, prolonged colonic motor response to meals and rectal distension; increased high-amplitude propagating contractions and rapid transit in IBS-D; slow transit/pelvic-floor dyssynergia in IBS-C.
- ▶ **Visceral hypersensitivity:** lowered thresholds for pain/discomfort on rectal balloon distension; *selective for visceral (not somatic) afferents*. **TRPV1 (vanilloid) channel** upregulation correlates with pain.
- ▶ **Central neural dysregulation:** functional MRI shows heightened activation of the **mid-cingulate** and **prefrontal cortex** (hypervigilance to visceral pain); stress and emotion alter sensory thresholds.
- ▶ **Psychological factors:** anxiety, depression, somatisation in up to 80% of referral patients; association with prior **physical/sexual abuse**.
- ▶ **Post-infectious IBS:** >10% develop IBS after infectious enteritis (**≈4-fold** risk); commoner in young women, after severe/bacterial/parasitic infection and with psychological comorbidity; mediated by residual enteroendocrine cells, T-lymphocytes and dysbiosis.
- ▶ **Low-grade immune activation/mucosal inflammation:** activated **mast cells** in proximity to nerves, raised IL-6, IL-1 β , TNF; mast-cell mediators (histamine, proteases, PGE₂) drive hypersensitivity.
- ▶ **Altered intestinal permeability** (“leaky gut”) — especially IBS-D and post-infectious IBS; reduced tight-junction proteins.
- ▶ **Gut dysbiosis:** reduced microbial diversity, ↓ *Bifidobacterium* and *Faecalibacterium*, ↑ Enterobacteriaceae; up to 4-fold higher odds of **SIBO** on breath testing (contested).
- ▶ **Serotonin (5-HT) pathways:** ↑ enterochromaffin cells and postprandial plasma 5-HT in IBS-D; **TPH1** polymorphism; downregulated mucosal **SERT** (serotonin reuptake transporter).
- ▶ **Bile-acid malabsorption:** in up to 25% of IBS-D (reduced ileal FGF-19) → accelerated colonic transit.
- ▶ **Genetic:** twin studies and **SERT polymorphisms** support heritability.

Clinical features

- ▶ **Abdominal pain** (prerequisite): variable, often **crampy/episodic**, anywhere in the abdomen; *exacerbated by eating or stress, relieved by defecation or flatus*; worse premenstrually; **almost never nocturnal** and does not disturb sleep. Malnutrition is exceedingly rare.
- ▶ **Altered bowel habit** (most consistent feature): IBS-C — hard, narrow-calibre, infrequent stools (<3/week), straining, sense of anal blockage; IBS-D — small-volume loose stools (<200 mL), urgency, mucus, occasional incontinence.
- ▶ **Gas/bloating/distension** — common; most generate a *normal* amount of gas but tolerate gas loads poorly.

- ▶ **Upper-GI/extra-intestinal overlap:** dyspepsia, heartburn, nausea in 25–50%; overlap with fibromyalgia, chronic fatigue, headache, backache, urologic and gynaecologic symptoms.

Alarm (“red-flag”) features that argue AGAINST IBS

- ▶ Onset after **age 40–45**, progressive course, **rectal bleeding/hematochezia**, **nocturnal pain** or diarrhoea, significant **weight loss**, fever, persistent diarrhoea after a 48-h fast, steatorrhea.
- ▶ **Anaemia**, raised inflammatory markers, leucocytes/blood in stool, stool volume **>200–300 mL/day**.
- ▶ **Family history** of colorectal cancer, IBD or coeliac disease.
- ▶ *Any* alarm feature mandates targeted investigation (e.g. colonoscopy with random biopsies for microscopic colitis).

Investigations (diagnosis of positive features + limited exclusion)

- ▶ Diagnosis is **clinical**; over-testing in a young patient with typical symptoms and no alarm features is harmful and costly.
- ▶ **Baseline:** complete blood count; **CRP** and **faecal calprotectin** (or lactoferrin) to screen for IBD — IBD risk $\leq 1\%$ if CRP ≤ 0.5 mg/dL or calprotectin ≤ 40 $\mu\text{g/g}$ (>50 $\mu\text{g/g}$ warrants endoscopy).
- ▶ **Coeliac serology** (tissue-transglutaminase IgA) in IBS-D.
- ▶ **Stool studies** for ova/parasites/*Giardia* only where prevalence is high or history suggestive.
- ▶ **Colonoscopy** if alarm features, onset >45 years, or failure of therapy — with **random biopsies** to exclude microscopic colitis; lactose/glucose **hydrogen breath test** selectively; **SeHCAT/bile-acid** testing in refractory IBS-D; **anorectal manometry + balloon expulsion** if pelvic-floor dyssynergia suspected.

Management (stepwise, severity- and symptom-directed)

- ▶ **Foundation (all patients):** strong **therapeutic relationship**, reassurance, explanation of the gut–brain nature, realistic goals, identifying triggers; regular **exercise**.
- ▶ **Diet:** eliminate identified food triggers (avoid nutritionally depleted diets); **soluble fibre** (psyllium 3–4 g BD — *not* insoluble wheat bran); **low-FODMAP diet** as a 3-step *restriction* → *reintroduction* → *personalised maintenance* protocol relieves symptoms in **50–80%** (avoid in eating disorders).
- ▶ **Antispasmodics** (pain/cramps): dicyclomine, hyoscyamine 30 min before meals; **enteric-coated peppermint oil** (superior to placebo for global symptoms/pain).
- ▶ **For IBS-D:** **loperamide** 2–4 mg (max 12 mg/day, prophylactic before stressful events; does not relieve pain); **bile-acid binders** (cholestyramine/colesevelam) for bile-acid diarrhoea; **eluxadoline** (mixed μ -/ κ -agonist, δ -antagonist; contraindicated post-cholecystectomy, pancreatitis history or heavy alcohol use); **alosetron** (5-HT₃ antagonist; restricted to women with

severe IBS-D — risk of **ischaemic colitis** ~1.03/1000 patient-years); **rifaximin** 550 mg TDS × 14 days (FDA-approved, especially bloating).

- ▶ **For IBS-C:** osmotic laxative **PEG 3350** (*avoid lactulose/sorbitol* — gas); **secretagogues** — lubiprostone (Cl⁻-channel ClC-2 activator), linaclotide and plecanatide (guanylate cyclase-C agonists), tenapanor (NHE3 inhibitor); **tegaserod** (5-HT₄ agonist) re-approved 2019 for women <65 without cardiovascular disease.
- ▶ **Neuromodulators (pain-predominant/severe):** low-dose **tricyclic antidepressants** (amitriptyline/nortriptyline/imipramine 10–50 mg at night — benefit independent of mood effect; TCAs favour IBS-D); **SSRIs** may help IBS-C and comorbid mood disorder. Avoid chronic anxiolytics.
- ▶ **Psychological therapies (refractory/severe):** **cognitive behavioural therapy** (NNT ≈ 3) and **gut-directed hypnotherapy** (NNT ≈ 4).
- ▶ **Severity spectrum:** **mild** (~70%) — primary care, education/diet; **moderate** (~25%) — gut-acting drugs; **severe** (~5%) — referral centres, constant pain + psychosocial difficulty, best managed with neuromodulators and psychological treatment.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Brain–gut axis pathophysiology of IBS** (central hub “IBS” with radiating arrows): label *CNS hypervigilance* — mid-cingulate/prefrontal cortex, *Brain–gut axis* — HPA axis, *autonomic dysfunction*, *Visceral hypersensitivity (TRPV1)*, *Motility abnormalities*, “*Leaky*” gut / *altered permeability*, *Mast-cell activation & low-grade inflammation*, *Gut dysbiosis* (↓*Bifidobacterium*, ↓*Faecalibacterium*, ↑*Enterobacteriaceae*), *Bile-acid malabsorption* (↓*FGF-19*), *Serotonin/SERT polymorphism*, *Psychological* — *anxiety/depression/somatisation*, *Genetic* — *twin studies/SERT*.
- ▶ **Bristol Stool Form Scale & IBS subtyping graph:** Y-axis % *BM hard or lumpy* (Bristol 1–2), X-axis % *BM loose or watery* (Bristol 6–7), with **25% threshold** lines partitioning four quadrants labelled IBS-C, IBS-D, IBS-M, IBS-U; depict Bristol types 1–7 alongside.

Clinical / Diagnostic significance

- ▶ IBS is a **positive clinical diagnosis** by Rome IV plus *absence of red flags* — not purely a diagnosis of exclusion; limited testing avoids reinforcing illness behaviour.
- ▶ **Differential diagnosis** is broad: IBD (UC/Crohn, **microscopic colitis**), coeliac disease, bile-acid diarrhoea, lactase deficiency, SIBO, colorectal neoplasia, thyroid disease, carcinoid, endometriosis/ovarian cancer, and porphyria/lead poisoning (painful constipation).
- ▶ **Subtype-directed therapy** (pain vs constipation vs diarrhoea vs bloating) is the practical framework; agents are *adjunctive, not curative*.

- ▶ Failure to respond to a 2–4 week empiric trial or emergence of alarm features should prompt further evaluation.

High-yield exam pointers

- ▶ **Rome IV**: abdominal pain ≥ 1 day/week $\times$ 3 months + ≥ 2 of (defecation-related / change in stool frequency / change in stool form); onset ≥ 6 months prior.
- ▶ **Subtypes** by Bristol scale, **25% rule**: IBS-C, IBS-D, IBS-M, IBS-U — *unstable over time*.
- ▶ Female:male $\approx$ 2–3:1; prevalence $\sim$ 10%; onset usually <45 years.
- ▶ **Pain is essential**, is **never nocturnal**, relieved by defecation — *painless* altered habit is not IBS.
- ▶ Up to 25% of IBS-D have **bile-acid malabsorption**; $>10\%$ develop **post-infectious IBS** (4-fold risk).
- ▶ Screen IBS-D with **CRP + faecal calprotectin** ($>50 \mu\text{g/g} \rightarrow$ scope) and **coeliac serology**.
- ▶ **Low-FODMAP diet** helps 50–80%; **psyllium** (soluble) not wheat bran (insoluble).
- ▶ Drug pearls: **eluxadoline** contraindicated post-cholecystectomy/alcohol (pancreatitis); **alosetron** $\rightarrow$ ischaemic colitis (restricted); **rifaximin** for IBS-D/bloating; **linaclotide/plecanatide** (GC-C agonists), **lubiprostone** (Cl⁻ channel), **tenapanor** (NHE3) for IBS-C; TCAs for pain.
- ▶ CBT (NNT 3) and **gut-directed hypnotherapy** (NNT 4) for refractory disease.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Irritable Bowel Syndrome” (Owyang & Singh): Rome IV criteria, pathophysiology, drugs/doses, low-FODMAP protocol, severity spectrum.
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Irritable Bowel Syndrome”: Bristol-scale subtyping, diagnostic algorithm, CRP/calprotectin thresholds, NNT for hypnotherapy/CBT.
- ▶ **CMDT 2026** — “Gastrointestinal Disorders: Irritable Bowel Syndrome”: current pharmacologic management, drug doses, alarm features, FODMAP food groups.



List the complications of chronic pancreatitis? How do you manage them?

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Chronic pancreatitis (CP) is an irreversible inflammatory disease characterised histologically by chronic inflammation, fibrosis and progressive destruction (atrophy) of both the exocrine and endocrine pancreas, driven by stellate-cell activation, cytokine release and collagen deposition. Its cardinal manifestations are abdominal pain, steatorrhoea, weight loss and diabetes mellitus. Aetiology is summarised by the **TIGAR-O** system (Toxic-metabolic [alcohol, tobacco,

hypercalcaemia, hypertriglyceridaemia], Idiopathic, Genetic [*PRSS1*, *SPINK1*, *CFTR*, *CTRC*, *CASR*], Autoimmune, Recurrent/severe acute pancreatitis, Obstructive). Because no therapy reverses the disease, management is centred on screening for and treating its complications.

Complications of chronic pancreatitis (Harrison Table 359-7)

Domain	Complication	Key facts
Pain	Chronic abdominal pain	Most common/disabling symptom; complex mechanism; narcotic dependence frequent
Exocrine	Exocrine pancreatic insufficiency (EPI) → steatorrhea, malnutrition	Cumulative prevalence >80%; fat-soluble vitamin (A, D, E, K) deficiency; B12 malabsorption in ~40%
Endocrine	Pancreatogenic (type 3c) diabetes mellitus	Lifetime prevalence >80%; brittle, prone to hypoglycaemia (loss of glucagon reserve); ketoacidosis/end-organ damage uncommon
Ductal/cystic	Pseudocyst; pancreatic duct stricture/stones	Pseudocyst in ~25% (commonest in alcoholic CP); ~70% communicate with the duct
Biliary	Distal CBD stricture → jaundice, cholangitis, secondary biliary cirrhosis	Symptomatic in ~10%; long tapered stenosis of intrapancreatic CBD
Luminal	Duodenal (gastric-outlet) obstruction	~5%; from head fibrosis/inflammatory mass
Vascular	Splanchnic (splenic > portal) vein thrombosis; pseudoaneurysm	Splenic-vein thrombosis → left-sided (“sinistral”) portal hypertension + gastric varices; pseudoaneurysm (splenic artery commonest)
Haemorrhagic	GI bleeding	Pseudoaneurysm, ruptured varices, hemosuccus pancreaticus, peptic ulcer
Fistula	External (pancreaticocutaneous); internal (pancreatic ascites, pancreaticopleural effusion)	High-amylase ascites/effusion; from duct disruption/pseudocyst rupture
Skeletal	Metabolic bone disease	Osteopenia/osteoporosis in ~65% (alcohol, smoking, vitamin-D deficiency, inflammation)

Domain	Complication	Key facts
Malignant	Pancreatic adenocarcinoma	~4–5% cumulative risk at 20 yr; hereditary <i>PRSS1</i> ~10% (rising to ~19% by age 70)

General principles of management

- ▶ **Remove the driver:** absolute alcohol abstinence and **smoking cessation** (both are independent, dose-dependent drivers of progression, fibrosis and calcification).
- ▶ **Diet:** a low-fat or heart-healthy/Mediterranean diet; avoid very-low-fat diets that worsen fat-soluble-vitamin deficiency.
- ▶ **Treat the specific complication** (below); refer all CP patients to a centre offering endoscopic/surgical therapy.

Management of pain

- ▶ **Stepwise analgesia:** acetaminophen and NSAIDs first; **tramadol** if an opioid is needed; *avoid strong opioids* where possible (addiction is common).
- ▶ **Adjuvant pain-modifiers:** **pregabalin** (RCT-proven to reduce pain and opioid need) or gabapentin, tricyclic antidepressants, SSRIs. Antioxidants give mixed results; pancreatic enzymes do **not** reliably relieve pain.
- ▶ **Coeliac plexus block** (CT- or EUS-guided): relief in ~50% but typically **short-lived** — a conditional, low-evidence recommendation.
- ▶ **Endoscopic therapy** for a dominant duct stricture/obstructing stone: pancreatic sphincterotomy, stone extraction ± ESWL, and ductal stenting; successful in ~50%.
- ▶ **Surgery for a dilated duct:** ductal decompression by **lateral pancreaticojejunostomy** (**modified Puestow**) relieves pain in ~80%; head-resecting variants (**Frey / Beger** — duodenum-preserving pancreatic head resection) for an inflammatory head mass. Two RCTs show **surgery is superior to endoscopy** for pain/quality of life in dilated-duct disease, and early surgery may give superior short-term relief.
- ▶ **Total pancreatectomy with islet autotransplantation (TPIAT):** last resort for intractable **small-duct** or hereditary CP; benefits those with shorter symptom duration and low opioid use.

Management of exocrine insufficiency / steatorrhoea

- ▶ **Pancreatic enzyme replacement therapy (PERT)** is the cornerstone — diagnosis of EPI confirmed by **faecal elastase-1 <100 µg/g** (200 = normal; 100–200 = mild-moderate).
- ▶ Start **25,000–50,000 units of lipase with each meal**, titrating up to **90,000–100,000 units/meal**; aim for adequate lipase across the prandial/postprandial phase. Take enzymes spread throughout the meal.

- ▶ Add **acid suppression** (PPI or H₂-blocker) — *mandatory* with non-enteric-coated preparations and useful to improve response with enteric-coated preparations.
- ▶ Judge response clinically (stool consistency, visible fat, weight gain). If refractory: increase dose/change formulation, exclude **coeliac disease** / **SIBO**, and substitute **medium-chain triglycerides** (lipase-independent absorption).
- ▶ **Monitor and replace** fat-soluble vitamins (esp. vitamin D) and zinc; check body weight and **bone mineral density** (DEXA) — treat osteopenia/osteoporosis.

Management of endocrine insufficiency (type 3c diabetes)

- ▶ Annual **fasting glucose** and **HbA1c** screening; C-peptide estimates residual β -cell mass.
- ▶ **Metformin** preferred (associated with lower secondary pancreatic-cancer risk); **insulin** is frequently required, but requirements are lower than in type 1 DM.
- ▶ **Avoid over-tight glycaemic control** — brittle diabetes with impaired glucagon reserve and malnutrition predisposes to dangerous treatment-induced **hypoglycaemia**.

Management of structural / vascular complications

- ▶ **Pseudocyst**: observe if asymptomatic. Drain if symptomatic, complicated, rapidly enlarging or generally >6 cm — preferred is **EUS-guided endoscopic cystogastrostomy/cystojejunostomy** (success 80–90%); surgical drainage (often with a Puestow) where endoscopy fails; **percutaneous drainage is discouraged** (downstream duct stricture → fistula/recurrence). Address an associated duct stricture/disruption (bridging stent) to prevent recurrence.
- ▶ **Biliary obstruction: cholangitis is an absolute indication** for intervention. **Surgical biliary bypass** (choledochojejunostomy/choledochoduodenostomy ± Whipple/head resection) is definitive; endoscopic stenting (multiple plastic stents or a fully-covered SEMS for 6–12 months) is a temporising option with lower long-term success. A new stricture may signal malignancy — assess with EUS.
- ▶ **Duodenal obstruction**: trial of conservative therapy (inflammation may settle); **gastrojejunostomy** (± duct drainage) or head resection if it fails.
- ▶ **Pseudoaneurysm / haemorrhage**: the **splenic artery** is most often involved; beware a **sentinel bleed** preceding exsanguination, and **hemosuccus pancreaticus** (bleeding via the ampulla/duct). CT angiography then **angiographic embolisation or covered stent-graft** is first-line (has replaced surgery); treat once identified even if not yet bleeding — mortality after bleeding is ~40%.
- ▶ **Splenic-vein thrombosis with gastric varices**: therapy only if bleeding (risk ~10%) — **splenectomy is curative**; endoscopic cyanoacrylate injection controls acute bleeding.
- ▶ **Pancreatic fistula**: internal (pancreatic ascites/pleural effusion) or external — bowel rest, parenteral nutrition and **octreotide** (100 μ g SC 8-hourly), with **endoscopic**

transpapillary/bridging stent across the duct disruption; surgery (distal resection or fistulojejunostomy) if endoscopy fails.

- ▶ **Autoimmune pancreatitis** (a treatable cause/mimic): **prednisone 40 mg/day** for 4 weeks then taper; **rituximab** (or azathioprine/MMF) for relapse.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — “Complications map of the pancreas in CP”**: outline the pancreas (atrophic, with punctate parenchymal calcifications) and label: *dilated main pancreatic duct with intraductal calculus, pancreatic-duct stricture, pseudocyst (tail), distal common bile duct stricture → biliary dilatation, duodenal compression, splenic-vein thrombosis with gastric (fundal) varices, splenic-artery pseudoaneurysm.*
- ▶ **Diagram 2 — “Pain-management ladder in CP”**: stacked steps labelled *Abstinence (alcohol + tobacco) → Acetaminophen/NSAID → tramadol + pregabalin/TCA → Coeliac plexus block → Endoscopy (sphincterotomy, ESWL, stent) → Surgery (Puestow / Frey-Beger) → TPIAT.*

Clinical / Diagnostic significance

- ▶ **Diagnosis of CP**: CT/MRI is first-line (calcifications, ductal dilatation, atrophy); MRCP/EUS for early disease (≥ 5 of 9 EUS / Rosemont features); the **secretin test** (most sensitive functional test) becomes abnormal once $\geq 60\%$ of exocrine function is lost.
- ▶ **Steatorrhea appearing in CP** strongly implies EPI; a **new biliary stricture or unexplained weight loss** must trigger exclusion of **pancreatic cancer** (tumefactive CP can mimic carcinoma).
- ▶ **Any GI bleed or unexplained anaemia** in a CP patient mandates urgent search for a **pseudoaneurysm**.
- ▶ **Surveillance bundle**: annual HbA1c (diabetes), periodic fat-soluble vitamins/zinc and DEXA (bone disease, EPI), and cancer vigilance — especially in hereditary *PRSS1*/tropical CP.

High-yield exam pointers

- ▶ TIGAR-O classifies aetiology; alcohol + smoking drive progression — **abstinence is therapy**.
- ▶ EPI prevalence $>80\%$; diagnose with **faecal elastase-1 $<100 \mu\text{g/g}$** ; treat with PERT 25,000–50,000 → 90,000–100,000 U lipase/meal + PPI.
- ▶ **Type 3c (pancreatogenic) diabetes** is *brittle* — guard against hypoglycaemia; metformin preferred.
- ▶ **Pseudocyst ($\sim 25\%$)** → EUS-guided endoscopic drainage; **percutaneous drainage discouraged**.
- ▶ **Splenic-vein thrombosis** → **sinistral portal hypertension + gastric varices** → **splenectomy is curative**.

- ▶ **Pseudoaneurysm** (splenic artery) — **sentinel bleed**, **hemorrhage pancreaticus**, mortality ~40% — treat by **angiocoilisation/stent-graft**.
- ▶ Biliary stricture (~10%): **cholangitis** = **absolute indication**; surgical bypass is definitive.
- ▶ **Dilated duct + pain** → **surgery (Puestow)** beats **endoscopy** (RCT evidence); intractable small-duct/hereditary → **TPIAT**.
- ▶ Pancreatic cancer cumulative risk ~4–5% at 20 yr (~10–19% in hereditary CP); ~65% have **metabolic bone disease**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Acute and Chronic Pancreatitis” (chronic pancreatitis pathophysiology, TIGAR-O classification, complications [Table 359-7], steatorrhea/PERT, pain and surgical therapy, hereditary pancreatitis).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Chronic Pancreatitis” (deep detail on pseudocyst, GI bleeding, pseudoaneurysm, splenic-vein thrombosis/varices, bile-duct and duodenal obstruction, pancreatic fistulas, diabetes management).
- ▶ **CMDT 2026** — “Liver, Biliary Tract, & Pancreas Disorders” (current management: enzyme [pancrelipase] dosing, pain pharmacotherapy, endoscopic/surgical algorithm — Puestow/Beger/Frey, autoimmune pancreatitis steroids/rituximab, cancer risk).



List the sites of portosystemic anastomosis and explain the clinical relevance

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — A **portosystemic (porto-systemic) anastomosis** is a site where tributaries of the valveless **portal venous system** communicate with veins of the **systemic (caval) circulation**. In health these channels carry negligible flow *towards* the portal vein. When the **hepatic venous pressure gradient (HVPG)** rises (portal hypertension is defined as HVPG >5 mmHg; *clinically significant* portal hypertension is HVPG ≥10 mmHg), flow **reverses**, the collaterals dilate, and varices form as decompressing channels. They are the anatomical basis of the lethal complication of cirrhosis — **variceal haemorrhage** (20–30% mortality per episode).

Anatomy of the normal portal circulation (orientation)

- ▶ The **portal vein** is formed behind the neck of the pancreas by union of the **superior mesenteric vein** and the **splenic vein**; it is ~7.5 cm long, runs dorsal to the hepatic artery and bile duct, and divides at the hilum into right and left branches.

- ▶ The **inferior mesenteric vein** usually drains into the splenic vein; the **left gastric (coronary) vein** drains into the portal vein near the splenomesenteric confluence; the **umbilical vein** drains into the *left* portal branch.
- ▶ The portal system drains capillary blood from the **oesophagus, stomach, small and large intestine (to the upper anal canal), pancreas, gallbladder and spleen**, and supplies ~75% of total hepatic blood flow. Being **valveless**, it permits pressure to be transmitted retrogradely into collaterals.

Sites of portosystemic anastomosis (core of the answer)

Site	Portal (visceral) tributary	Systemic vein	Clinical lesion / sign
Lower oesophagus / gastro-oesophageal junction	Left gastric (coronary) & short gastric veins → splenic/portal	Oesophageal tributaries of the azygos/hemiazygos (perioesophageal) veins → SVC	Oesophageal & gastro-oesophageal varices — the principal, bleeding collateral
Gastric fundus / cardia	Short gastric & posterior gastric → splenic vein	Left renal vein via spontaneous spleno-renal shunt	Fundal (gastric) varices ; isolated in splenic-vein thrombosis
Anal canal / rectum	Superior rectal vein (from inferior mesenteric)	Middle & inferior rectal veins → internal iliac / internal pudendal → IVC	Ano-rectal varices (to be distinguished from haemorrhoids)
Peri-umbilical anterior abdominal wall	Para-umbilical veins in the falciform/round ligament (from left portal vein)	Superficial & inferior epigastric / thoraco-epigastric veins	Caput medusae ; <i>Cruveilhier–Baumgarten</i> venous hum
* <i>Retroperitoneum (veins of Retzius)*</i>	Colonic & other splanchnic veins; ovarian veins (esp. in women)	Retroperitoneal, renal, lumbar and iliac veins	Ectopic / retroperitoneal varices; rarely bleed
* <i>Bare area of liver / diaphragm (veins of Sappey)*</i>	Hepatic capsular & diaphragmatic portal twigs	Phrenic veins → IVC	Adhesion collaterals; clinically silent
Patent / recanalised ductus venosus	Left portal vein	IVC	Rare congenital shunt

- ▶ **Mechanistic note (Sleisenger)**: the GE-junction collaterals (left gastric/coronary + short gastric draining to the azygos system) are the dominant route in *intra-hepatic* portal hypertension; an increase in azygos blood flow is a hallmark. The fundus drains via short gastric veins into the splenic vein, hence **splenic-vein thrombosis** (“**left-sided**” portal hypertension) produces *isolated* fundal varices, often with a spleno-renal shunt.

Four venous zones at the gastro-oesophageal junction (why varices bleed here)

- ▶ **Gastric zone** (2–3 cm below junction) — submucosal longitudinal veins draining to short/left gastric veins.
- ▶ **Palisade zone** (2–3 cm of distal oesophagus) — the **dominant portosystemic watershed**; perforating veins do *not* connect to peri-oesophageal veins, so these varices **cannot decompress** and are **most prone to rupture**.
- ▶ **Perforating zone** — network of veins connecting submucosal and external (peri-oesophageal) veins.
- ▶ **Truncal zone** (~10 cm, proximal) — 4 longitudinal veins; communicate with peri-oesophageal veins (which drain to the azygos), so they decompress and **rarely bleed**.

Pathophysiology — pressure thresholds and rupture

- ▶ Collaterals form because portal pressure **exceeds** systemic venous pressure → flow reverses out of the portal bed.
- ▶ **Gradient thresholds**: varices develop at an HVPG ≥ 10 mmHg; bleeding requires a gradient ≥ 12 mmHg (reducing HVPG < 12 mmHg almost abolishes bleeding risk).
- ▶ Rupture follows **Laplace's law**: $\text{wall tension } T = (P \times r)/w$ — large varices (r), thin wall (w), and high transmural pressure (P), with limited soft-tissue support at the GE junction, predispose to rupture. Endoscopic risk stigmata: **red wale signs, cherry-red spots, haematocystic spots, white-nipple sign**.

Gastric varices — Sarin classification

Type	Location	Association
GOV1	Extend 2–5 cm below GE junction, contiguous with oesophageal varices	Commonest (~70% of gastric varices); intra-hepatic portal HTN
GOV2	Cardia/fundus, contiguous with oesophageal varices	Intra-hepatic portal HTN
IGV1	Isolated fundal varices, no oesophageal varices	Splenic-vein thrombosis (left-sided) / cirrhosis
IGV2	Isolated, gastric body/antrum/pylorus	Least common

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1** — “Sites of portosystemic anastomosis.” Draw the portal vein (SMV + splenic vein confluence), spleen and gut. Label the four classic sites with their venous pairs: (i) *Lower oesophagus* — left gastric/coronary vein ↔ azygos vein; (ii) *Rectum* — superior

Type	Location	Association
	rectal vein ↔ middle/inferior rectal veins; (iii) <i>Umbilicus</i> — para-umbilical veins ↔ epigastric veins (caput medusae); (iv) <i>Retroperitoneum</i> — colonic/splanchnic veins ↔ renal/lumbar veins (veins of Retzius). Mark arrows showing reversed (hepatofugal) flow and the resulting lesion at each site.	
	▶ Diagram 2 — “Four zones of the gastro-oesophageal junction.” Vertical strip of distal oesophagus/cardia labelled gastric → palisade (watershed, bleeds) → perforating → truncal, with the palisade zone starred as the rupture site and peri-oesophageal veins draining to the azygos system.	

Clinical / Diagnostic significance

- ▶ **Oesophageal/gastric varices:** life-threatening upper-GI bleed; screen at diagnosis of cirrhosis by endoscopy (skip if liver stiffness <20 kPa and platelets normal). **Primary prophylaxis** = non-selective β -blocker (**carvedilol** preferred; or propranolol/nadolol titrated to HR 55–60, SBP >90 mmHg) **or** endoscopic variceal ligation.
- ▶ **Acute variceal bleed:** restrictive transfusion (transfuse at Hb <7 g/dL, target 7–9), **vasoactive drug** (somatostatin/octreotide/terlipressin), **prophylactic ceftriaxone**, urgent endoscopic band ligation; **balloon tamponade** (Sengstaken–Blakemore/Minnesota tube) or self-expanding metal stent as a bridge to **TIPS** (transjugular intrahepatic portosystemic shunt) on endoscopic failure.
- ▶ **Gastric (fundal) varices:** cyanoacrylate glue injection; **BRT**O (balloon-occluded retrograde transvenous obliteration) when a spleno-renal shunt is present, $\pm$ TIPS. **Isolated fundal varices** → **exclude splenic-vein thrombosis** → **splenectomy is curative** for that pattern.
- ▶ **Caput medusae & Cruveilhier–Baumgarten hum:** clinical bedside signs of a recanalised umbilical/para-umbilical collateral — distinguish radiating peri-umbilical veins of portal hypertension from the “**flow away from umbilicus**” of IVC obstruction.
- ▶ **Ano-rectal varices** occur in 10–40% of cirrhotics at colonoscopy: they are dilated **superior and middle rectal (haemorrhoidal) veins**, **collapse with digital pressure**, and must not be confused with haemorrhoids (which do not collapse and are cushions in the anal canal).
- ▶ **Ectopic varices** (duodenum, peristomal after proctocolectomy, biliary) cause <5% of variceal bleeds but are easily missed; suspect with obscure GI bleed or bloody ascites.
- ▶ **Encephalopathy:** large spontaneous or surgical/TIPS shunts divert nitrogenous blood past the liver → portosystemic (hepatic) encephalopathy (occurs in up to ~20% after TIPS).

High-yield exam pointers

- ▶ **Four classic sites:** lower oesophagus, ano-rectum, peri-umbilicus, retroperitoneum (add fundus, bare area of liver).

- ▶ Most clinically important & dangerous collateral = gastro-oesophageal varices (left gastric/coronary + short gastric ↔ azygos).
- ▶ Palisade zone of the distal oesophagus is the watershed that **cannot decompress** → commonest bleeding site.
- ▶ HVPg ≥ 10 mmHg → varices form; ≥ 12 mmHg → varices bleed. Laplace's law governs rupture.
- ▶ Caput medusae = recanalised para-umbilical veins (left portal vein); a venous hum = Cruveilhier–Baumgarten sign.
- ▶ Rectal varices $\neq$ haemorrhoids: varices collapse on digital pressure and connect superior ↔ middle rectal veins.
- ▶ Isolated gastric fundal varices (IGV1) → think splenic-vein thrombosis; treat with splenectomy/BRTO, *not* β -blockers alone.
- ▶ Sarin classification: GOV1 (commonest), GOV2, IGV1, IGV2.
- ▶ “Downhill” oesophageal varices (upper third, from SVC obstruction) are NOT portal-hypertensive — a key differential.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — “Cirrhosis and Its Complications” (portal hypertension definition, HVPg thresholds, classification of portal hypertension, complications, variceal-bleed management, TIPS).
- ▶ Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e — “Portal Hypertension and Variceal Bleeding” (normal portal anatomy; the four sites of porto-systemic collateral formation; the four gastro-oesophageal venous zones; Laplace's law; Sarin classification of gastric varices; ectopic and ano-rectal varices) and used for collateral/watershed detail.
- ▶ CMDT 2026 — Gastrointestinal & Liver disorders (current management of variceal bleeding; haemorrhoids vs rectal varices).

Coverage note: The named venous eponyms **veins of Retzius** (retroperitoneal), **veins of Sappey** (bare area/diaphragm), the **Cruveilhier–Baumgarten** hum, and “**downhill**” varices are standard, universally accepted internal-medicine/anatomy facts included to satisfy the “list the sites” phrasing; the corpus describes the corresponding retroperitoneal (ovarian–iliac) and para-umbilical collaterals but does not use these eponyms verbatim. Harrison Ch 355's coverage of collateral *anatomy* is thin (as flagged in the spec); the anatomical depth here is drawn chiefly from Sleisenger.



Management of Active Ulcerative Colitis

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Ulcerative colitis (UC) is a chronic, relapsing, idiopathic inflammatory bowel disease characterised by *continuous*, diffuse mucosal inflammation that invariably involves the rectum and extends proximally in an uninterrupted fashion to involve part or all of the colon. The hallmark of active disease is **bloody diarrhoea** with tenesmus, urgency, passage of mucus and crampy lower-abdominal pain. Management of the *active* attack is governed by two axes — the **anatomical extent** (proctitis / left-sided / extensive) and the **severity of the flare** (mild, moderate, severe/fulminant) — and follows a “step-up / accelerated step-up” strategy with three goals: terminate the acute attack, achieve steroid-free clinical and endoscopic (mucosal) remission, and prevent recurrence.

Assessment of disease activity & severity (basis of all treatment decisions)

Severity is graded clinically (*Truelove & Witts*, refined as the *Montreal S-classification*) and endoscopically (*Mayo subscore*), supported by labs (Hb, albumin, ESR, CRP, faecal calprotectin).

Parameter	Mild (S1)	Moderate (S2)	Severe (S3)
Stools/day	≤4	4–6	>6, bloody
Blood in stool	intermittent	frequent	continuous
Pulse	normal	normal	≥90/min
Temperature	normal	normal	≥37.5°C
Haemoglobin	normal	≥10.5 g/dL	<10.5 g/dL
ESR	<30 mm/h	≤30	≥30 mm/h
Mayo endoscopic subscore	1	2–3	3 (ulceration, spontaneous bleeding)

- ▶ **Montreal extent:** E1 — proctitis; E2 — left-sided (distal to splenic flexure); E3 — extensive/pancolitis (proximal to splenic flexure). Extent dictates whether topical, oral or systemic therapy is appropriate.
- ▶ **Truelove & Witts severe attack** = ≥6 bloody stools/day **plus** ≥1 systemic sign (pulse >90, temp >37.8°C, Hb <10.5 g/dL, ESR >30) — the classic trigger for hospital admission.
- ▶ Before treating, **exclude infective mimics:** stool for *Salmonella*, *Shigella*, *Campylobacter*, Shiga-toxin *E. coli*, *Clostridioides difficile* toxin, ova/parasites (multiplex PCR preferred); consider **CMV superinfection** (mucosal biopsy) in steroid-refractory immunosuppressed patients.

Mild–moderate disease (out-patient, oral/topical therapy)

- ▶ **Proctitis / proctosigmoiditis (distal):** topical mesalamine is the drug of choice — suppository 1 g at bedtime (proctitis) or enema 4 g at bedtime (proctosigmoiditis) for 4–8 weeks (~75% improve). Topical mesalamine is *superior to* topical steroids and to oral 5-ASA for distal disease.

- ▶ **Extensive (above sigmoid):** combine oral mesalamine 2–4.8 g once daily with a nightly mesalamine enema/suppository; 50–75% improve, dose-response continues to 4.8 g/day. Sulfasalazine 3–6 g/day (acute) is effective but limited by sulfapyridine intolerance — give **folic acid** supplementation.
- ▶ **Oral budesonide MMX (Uceris) 9 mg/day** for 4–8 weeks (colonic release, minimal systemic steroid effect, no taper needed) or **oral prednisone** if no response to 5-ASA within 4–8 weeks.
- ▶ 5-ASA achieves clinical improvement in ~75% and remission in 20–30%; **maintenance 5-ASA** reduces 12-month relapse from 75% to <40%.

Moderate–severe disease (oral/systemic immunosuppression & biologics)

- ▶ **Oral corticosteroids: prednisone 40 mg/day** (Harrison: 40–60 mg/day); rapid response in ~2 weeks, then taper **5 mg/week** (slower, 2.5 mg/week below 20 mg). Steroids **induce but never maintain** remission; up to 30% become steroid-dependent/refractory.
- ▶ **Thiopurines** (steroid-sparing maintenance, not for induction — slow onset 3–6 months): azathioprine 2–3 mg/kg/day or 6-mercaptopurine 1–1.5 mg/kg/day. Check/keep in mind TPMT status (1 in 300 deficient → marrow toxicity); monitor CBC and LFTs; ~4-fold lymphoma risk.
- ▶ **Biologics / small molecules** are increasingly used early (“treat-to-target”, aiming for deep remission). Choice depends on prior biologic exposure, severity, comorbidity and route preference.

Agent	Class / target	Induction dosing
Infliximab	anti-TNF (chimeric IgG1)	5 mg/kg IV at 0, 2, 6 wk → q8 wk (↑10 mg/kg q4 wk by trough)
Adalimumab	anti-TNF (human IgG1, SC)	160 mg day 0, 80 mg day 14, then 40 mg q2 wk
Golimumab	anti-TNF (human IgG1, SC)	approved for moderate–severe UC
Vedolizumab	anti- $\alpha 4\beta 7$ integrin (gut-selective)	IV; preferred first-line in older/comorbid patients; superior to adalimumab
Ustekinumab	anti-IL-12/23 (p40)	IV induction → SC maintenance
Mirikizumab / risankizumab	anti-IL-23 (p19)	injectable; 2nd/3rd-line
Tofacitinib	pan-JAK inhibitor (oral)	10 mg BID × 8–16 wk
Upadacitinib	selective JAK1 (oral)	45 mg/day × 8 wk
Ozanimod / etrasimod	S1P-receptor modulator (oral)	once-daily (ozanimod needs dose escalation)

- ▶ **Combination therapy** (anti-TNF + immunomodulator) is superior to either alone for moderate–severe UC and reduces anti-drug antibody formation; do **proactive trough/antibody monitoring**.
- ▶ **JAK-inhibitor caution:** boxed warning — thrombosis, MACE, malignancy, serious infection, herpes zoster (give Shingrix); relegated to 2nd-line, avoid in >50 y, smokers, cardiovascular risk.
- ▶ **Pre-biologic screening:** latent TB (PPD/QuantIFERON-TB Gold) and hepatitis B (HBsAg/HBsAb/HBcAb) before anti-TNF.

Acute severe ulcerative colitis (ASUC) — a medical emergency

A hospitalised severe attack (Truelove–Witts criteria) carries real risk of toxic megacolon, perforation and death; **up to 30% require colectomy**. Managed jointly with surgery from day 1.

- ▶ **General measures:** admit; IV fluids and electrolyte correction; transfuse if Hct <25–28%; **stop opioids/anticholinergics/antidiarrhoeals** (precipitate toxic megacolon); plain AXR/CT on admission; stool studies + *C. difficile*; nutritional support (TPN only if malnourished/prolonged NPO — enteral/elemental diets do **not** treat active UC). **VTE pharmacological prophylaxis for ALL hospitalised IBD patients** (high thrombotic risk).
- ▶ **First-line: IV corticosteroids** — methylprednisolone **40–60 mg/day** or hydrocortisone **300 mg/day**; ± hydrocortisone enema for tenesmus. Assess response at **day 3**.
- ▶ **Day-3 non-response (Oxford/Travis criteria)** = >8 stools/day, OR 3–8 stools/day with CRP >45 mg/L → escalate to **rescue therapy** or surgery.
- ▶ **Rescue (salvage) therapy:**
 - **Infliximab 5–10 mg/kg IV** — colectomy at 3 months fell from 69% (placebo) to 47%; intensive/accelerated dosing for hospitalised patients (low albumin → faecal drug loss).
 - **IV cyclosporine 2–4 mg/kg/day continuous infusion** — ~82% respond; trough **150–350 ng/mL** (Harrison) / 200–400 ng/mL (Sleisenger). A *bridge* to thiopurine/vedolizumab maintenance or to surgery.
 - **CYSIF & CONSTRUCT trials:** infliximab and cyclosporine are **equally effective** as rescue therapy — choice rests on local expertise and comorbidity.
 - Add PCP prophylaxis (co-trimoxazole) and monitor renal function/electrolytes/Mg/cholesterol with cyclosporine (seizure risk if cholesterol <120 mg/dL).
- ▶ **Toxic megacolon** (transverse/right colon >6 cm with loss of haustration): NG suction, roll-over manoeuvre, serial films; **colectomy if no improvement in 48–72 h** to pre-empt perforation (perforation mortality ~15%).

Surgery

- ▶ Surgery is **curative** in UC. **Indications:** intractable/steroid-refractory disease, fulminant colitis/toxic megacolon unresponsive to medical therapy (48–72 h), colonic perforation, massive haemorrhage, and dysplasia/carcinoma (cancer prophylaxis).
- ▶ **Operation of choice** = **restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA)** preserving the sphincter; ~6–10 (typically 5–7) bowel motions/day.
- ▶ **Pouchitis** complicates ~30–50% (up to 80% long-term); responds to **metronidazole** or **ciprofloxacin**. Emergency/fulminant cases are usually staged (subtotal colectomy with end ileostomy first).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **ASUC management algorithm (flowchart):** Box 1 “Severe UC — Truelove & Witts: ≥ 6 bloody stools/day + pulse >90 / temp $>37.8^{\circ}\text{C}$ / Hb <10.5 / ESR >30 ” → “Admit; IV fluids, stop opioids/anticholinergics, VTE prophylaxis, AXR/CT, stool + *C. difficile*/CMV, surgical referral” → “IV methylprednisolone 40–60 mg/day” → **Day 3 assessment:** branch (a) *Responds* → switch to oral prednisone, taper, start maintenance (5-ASA/thiopurine/biologic); branch (b) *No response* (>8 stools/day OR $3-8 + \text{CRP} >45$) → “Rescue: infliximab 5–10 mg/kg OR IV cyclosporine 2–4 mg/kg/day” → response → maintenance; no response → “Colectomy (IPAA)”.
- ▶ **Treatment pyramid by severity:** base “Topical/oral 5-ASA (mesalamine, sulfasalazine)” → “Budesonide MMX / oral prednisone” → “Thiopurines (AZA/6-MP)” → “Biologics (anti-TNF, vedolizumab, ustekinumab) & small molecules (JAK-i, S1P modulators)” → apex “IV steroids → rescue therapy → colectomy”.

Clinical / Diagnostic significance

- ▶ **Severity assessment is the single most important determinant of therapy** — distal mild disease is treated topically, whereas severe disease mandates hospitalisation and parenteral therapy.
- ▶ **Faecal calprotectin >150 mcg/g or CRP >5 mg/L** in a previously remitting patient strongly suggests relapse and warrants endoscopic confirmation; calprotectin tracks mucosal healing and predicts pouchitis.
- ▶ **Avoid colonoscopy in fulminant disease/toxic megacolon** (perforation risk) — flexible sigmoidoscopy suffices to confirm activity.
- ▶ **Cancer surveillance:** colonoscopy from **8 years after diagnosis**, then every 1–5 years (chromoendoscopy enhances dysplasia detection); cumulative cancer risk ~3–4.8% at 20 y, 7–13.9% at 30 y.
- ▶ Antibiotics have **no role** in active or quiescent UC (unlike pouchitis); diet/TPN does not induce remission in UC.

High-yield exam pointers

- ▶ UC is continuous, mucosal, rectum-upward; treatment is by extent × severity.
- ▶ Topical mesalamine = drug of choice for distal/mild-moderate UC, superior to topical steroids.
- ▶ Oral mesalamine 2–4.8 g/day for extensive mild-moderate disease; combine oral + rectal for best effect.
- ▶ Steroids induce, never maintain; budesonide MMX 9 mg/day spares systemic effects.
- ▶ ASUC: IV steroids → reassess day 3 → rescue with infliximab or cyclosporine → colectomy; CYSIF/CONSTRUCT = equal efficacy.
- ▶ VTE prophylaxis for every hospitalised IBD patient; stop opioids/anticholinergics.
- ▶ Toxic megacolon = colon >6 cm + loss of haustration; colectomy if no response in 48–72 h.
- ▶ Screen for TB and hepatitis B before anti-TNF; JAK inhibitors carry thrombosis/MACE warnings.
- ▶ IPAA is the curative operation of choice; pouchitis (30–50%) responds to metronidazole/ciprofloxacin.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — “Inflammatory Bowel Disease” (clinical activity/Montreal classification, drug classes and doses, biologics/small-molecules table, indications for surgery, IPAA, toxic megacolon).
- ▶ Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e — “Management of Inflammatory Bowel Diseases” (acute severe UC algorithm, cyclosporine dosing/trough, CYSIF and CONSTRUCT rescue-therapy trials, thiopurine/methotrexate data).
- ▶ CMDT 2026 — “Gastrointestinal Disorders: Ulcerative Colitis” (Table 17–12 activity assessment, mild-moderate/severe-fulminant management, day-3 Oxford non-response criteria, VTE prophylaxis, surgery and cancer-surveillance figures).



Management of Ulcerative colitis

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Ulcerative colitis (UC) is a chronic, relapsing idiopathic inflammatory bowel disease limited to the colon, with diffuse mucosal inflammation beginning in the rectum and extending proximally in a continuous manner. It presents chiefly with bloody diarrhea, urgency, tenesmus, mucus, and crampy lower abdominal pain. Management is extent- and severity-based, with the aims of terminating the acute attack, achieving steroid-free clinical and endoscopic remission, preventing relapse, and avoiding cancer, toxic megacolon, and unnecessary colectomy.

Initial assessment and treatment targets

- ▶ **Confirm diagnosis before escalation:** exclude infectious colitis with stool testing for *Salmonella*, *Shigella*, *Campylobacter*, Shiga-toxin-producing *E. coli*, *C. difficile*, and amebiasis; consider CMV on biopsy in corticosteroid-exposed or immunosuppressed patients.
- ▶ **Define extent:** E1 proctitis is limited to rectum; E2 left-sided/distal UC extends distal to the splenic flexure; E3 extensive UC/pancolitis extends proximal to the splenic flexure.
- ▶ **Grade severity:** mild ≤ 4 stools/day, no systemic illness, normal inflammatory markers; moderate ≥ 4 stools/day with minimal systemic toxicity; severe ≥ 6 bloody stools/day with pulse ≥ 90 /min, temperature $\geq 37.5^\circ\text{C}$, hemoglobin < 10.5 g/dL, and ESR ≥ 30 mm/hour.
- ▶ **Baseline activity work-up:** stool frequency and bleeding diary, fever/pulse/BP and volume status, abdominal tenderness or peritonism, Hb, WBC, platelets, ESR/CRP, serum albumin, electrolytes, renal and liver tests, fecal calprotectin/lactoferrin, and flexible sigmoidoscopy with biopsy.
- ▶ **Endoscopy:** sigmoidoscopy is preferred in acute colitis; avoid full colonoscopy in fulminant disease because of perforation risk. Mild endoscopy shows erythema and reduced vascular pattern; severe disease shows spontaneous bleeding and ulceration.
- ▶ **Targets:** symptom control alone is insufficient; aim for **steroid-free remission**, mucosal healing, normalization of CRP/fecal calprotectin, restored nutrition, preserved quality of life, and prevention of dysplasia.

General and supportive measures

- ▶ Explain the chronic relapsing course, adherence, drug adverse effects, need for surveillance, and early reporting of fever, increasing bleeding, distension, or severe pain.
- ▶ Avoid precipitating or worsening factors during acute attacks: NSAIDs, opioids, anticholinergics, unnecessary antidiarrheals in severe colitis, dehydration, hypokalemia, and delayed surgical review.
- ▶ Treat anemia, iron deficiency, hypoalbuminemia, fluid and electrolyte depletion, malnutrition, osteoporosis risk, anxiety/depression, and extraintestinal manifestations.
- ▶ Before immunosuppression or biologics: screen for **latent TB** and **hepatitis B**, update inactivated vaccines including influenza, pneumococcal and recombinant zoster vaccine where indicated, and avoid live vaccines once immunosuppressed.
- ▶ Antibiotics have **no routine role** in active or quiescent uncomplicated UC; use them for documented infection, perioperative indications, or pouchitis.
- ▶ All hospitalized severe UC patients require **VTE prophylaxis**, because active IBD is prothrombotic even when rectal bleeding is present.

Induction therapy by extent and severity

Clinical setting	Preferred induction	Escalation / notes
Mild proctitis	Mesalamine suppository 1 g nightly for 4-8 weeks	If inadequate, add oral 5-ASA or topical steroid.
Mild proctosigmoiditis / left-sided UC	Mesalamine enema 4 g nightly; suppository treats only distal 15-20 cm	Topical 5-ASA is superior to topical steroid; oral + rectal 5-ASA is better than either alone.
Mild-moderate extensive UC	Oral mesalamine 2-4.8 g/day plus rectal mesalamine	Most improve in 4-8 weeks; sulfasalazine 3-6 g/day works but intolerance is common; give folate with sulfasalazine.
5-ASA inadequate after 4-8 weeks	Budesonide MMX 9 mg/day for 8 weeks or oral prednisone	Budesonide has lower systemic exposure; no role for budesonide or prednisone as maintenance.
Moderate nonhospitalized UC	Prednisone 40 mg/day (or 40-60 mg/day equivalent)	Taper after response, usually 5 mg/week, slower below 20 mg if needed.

- ▶ Monitor 5-ASA toxicity with renal function and urinalysis periodically; recognize paradoxical 5-ASA worsening, pancreatitis, nephritis, headache, nausea, and rash.
- ▶ Requiring repeated corticosteroids, inability to taper, severe endoscopic ulceration, low albumin, anemia, or high CRP indicates high-risk disease and should prompt steroid-sparing therapy.

Moderate-to-severe steroid-sparing therapy

- ▶ **Thiopurines:** azathioprine 2-3 mg/kg/day or 6-mercaptopurine 1-1.5 mg/kg/day are slow-onset agents used mainly for maintenance or with anti-TNF therapy. Check TPMT activity if available; monitor CBC and liver tests. Pancreatitis, myelosuppression, hepatotoxicity, infection, lymphoma, HPV-related cervical dysplasia, and nonmelanoma skin cancer are key risks.
- ▶ **Anti-TNF agents:** infliximab 5 mg/kg IV at 0, 2, 6 weeks then every 8 weeks is useful for moderate-severe UC and rescue in acute severe UC; adalimumab and golimumab are subcutaneous alternatives for moderate disease. Combination infliximab + azathioprine improves steroid-free remission and reduces antidrug antibodies in selected patients.
- ▶ **Vedolizumab:** 300 mg IV at 0, 2, 6 weeks then every 8 weeks; gut-selective anti- $\alpha_4\beta_7$ therapy, useful first-line in moderate-severe UC, especially in older patients or those at higher infection risk.
- ▶ **Anti-IL therapy:** ustekinumab weight-based IV induction then 90 mg SC every 8 weeks; IL-23 agents such as mirikizumab, risankizumab, and guselkumab are options after biologic failure or when safety profile is favored.
- ▶ **JAK inhibitors:** tofacitinib 10 mg twice daily induction, then 5 mg twice daily; upadacitinib 45 mg daily for 8 weeks, then 15 or 30 mg daily. Reserve especially after TNF-blocker failure; avoid

in high cardiovascular/thrombosis risk when possible, vaccinate against zoster, and monitor CBC, lipids, liver tests, and infections.

- ▶ **S1P receptor modulators:** ozanimod is titrated **0.23 mg days 1-4, 0.46 mg days 5-7, then 0.92 mg daily**; etrasimod **2 mg daily**. Check ECG/cardiac risk, CBC and liver tests; watch for bradycardia, AV block, hypertension, macular edema, lymphopenia, and herpes reactivation.
- ▶ For anti-TNF loss of response, measure trough and antidrug antibodies: low trough without antibodies needs dose escalation/shorter interval; high antibodies need switch; active disease with therapeutic trough needs another class.

Acute severe UC, fulminant colitis and toxic megacolon

- ▶ **Admit immediately** if ≥ 6 bloody stools/day with systemic toxicity, severe anemia, hypoalbuminemia, fever, tachycardia, weight loss, dehydration, or abdominal tenderness.
- ▶ Initial care: bowel rest for 24-48 hours if very ill, IV fluids, correction of potassium/magnesium, transfusion for significant anemia, stool pathogen testing, CMV assessment if refractory, abdominal radiograph/CT for dilatation, daily labs, strict stool chart, stop opioids/anticholinergics, VTE prophylaxis, and early colorectal surgical consultation.
- ▶ **IV corticosteroid:** methylprednisolone **40-60 mg/day** or hydrocortisone **300 mg/day**. Clinical improvement should be evident within **3 days**.
- ▶ Non-response predictors include **>8 stools/day** or **3-8 stools/day with CRP >45 mg/L** after IV steroids; do not continue ineffective steroids.
- ▶ **Rescue therapy:** infliximab **5-10 mg/kg IV** or cyclosporine **2-4 mg/kg/day IV**. Cyclosporine requires renal, BP, electrolyte, magnesium/cholesterol and drug-level monitoring; give Pneumocystis prophylaxis when using combined intense immunosuppression.
- ▶ **Toxic megacolon:** colonic dilatation **>6 cm** with systemic toxicity; manage with intensive monitoring, serial abdominal films, correction of electrolytes, decompression measures, antibiotics if sepsis/perforation is suspected, and urgent surgery if worsening or no improvement in **48-72 hours**.
- ▶ Colectomy is mandatory for perforation, uncontrolled hemorrhage, peritonitis, progressive distension, hemodynamic instability, carcinoma, or failed steroid/rescue therapy.

Maintenance, monitoring and cancer prevention

- ▶ Continue the drug that achieved remission: oral mesalamine usually **2-4 g/day**; topical mesalamine may be nightly to every 3 days for distal disease. Maintenance 5-ASA reduces relapse substantially; topical steroids are ineffective for maintenance.
- ▶ **Never use corticosteroids for maintenance.** Steroid-dependence, steroid-refractoriness, or >1 steroid course every 1-2 years requires thiopurine, biologic, or small-molecule therapy.

- ▶ Follow remission with stool frequency/bleeding, Hb, albumin, CRP, fecal calprotectin, and proctoscopy/endoscopy when relapse or treatment target assessment is needed. CRP >5 mg/L or fecal calprotectin >150 mcg/g during relapse suggests active inflammation.
- ▶ Cancer surveillance is required for UC proximal to the rectum: begin colonoscopy **8 years after diagnosis**, then every **1-5 years** according to extent, activity, scarring, pseudopolyps, dysplasia, PSC, and family history. Use high-definition colonoscopy with chromoendoscopy or electronic enhancement when available.
- ▶ Endoscopically resectable visible dysplasia can be removed with close surveillance; invisible high-grade dysplasia, multifocal low-grade dysplasia, unresectable lesions, carcinoma, or suspicious strictures generally require colectomy.

Surgery and pouch care

- ▶ Indications include **intractable disease**, fulminant colitis, toxic megacolon, perforation, massive hemorrhage, obstruction/stricture suspicious for cancer, dysplasia/carcinoma, recurrent unmanageable systemic complications, growth failure, and intolerable drug toxicity.
- ▶ Emergency setting: subtotal colectomy with end ileostomy and rectal stump/mucus fistula is safest and allows later reconstruction.
- ▶ Elective operation of choice for most fit patients is **restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA)**; expected function is about 5-10 stools/day, with possible nocturnal seepage early.
- ▶ Total proctocolectomy cures colitis and removes colorectal cancer risk, but pouch patients still need assessment of retained cuff/pouch symptoms.
- ▶ **Pouchitis** presents with increased stool frequency, watery stool, urgency, cramping, nocturnal leakage, fever/malaise/arthritis, or bleeding; confirm endoscopically and treat usually with ciprofloxacin or metronidazole. Chronic refractory pouchitis may need rotating antibiotics, budesonide/mesalamine, biologics, or pouch revision/removal.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Extent-severity-treatment flowchart:** E1 proctitis, E2 left-sided colitis, E3 extensive colitis; mild/moderate/severe; arrows to rectal 5-ASA, oral + rectal 5-ASA, steroids, biologic/small molecule, IV steroid, infliximab/cyclosporine, colectomy.
- ▶ **Toxic megacolon algorithm:** severe UC → abdominal X-ray showing transverse colon >6 cm → stop opioids/anticholinergics, fluids/electrolytes, IV steroids, serial films, rescue therapy, surgery at 48-72 hours or earlier for perforation/peritonitis.

Clinical / Diagnostic significance

- ▶ UC is a diagnosis of exclusion during first presentation and relapse; missing *C. difficile*, CMV, ischemic colitis, STI proctitis, amebiasis, or Crohn colitis leads to dangerous steroid escalation.

- ▶ Severe UC is a medical-surgical emergency: early surgical consultation is good practice, not treatment failure.
- ▶ Extraintestinal disease may determine drug choice: peripheral arthritis, erythema nodosum and pyoderma often parallel colitis; axial spondyloarthritis may need anti-TNF therapy; PSC increases colorectal cancer risk and needs close surveillance.
- ▶ Pregnancy planning: aim remission for 3-6 months before conception; 5-ASA, many biologics and corticosteroids when indicated are generally usable, whereas methotrexate is teratogenic and JAK inhibitors should be avoided.

High-yield exam pointers

- ▶ Write the **three treatment objectives**: stop attack, achieve clinical/endoscopic remission, prevent relapse.
- ▶ Always classify by **extent + severity** before treatment.
- ▶ **Topical mesalamine is first-line and superior to topical steroid** for distal mild-moderate UC.
- ▶ **Oral + rectal mesalamine** is better than either alone for left-sided or extensive mild-moderate UC.
- ▶ **Steroids induce but never maintain remission.**
- ▶ Acute severe UC: reassess after **3 days** of IV steroids; rescue with **infliximab or cyclosporine**, or operate.
- ▶ Toxic megacolon is **colon >6 cm + toxicity**; no improvement by **48-72 hours** means colectomy.
- ▶ Screen for **TB, hepatitis B, vaccination status, zoster risk, skin cancer, CBC/LFT/renal toxicity** before and during immunosuppressive therapy.
- ▶ Surveillance colonoscopy starts **8 years** after diagnosis for colitis beyond rectum.

SOURCE & COVERAGE

Harrison 22e — “Inflammatory Bowel Disease”; Sleisenger & Fordtran’s GI & Liver 11e — “Management of Inflammatory Bowel Diseases”; CMDT 2026 — “Gastrointestinal Disorders”.



Non-Alcoholic Fatty Liver Disease (NAFLD / MASLD)

Asked in: Paper II Sep 2025 · Paper II Nov 2021 (2×) — RGUHS MD General Medicine

Definition / Introduction — Non-alcoholic fatty liver disease (NAFLD) is excess macrovesicular triglyceride accumulation in **>5% of hepatocytes** in a person who drinks little to no alcohol and has no competing cause of steatosis. It is regarded as the **hepatic manifestation of the metabolic syndrome** and is now the commonest cause of chronic liver disease worldwide. In 2023 a multi-society consensus replaced the stigmatising terms NAFLD/NASH with **MASLD** (metabolic dysfunction-associated

steatotic liver disease) and **MASH** (steatohepatitis) under the umbrella of *steatotic liver disease (SLD)* — with **≥98% population overlap** between the old and new definitions. It spans a dynamic spectrum from benign **simple steatosis (MASL)** → **steatohepatitis (MASH)** → **fibrosis** → **cirrhosis / hepatocellular carcinoma (HCC)**.

Nomenclature & Diagnostic Criteria

- ▶ **Steatotic liver disease (SLD)** is the new umbrella term for excess hepatic fat; its two main causes are alcohol-associated and metabolic.
- ▶ **MASLD** = hepatic steatosis + drinks little alcohol + **≥1 cardiometabolic risk factor** (overweight/obesity, hypertension, dyslipidaemia, insulin resistance/T2DM — i.e. ≥1 of the 5 metabolic-syndrome criteria).
- ▶ A new intermediate category **MetALD** captures metabolic-risk patients who also drink “social” amounts of alcohol; higher intake regardless of metabolic factors is **ALD** (alcohol-associated liver disease).

Category	Alcohol intake (women / men)	Metabolic risk factor
MASLD	<20 g/d / <30 g/d	≥1 present
MetALD	20–50 g/d / 30–60 g/d	present
ALD	≥50 g/d / ≥60 g/d	irrelevant to definition

- ▶ Reference: 10 g alcohol ≈ one can beer / 4 oz wine / 1.5 oz (one shot) spirits. A diagnosis of MASLD still requires **exclusion** of other causes of steatosis (Table below).

Epidemiology & Risk Factors

- ▶ **Prevalence:** ~25–30% of US adults (global ~30%); **MASH in 3–6%**. Highest in **Hispanics and Asian-Indians (~50%)**, intermediate in whites (~30%), lowest in African-Americans (~25%). Highest regional prevalence: Latin America (44%), MENA (36.5%), South Asia (33.8%).
- ▶ **Lean MASLD** (BMI <25, or <23 in Asians) occurs in 4% (US) to 19% (Asia) — driven by visceral adiposity, insulin resistance and sarcopenia despite normal BMI.
- ▶ **Type 2 diabetes mellitus is the strongest risk factor** for acquisition, fibrosis progression and HCC; the MASLD–T2DM relationship is **bidirectional** (MASLD raises incident T2DM 2–5 fold). Screen every diabetic for MASLD and every MASLD patient for T2DM.
- ▶ Other associations: central (android) obesity, dyslipidaemia, hypertension, **PCOS**, hypothyroidism, hypogonadism, GH deficiency, **obstructive sleep apnoea (OSA)** and cardiovascular disease (CVD).
- ▶ **Genetics:** **PNPLA3 I148M** (adiponutrin, rs738409) — the strongest variant, increases steatosis, MASH and fibrosis; **TM6SF2** and **MBOAT7** also raise risk; **HSD17B13** loss-of-function is

protective. First-degree relatives of MASH-cirrhosis probands carry a **12-fold** higher risk of advanced fibrosis; twin studies attribute ~half of cirrhosis risk to heritability.

Pathogenesis (Multiple-Hit Model)

- ▶ The old “two-hit hypothesis” (Day & James) is now a **multiple-parallel-hit** model: *first hit* = hepatic steatosis from insulin resistance; *subsequent hits* = lipotoxic, oxidative and inflammatory insults causing hepatocyte injury and fibrosis.
- ▶ **Steatosis** results when free fatty acid (FFA) supply exceeds disposal — from (1) dietary fat uptake, (2) adipose lipolysis (driven by peripheral **insulin resistance**), and (3) hepatic **de novo lipogenesis (DNL)**. Dietary fructose is delivered directly via the portal vein and activates ChREBP/SREBP-1 to drive DNL. Triglyceride storage *per se* is a relatively safe, benign biomarker of metabolic dysfunction.
- ▶ **Steatohepatitis** is defined by **lipotoxicity** — toxic lipid intermediates (palmitate, cholesterol, lysophosphatidylcholine, ceramides) cause ER and oxidative stress, hepatocyte apoptosis/ballooning and **hepatic stellate-cell activation** → fibrosis.
- ▶ **Adipokine imbalance**: ↑leptin, TNF- α , IL-6, resistin, PAI-1 with ↓**adiponectin**. Obesity-related **gut dysbiosis** increases intestinal permeability and energy harvest, exposing the liver to inflammatory gut-derived products. Cirrhosis is the result of **futile/maladaptive repair** replacing parenchyma with scar.

Histopathology, Staging & Natural History

- ▶ **Macrovesicular steatosis in >5% hepatocytes** is the minimum. MASH additionally requires **hepatocyte ballooning + lobular (mixed) inflammation**; *Mallory-Denk bodies*, glycogenated nuclei, megamitochondria and lipogranulomas may be seen.
- ▶ Fibrosis is characteristically **perisinusoidal/pericellular “chicken-wire” fibrosis in acinar zone 3**, later becoming portal and bridging.
- ▶ **NAFLD Activity Score (NAS, NASH-CRN/Brunt)**: unweighted sum of steatosis (0–3) + lobular inflammation (0–3) + ballooning (0–2) = 0–8; ≤ 2 “not-NASH”, ≥ 5 “likely NASH”. Fibrosis is **staged separately F0–F4** (F0 none → F1 mild → F2 significant → F3 advanced/bridging → F4 cirrhosis).

Fibrosis stage	Description	Fibrosis progression rate
Simple steatosis (MASL)	fat only, no injury	~1 stage / 14 years
MASH (steatohepatitis)	ballooning + inflammation	~1 stage / 7 years
“At-risk MASH”	MASH + fibrosis $\geq$ F2	high-risk; warrants therapy
F4 cirrhosis	bridging + nodules	decompensation 3–20%/yr; HCC 1–2%/yr

- ▶ **Fibrosis stage is the single strongest predictor of liver-related morbidity and mortality.** Most patients are asymptomatic until cirrhosis; the leading overall cause of death is **cardiovascular disease**, not liver disease.

Diagnosis & Non-Invasive Staging

- ▶ Usually an **incidental finding** — raised ALT or steatosis on imaging. Exclude alternatives: alcohol, hepatitis C (esp. genotype 3), autoimmune hepatitis, Wilson disease, haemochromatosis, α 1-antitrypsin deficiency, drugs (amiodarone, methotrexate, tamoxifen, valproate, glucocorticoids, NRTIs).
- ▶ **Biochemistry:** mild aminotransferase rise; **ALT/AST ratio is usually >1 in MASLD** (reverses to <1 with advanced fibrosis — contrast with the AST>ALT of alcohol). *Normal ALT does not exclude MASLD* (up to 80% have normal enzymes). ANA/SMA and ferritin may each be mildly raised in ~30%.
- ▶ **Two-step non-invasive testing (NITs):**
 - **Step 1 – FIB-4 index** (age, AST, ALT, platelet count): <1.3 → low risk, manage/recheck in primary care; ≥ 2.67 → high risk, refer.
 - **Step 2 – VCTE (transient elastography) liver stiffness:** <8 kPa rules out advanced fibrosis; 8–12 kPa = possible fibrotic MASH; >12 kPa = high likelihood advanced fibrosis. **ELF panel** (hyaluronic acid + TIMP-1 + PIIINP; FDA-approved, ≥ 9.8 = high progression risk) is an alternative blood-based test.
 - Other scores/tools: NAFLD Fibrosis Score, **CAP** (steatosis quantitation with VCTE), **MRI-PDFF** (most accurate fat quantitation) and **MRE** (most accurate fibrosis tool).
- ▶ **Liver biopsy** (gold standard, NAS + fibrosis stage) is now reserved for diagnostic uncertainty, discordant/indeterminate NITs, or suspected competing diagnosis — limited by sampling error and inter-observer variability.

Treatment

- ▶ **Lifestyle modification is foundational for all patients:** graded weight loss — 5% reduces steatosis, 7–10% reduces inflammation/MASH, >10% can regress fibrosis. **Mediterranean diet**, avoid saturated fat / refined carbohydrate / sugar-sweetened (fructose) beverages; ≥ 150 min/week moderate exercise (aerobic and resistance both effective); **coffee ≥ 3 cups/day** lowers fibrosis/HCC risk; abstain from alcohol.
- ▶ **Pharmacotherapy** is reserved for at-risk MASH ($\geq F2$) without cirrhosis — *not* for simple steatosis:

Agent	Class / mechanism	Evidence
Resmetirom	Selective THR- β agonist	FDA accelerated approval (2024) for non-cirrhotic at-risk MASH; MAESTRO-NASH — NASH

Agent	Class / mechanism	Evidence
		resolution 26–30% vs 10%, fibrosis improvement 24–26% vs 14%
Pioglitazone (30 mg/d)	TZD, PPAR- γ ligand	PIVENS — NASH resolution 47% vs 21%; weight gain, fracture, bladder-cancer/CHF caution
Vitamin E (RRR- α -tocopherol 800 IU/d)	Antioxidant	PIVENS — histologic improvement 43% vs 19% (non-diabetics); caution: haemorrhagic stroke, ?prostate cancer
GLP-1 RA (semaglutide, liraglutide); tirzepatide (GLP-1/GIP)	Incretin mimetics	NASH resolution (semaglutide 0.4 mg 59% vs 17%); weight loss, CV benefit; fibrosis benefit not yet proven
SGLT-2 inhibitors	Glycosuric	↓ALT and steatosis; histologic benefit unproven
Statins	—	Safe in MASLD/compensated cirrhosis; treat dyslipidaemia, lower portal pressure, ?↓HCC

- ▶ **Not recommended / no benefit:** metformin (no histologic benefit – TONIC study; may ↓HCC risk), ursodeoxycholic acid, betaine, silymarin.
- ▶ **Bariatric surgery** for BMI ≥ 40 , or ≥ 35 with comorbidity — resolves MASH and improves fibrosis in ~80% at 1 year; avoid in decompensated cirrhosis.
- ▶ **Liver transplantation** for decompensated MASH cirrhosis/HCC; MASLD is now a leading transplant indication and **may recur** in the graft.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Spectrum/natural-history flow diagram:** Normal liver $\rightarrow$ Simple steatosis (MASL) $\rightarrow$ Steatohepatitis (MASH: ballooning + inflammation) $\rightarrow$ Fibrosis (F1 $\rightarrow$ F2 $\rightarrow$ F3 bridging) $\rightarrow$ Cirrhosis (F4) $\rightarrow$ HCC. Label progression rates (1 stage/14 yr for steatosis, 1 stage/7 yr for MASH) and mark “at-risk MASH = MASH + $\geq$ F2”.
- ▶ **Two-step risk-stratification algorithm:** Box 1 FIB-4 (<1.3 low / ≥ 2.67 high) $\rightarrow$ Box 2 VCTE (<8 / 8–12 / >12 kPa) or ELF $\rightarrow$ “refer to hepatology / consider biopsy”. Label axes “Primary care $\rightarrow$ Specialist”.

Clinical / Diagnostic significance

- ▶ **CVD is the leading cause of death** in MASLD — aggressive cardiovascular risk reduction (statins, BP, glycaemic control) is central, not optional.
- ▶ MASLD is an independent risk factor for **incident T2DM, CKD, colorectal cancer and metabolic syndrome**; it can cause **HCC even without cirrhosis**, complicating surveillance.
- ▶ Once **cirrhosis** is diagnosed: 6-monthly **HCC surveillance** (USS ± AFP), endoscopic **variceal screening per Baveno**, and monitoring for decompensation.
- ▶ A large share of “**cryptogenic cirrhosis**” is burnt-out MASH (steatosis disappears as fibrosis advances).
- ▶ Targeted (not universal) screening of high-risk groups — T2DM, obesity-with-metabolic-complications, family history of cirrhosis — using FIB-4 is cost-effective.

High-yield exam pointers

- ▶ **New nomenclature (2023): SLD umbrella** → MASLD / MetALD / MASH; ~98% overlap with old NAFLD/NASH.
- ▶ MASLD = steatosis + ≥1 **cardiometabolic risk factor** + alcohol <20 g/d (F) / <30 g/d (M).
- ▶ >5% **steatotic hepatocytes** = minimum; MASH = **ballooning + lobular inflammation**; “chicken-wire” zone-3 fibrosis.
- ▶ T2DM = **strongest risk factor**; PNPLA3 I148M = key gene; HSD17B13 protective.
- ▶ Fibrosis stage = **best prognostic marker**; CVD = **commonest cause of death**.
- ▶ NAS 0–8 (steatosis+inflammation+ballooning); fibrosis staged separately F0–F4.
- ▶ FIB-4 then VCTE/ELF is the non-invasive pathway; FIB-4 <1.3 excludes advanced fibrosis.
- ▶ **Weight loss 5/7/10%** = steatosis/MASH/fibrosis benefit; **resmetirom** (THR-β agonist) = first FDA-approved drug (2024); pioglitazone & vitamin E from PIVENS.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Metabolic Dysfunction–Associated Steatotic Liver Disease and Steatohepatitis” (primary spine: nomenclature, criteria, pathogenesis, FIB-4/VCTE/ELF staging, resmetirom/PIVENS, bariatric surgery, transplant).
- ▶ **Sleisenger & Fordtran’s Gastrointestinal and Liver Disease, 11e** — “Nonalcoholic Fatty Liver Disease” (two-hit/multiple-hit pathogenesis, NAS/Brunt histology, PNPLA3/MBOAT7 genetics, natural history).
- ▶ **CMDT 2026** — “Metabolic Dysfunction–Associated Steatotic Liver Disease” (ALT/AST ratio, weight-loss thresholds, current drug regimens, prognosis).



Portocaval anastomosis and management of portal hypertension

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — **Portal hypertension** is defined as elevation of the **hepatic venous pressure gradient (HVPG)** to **>5 mmHg**. The portal venous system normally drains blood from the stomach, small and large intestines, spleen, pancreas, and gallbladder into the liver. When portal pressure rises, blood is diverted through **portosystemic (portocaval) collateral channels** — pre-existing communications between the portal and systemic venous systems that dilate to decompress the hypertensive portal bed; these collaterals are the anatomical basis of **varices, caput medusae and shunt-related complications**. The three primary clinical consequences are **gastroesophageal varices with haemorrhage, ascites, and splenomegaly with hypersplenism**.

Sites of portosystemic (portocaval) anastomosis

- ▶ **Lower oesophagus / gastro-oesophageal junction** — left gastric (coronary) and short gastric veins (portal) anastomose with the azygos/hemiazygos system (systemic) → **oesophageal and gastric varices** (the most dangerous, cause variceal haemorrhage).
- ▶ **Anorectal junction** — superior rectal vein (portal, via inferior mesenteric vein) anastomoses with middle and inferior rectal veins (systemic) → **anorectal varices** (distinct from haemorrhoids).
- ▶ **Periumbilical / anterior abdominal wall** — recanalised paraumbilical vein (via left branch of portal vein) anastomoses with superficial epigastric veins → **caput medusae**; a venous hum over it = *Cruveilhier–Baumgarten murmur*.
- ▶ **Retroperitoneal / bare areas** — veins of *Retzius* and *Sappey* between gut/liver and retroperitoneal systemic veins.
- ▶ **Spontaneous splenorenal shunt** — splenic vein to left renal vein; relevant to gastric varices and amenable to BRTO.

Classification of portal hypertension (Harrison Table 355-3)

Anatomical level	Site relative to sinusoid	Representative causes
Prehepatic	—	Portal vein thrombosis; splenic vein thrombosis; massive splenomegaly (<i>Banti's syndrome</i>)
Intrahepatic — presinusoidal	Before sinusoid	Schistosomiasis; congenital hepatic fibrosis
Intrahepatic — sinusoidal	At sinusoid	Cirrhosis (many causes) ; alcoholic hepatitis
Intrahepatic — postsinusoidal	After sinusoid	Hepatic sinusoidal obstruction (veno-occlusive syndrome)

Anatomical level	Site relative to sinusoid	Representative causes
Posthepatic	Hepatic veins → heart	Budd-Chiari syndrome; IVC webs; restrictive cardiomyopathy; constrictive pericarditis; severe congestive heart failure

- ▶ Intrahepatic causes account for >95% of cases, and cirrhosis is overwhelmingly the most common cause of portal hypertension.

Pathophysiology and haemodynamic staging

- ▶ Portal hypertension results from **two simultaneous processes**: (1) **increased intrahepatic resistance** to blood flow (cirrhosis, regenerative nodules, microthrombi), and (2) **increased splanchnic blood flow** from splanchnic vasodilation (mediated by nitric oxide and other vasodilators).
- ▶ In advanced disease, **neurohumoral activation** (renin-angiotensin-aldosterone and sympathetic systems) causes sodium/water retention, expanded blood volume, and a **hyperdynamic circulation** that further raises portal pressure.
- ▶ **Compensated cirrhosis**: HVPg 5–10 mmHg — may be asymptomatic for ≥10 years.
- ▶ **Clinically significant portal hypertension (CSPH)**: HVPg ≥10 mmHg — substantial risk of decompensation (variceal bleed, ascites, encephalopathy).
- ▶ **Variceal haemorrhage risk**: HVPg / gradient >12 mmHg. After decompensation, median survival is <2 years.

Clinical features and diagnosis

- ▶ **Three primary complications**: gastroesophageal varices ± haemorrhage; ascites with peripheral oedema; congestive splenomegaly with **hypersplenism** (thrombocytopenia, leukopenia) — often the *first* indication of portal hypertension.
- ▶ **Variceal haemorrhage** carries a 20–30% mortality per bleeding episode; ~5–15% of cirrhotics develop varices per year, and ~one-third of those with varices will bleed.
- ▶ **Predictors of bleeding**: severity of cirrhosis (Child-Pugh class, MELD score), height of wedged-hepatic-vein pressure, varix size and location, tense ascites, and endoscopic stigmata — *red wale signs, hematocystic spots, diffuse erythema, bluish colour, cherry-red spots, white-nipple spots*.
- ▶ **Diagnosis**: suggested by thrombocytopenia, splenomegaly, ascites, encephalopathy or varices. Endoscopy identifies varices; contrast CT/MRI shows nodular liver and intra-abdominal collateral circulation; HVPg can rarely be measured by interventional radiology.
- ▶ **Ascites work-up**: diagnostic paracentesis with SAAG — a SAAG >1.1 g/dL indicates portal hypertension as the cause; ascitic neutrophils >250/μL indicate spontaneous bacterial peritonitis.

Management of variceal haemorrhage

A. Primary prophylaxis (no prior bleed)

- ▶ Surveillance **endoscopy** at diagnosis of compensated cirrhosis, then every 2 years if liver disease is active or every 3 years if inactive; screening can be omitted if no thrombocytopenia and transient elastography liver stiffness <20 kPa.
- ▶ High-risk varices = medium/large varices, or small varices with high-risk stigmata or decompensated cirrhosis.
- ▶ **Nonselective beta-blockers (NSBB)** — propranolol or nadolol titrated to **heart rate 55–60 beats/min** with systolic BP >90 mmHg. **Carvedilol** is the NSBB of choice (added anti- α 1 vasodilation lowers portal pressure more, needs no HR goal, may prevent decompensation and improve survival in CSPH).
- ▶ **Endoscopic variceal ligation (EVL)** has equivalent efficacy to NSBB for primary prophylaxis; once prophylaxis is started, surveillance endoscopy is unnecessary.

B. Acute variceal bleeding

- ▶ **Resuscitate**: fluid and red-cell replacement using a **restrictive transfusion** strategy (start at Hb <7 g/dL, goal 7–9 g/dL) — reduces rebleeding and mortality. Do **not** correct prolonged PT with FFP unless there is active coagulopathic bleeding.
- ▶ **Vasoconstrictors** — **somatostatin** or **octreotide** improve initial bleeding control, reduce transfusion needs and all-cause mortality.
- ▶ **Prophylactic antibiotics** — **ceftriaxone** before endoscopy reduces infection, rebleeding and mortality.
- ▶ **Urgent upper endoscopy** is first-line — diagnoses and controls bleeding with EVL.
- ▶ **Balloon tamponade** (*Sengstaken-Blakemore* or *Minnesota* tube) or self-expandable metal stents can stabilise the patient as a **bridge to TIPS** after endoscopic failure.

C. TIPS and shunts (portal decompression)

- ▶ **Transjugular intrahepatic portosystemic shunt (TIPS)** is created percutaneously: an expandable metal stent is advanced under angiographic guidance into the hepatic vein and through the hepatic parenchyma to form a **direct portocaval shunt** that decompresses the portal system.
- ▶ Indications: failure of/ineligibility for endoscopic therapy; gastric or proximal-stomach varices where band ligation often fails; refractory recurrent bleeding; bridge to transplant.
- ▶ **Hepatic encephalopathy** occurs in up to 20% after TIPS, especially in the elderly and those with pre-existing encephalopathy.
- ▶ Gastric varices fed by a **splenorenal shunt** can be treated with **balloon-occluded retrograde transvenous obliteration (BRTO)**, sometimes combined with TIPS.
- ▶ Monitor TIPS patency with **Doppler ultrasound** for stenosis; all TIPS candidates should undergo transplant evaluation.

D. Recurrent bleeding (Harrison Fig. 355-3)

- ▶ Endoscopic therapy + pharmacologic therapy to control bleeding, then risk-stratify by Child class: **Child A** → consider TIPS and transplant evaluation; **Child B/C** → transplant evaluation with endoscopic therapy/beta-blockers and consideration of TIPS, progressing to **liver transplantation**.

Management of other portal-hypertensive complications

- ▶ **Ascites**: dietary **sodium restriction** (2 g/day); **spironolactone** 100 mg/d ± **furosemide** 40 mg/d, escalating to spironolactone 400 mg/d and furosemide 160 mg/d. **Refractory ascites** → large-volume paracentesis (give IV **25% albumin** 6–8 g per L removed if ≥5 L) or TIPS (effective but does *not* improve survival and increases encephalopathy). Avoid NSAIDs and aminoglycosides; use ACEi/ARB cautiously.
- ▶ **Spontaneous bacterial peritonitis**: ascitic neutrophils >250/μL; commonest organism *E. coli*; treat with IV **third-generation cephalosporin** × 5 days plus **albumin** (1.5 g/kg day 1, 1.0 g/kg day 3) to prevent renal failure; **quinolone prophylaxis** after an episode and at presentation with GI bleeding.
- ▶ **Hepatorenal syndrome**: stop diuretics, give albumin 1 g/kg/d; treat with **terlipressin** (or low-dose norepinephrine); midodrine + octreotide + albumin are third-line; **liver transplantation** is definitive.
- ▶ **Hepatic encephalopathy**: treat precipitants; **lactulose** titrated to 2–3 soft stools/day; **rifaximin** 550 mg twice daily (has replaced neomycin/metronidazole); closure of large portosystemic shunts in refractory cases; avoid protein restriction.
- ▶ **Portal hypertensive gastropathy**: *snakeskin mosaic* mucosa; treat with NSBB + iron; refractory bleeding → TIPS.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Sites of portosystemic anastomosis** — outline the portal vein with collaterals labelled: *Oesophageal varices* (left gastric/corony → azygos), *Anorectal varices* (superior ↔ middle/inferior rectal), *Caput medusae* (paraumbilical ↔ epigastric), *Retroperitoneal veins of Retzius*, *Splenorenal shunt* (splenic ↔ left renal vein).
- ▶ **TIPS schematic** — label: *Jugular vein* → IVC → *Hepatic vein*, *Expandable metal stent* through hepatic parenchyma, *Portal vein*, *Direct portocaval shunt*.

Clinical / Diagnostic significance

- ▶ HVPG is the gold-standard measure of portal pressure and stratifies risk: >5 = portal hypertension, ≥10 = CSPH/decompensation risk, >12 = variceal bleeding risk.
- ▶ SAAG >1.1 g/dL confirms portal hypertension as the cause of ascites; ascitic protein <1.5 g/dL flags increased SBP risk.

- ▶ Endoscopic surveillance and NSBB/carvedilol or EVL prevent first bleeds; vasoconstrictor + antibiotic + endoscopic therapy is the acute bleeding bundle.
- ▶ TIPS is the key non-surgical portal decompression but precipitates encephalopathy; liver transplantation is the definitive treatment for decompensated portal hypertension.

High-yield exam pointers

- ▶ Portal hypertension = HVPG >5 mmHg; variceal bleeding risk at >12 mmHg; CSPH = ≥ 10 mmHg.
- ▶ Cirrhosis (sinusoidal, intrahepatic) >95% of cases; classify pre-/intra-/post-hepatic.
- ▶ Three complications: varices, ascites, hypersplenism; variceal bleed mortality 20–30%/episode.
- ▶ Acute bleed bundle: restrictive transfusion (Hb 7–9), octreotide/somatostatin, ceftriaxone, urgent EVL.
- ▶ Carvedilol is now the NSBB of choice for primary prophylaxis of variceal bleeding.
- ▶ TIPS = direct portocaval shunt; complication = encephalopathy in up to 20%; bridge to transplant.
- ▶ Sengstaken-Blakemore / Minnesota tube = balloon tamponade rescue; BRTO for splenorenal-shunt gastric varices.
- ▶ Ascites: spironolactone + furosemide, albumin after LVP ≥ 5 L; SBP = neutrophils >250/ μ L.
- ▶ HE: lactulose + rifaximin 550 mg BD; *caput medusae* with a hum = Cruveilhier-Baumgarten sign.

SOURCE & COVERAGE

Harrison 22e — Ch 355 “Cirrhosis and Its Complications” (Tables 355-2/355-3; Figs 355-3, 355-4, 355-5). **Coverage note:** Harrison Ch 355 covers the definition, HVPG thresholds, classification, pathophysiology and full management of portal hypertension and its complications, and names gastroesophageal varices, the splenorenal shunt, intra-abdominal collateral circulation and the TIPS portocaval shunt. The detailed *named anatomical sites of portosystemic anastomosis* (caput medusae / Cruveilhier-Baumgarten, anorectal varices, periumbilical and retroperitoneal veins of Retzius/Sappey, splenorenal shunt drainage) are universally accepted standard anatomy supplied to satisfy the “portocaval anastomosis” phrasing, as this anatomical detail is thin in the provided chapter.



Serologic and virologic markers of Hepatitis “B”

Asked in: Paper II Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Hepatitis B virus (HBV) is a 42-nm, enveloped, partially double-stranded DNA hepadnavirus with an outer **hepatitis B surface antigen (HBsAg)** coat, an inner **hepatitis B core antigen (HBcAg)**, secreted **hepatitis B e antigen (HBeAg)**, and circulating HBV DNA. Serologic and virologic markers diagnose acute HBV, distinguish natural recovery from vaccination, define chronic infection beyond 6 months, assess infectivity and replication, and identify clinically important mutant or occult infection.

Virologic basis and chronology

- ▶ **HBsAg** is the envelope protein of virions and abundant noninfectious spherical/tubular particles; routine assays detect all forms. It is the **first serum marker**, detectable **1-12 weeks after exposure**, usually **8-12 weeks**, and precedes ALT rise and symptoms by **2-6 weeks**.
- ▶ **HBcAg** remains intracellular or within HBsAg-coated nucleocapsids; naked core antigen does not circulate, so **HBcAg is not a routine serum diagnostic test**. Its antibody, **anti-HBc**, is therefore more useful clinically.
- ▶ **HBeAg** is a secreted nucleocapsid protein from the precore/core gene. It appears with or shortly after HBsAg and is a **qualitative marker of replication, intact virions, high infectivity, and usually detectable HBV DNA**.
- ▶ **HBV DNA** is the direct virologic marker of replication and is more sensitive and precise than HBeAg; it is essential in chronic HBV, pregnancy transmission risk, antiviral decisions, and follow-up.
- ▶ **Anti-HBc** appears **1-2 weeks after HBsAg**. **IgM anti-HBc** predominates for the first **6 months** after acute infection; **IgG anti-HBc** persists indefinitely after either recovery or chronicity.
- ▶ **Anti-HBs** appears after HBsAg clearance, usually weeks to months after anti-HBc, persists long-term, and is the **protective neutralizing antibody** after natural infection or vaccination.
- ▶ **Anti-HBe** appears after HBeAg loss and usually indicates lower replication and reduced infectivity, but it does not exclude HBeAg-negative chronic hepatitis due to precore or basal core promoter mutants.

Individual markers and interpretation

Marker	What it detects	High-yield interpretation
HBsAg	Surface/envelope antigen in virions and subviral particles	Current HBV infection; persistence >6 months = chronic HBV. In self-limited acute HBV it disappears 1-2 months after jaundice and rarely persists beyond 6 months.
Anti-HBs	Antibody to HBsAg	Recovery, noninfectivity, and immunity when it follows natural infection; isolated anti-HBs

Marker	What it detects	High-yield interpretation
		indicates vaccination. Protective vaccine response is commonly taken as ≥ 10 mIU/mL.
Total anti-HBc	IgM + IgG antibody to core antigen	Marker of natural exposure; not produced by vaccination . Persists after recovery and in chronic HBV.
IgM anti-HBc	Recent anti-core response	Best marker of acute/recent HBV; sole marker in the window period ; may reappear during severe flares/reactivation of chronic HBV.
IgG anti-HBc	Remote or chronic anti-core response	Past natural infection or chronic HBV; predominates beyond 6 months.
HBeAg	Secreted e antigen	High replication and infectivity; persistence >3 months after acute HBV suggests higher likelihood of chronic infection.
Anti-HBe	Antibody to e antigen	Seroconversion marker, usually lower infectivity; can coexist with active HBV DNA replication in precore/core promoter mutant disease.
HBV DNA by PCR	Viral nucleic acid	Quantitative replication marker; correlates with infectivity, liver injury, progression, cirrhosis, HCC risk, and treatment response.
Quantitative HBsAg	Serum HBsAg level	Specialist follow-up marker; serial use may help distinguish inactive carrier state from HBeAg-negative active disease.

Acute hepatitis B: serologic sequence

- ▶ **Early incubation:** HBV DNA and HBsAg appear before clinical hepatitis; HBeAg follows shortly and indicates high infectivity. ALT rises later, with symptoms and jaundice.
- ▶ **Symptomatic/icteric phase:** HBsAg remains detectable; **IgM anti-HBc** is present and confirms acute HBV. HBeAg usually disappears near peak ALT before HBsAg clearance.
- ▶ **Resolution:** HBsAg becomes negative, **anti-HBe** appears first, then **anti-HBs** appears and persists. Anti-HBc switches from predominantly IgM to predominantly IgG.

- ▶ **Window period:** HBsAg has disappeared but anti-HBs is not yet detectable; **IgM anti-HBc may be the only serologic evidence** of current or recent infection. More sensitive modern HBsAg and anti-HBs assays make this less common.
- ▶ **Rare HBsAg-negative acute HBV:** in up to 1-5% of acute infections, HBsAg may be below assay detection; **IgM anti-HBc establishes the diagnosis.**
- ▶ **Progression to chronicity:** persistence of HBsAg >6 months or HBeAg >3 months after acute illness suggests chronic HBV. Immunocompetent adults usually recover; chronicity is far more common after neonatal, childhood, or immunosuppressed infection.

Common serologic patterns

HBsAg	Anti-HBs	Anti-HBc	HBeAg / anti-HBe	HBV DNA	Interpretation
-	-	-	-	-	Susceptible, no evidence of prior infection or vaccination.
-	+	-	-	-	Vaccinated immune; anti-HBs alone.
-	+	IgG +	Usually anti-HBe + or -	Usually undetectable	Recovered natural infection; immune due to past HBV.
+	-	IgM +	HBeAg often + early	+	Acute hepatitis B.
-	-	IgM +	Variable	Variable	Window period or rare HBsAg-negative acute HBV.
+ >6 months	-	IgG +	HBeAg +	High	HBeAg-positive chronic HBV/chronic hepatitis; high replication and infectivity.
+ >6 months	-	IgG +	HBeAg -, anti-HBe +	Low or undetectable, usually <2000 IU/mL	Inactive carrier / HBeAg-negative chronic HBV infection, if ALT normal and stable over serial follow-up.
+ >6 months	-	IgG +	HBeAg -, anti-HBe +	Detectable/high, often fluctuating	HBeAg-negative chronic hepatitis B from precore/core promoter mutant or

HBsAg	Anti-HBs	Anti-HBc	HBeAg / anti-HBe	HBV DNA	Interpretation
					reactivation; ALT often elevated or fluctuating.
-	-	IgG +	-	Usually negative; occasionally low-level positive	Isolated anti-HBc: remote infection with lost anti-HBs, false-positive, window period if IgM, or occult/low-level infection.
+	+	IgG +	Variable	Variable	Chronic HBV with low-affinity/nonneutralizing anti-HBs or heterotypic anti-HBs; not proof of imminent clearance.

Chronic HBV phases and virologic classification

- ▶ **HBeAg-positive chronic HBV infection (*immune-tolerant phase*):** HBeAg positive, very high HBV DNA, commonly $\geq 10^7$ IU/mL, normal or low ALT, and minimal necroinflammation/fibrosis; typical after perinatal or early-childhood infection.
- ▶ **HBeAg-positive chronic hepatitis B (*immune-active/clearance phase*):** HBeAg positive, HBV DNA high or intermediate, ALT elevated, and active necroinflammation. Harrison emphasizes that DNA is often well above 10^3 - 10^4 IU/mL and may exceed 10^9 IU/mL.
- ▶ **HBeAg-negative chronic HBV infection (*inactive carrier state*):** HBsAg positive, IgG anti-HBc positive, HBeAg negative, anti-HBe positive, normal ALT, minimal histologic activity, and HBV DNA undetectable or low, usually < 2000 IU/mL.
- ▶ **HBeAg-negative chronic hepatitis B (*reactivation phase*):** HBeAg negative but HBV DNA detectable, ALT elevated or fluctuating, and active liver injury. It is usually due to **precore stop-codon** or **basal core promoter** mutations, so absence of HBeAg does not prove inactive disease.
- ▶ **HBsAg-negative phase / functional cure:** HBsAg negative, anti-HBc positive, anti-HBs present or absent, normal ALT, and serum HBV DNA usually undetectable; intrahepatic cccDNA may persist, so reactivation remains possible under intense immunosuppression.
- ▶ The distinction between inactive carrier state and HBeAg-negative chronic hepatitis requires **serial ALT and HBV DNA monitoring over months**, because both DNA and aminotransferases may fluctuate.

Special patterns, mutants, and pitfalls

- ▶ **Precore mutation:** classically G1896A creates a stop codon and prevents HBeAg synthesis; patients have **anti-HBe with detectable HBV DNA** and may have progressive HBeAg-negative chronic hepatitis.
- ▶ **Basal core promoter mutations:** reduce HBeAg production while maintaining replication; they are associated with HBeAg-negative active disease and have been linked with more severe infection and HCC risk in specialist texts.
- ▶ **Occult HBV infection:** HBsAg negative with **detectable HBV DNA**, often low level, and sometimes without anti-HBc; important in cryptogenic liver disease, blood/organ donation, and immunosuppression.
- ▶ **Isolated anti-HBc** should not be equated automatically with active replication; common explanations are remote resolved infection with loss of anti-HBs, false positivity, window-period acute HBV if IgM, or rarely low-level occult infection.
- ▶ **HBsAg escape mutants** may alter the surface antigen “a” determinant, causing failure of commercial HBsAg detection or reduced neutralization by vaccine/HBIG-derived anti-HBs.
- ▶ **IgM anti-HBc is not always de novo acute HBV:** it may reappear in severe flares or spontaneous/reactivation episodes of chronic HBV; clinical history, old records, HBsAg duration, and serial follow-up are essential.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Acute HBV timeline:** x-axis weeks after exposure; label HBV DNA/HBeAg early, HBsAg first antigen, ALT and jaundice peak, IgM anti-HBc, IgG anti-HBc, anti-HBe, anti-HBs, and the **window period** between HBsAg loss and anti-HBs appearance.
- ▶ **Chronic HBV phase chart:** label immune-tolerant HBeAg-positive infection, immune-active HBeAg-positive hepatitis, inactive carrier HBeAg-negative infection, HBeAg-negative chronic hepatitis/reactivation, and HBsAg-negative functional cure; show ALT and HBV DNA trends.

Clinical / Diagnostic significance

- ▶ **Acute HBV diagnosis:** HBsAg plus **IgM anti-HBc** confirms acute infection; IgM anti-HBc is decisive in the window period and in rare low-HBsAg acute disease.
- ▶ **Chronic HBV diagnosis:** HBsAg persistence beyond 6 months with IgG anti-HBc establishes chronic HBV; HBeAg, anti-HBe, HBV DNA, ALT, and fibrosis assessment classify activity.
- ▶ **Infectivity and transmission:** HBeAg-positive, high-DNA serum is highly infectious; HBeAg-positive mothers transmit HBV to offspring far more often than anti-HBe-positive mothers. Maternal HBV DNA $\geq 200,000$ IU/mL supports third-trimester antiviral prophylaxis in addition to neonatal HBIG plus vaccine.

- ▶ **Treatment and prognosis:** HBV DNA is the key quantitative marker for antiviral decisions and monitoring; persistent high replication predicts cirrhosis and HCC risk. Short-term treatment endpoints include HBV DNA suppression, HBeAg loss/seroconversion, ALT normalization, and ideally HBsAg loss.
- ▶ **Screening before immunosuppression:** HBsAg and anti-HBc, often with anti-HBs, should be checked before chemotherapy, B-cell-depleting agents, transplantation, or prolonged immunosuppression because resolved or inactive HBV can reactivate.
- ▶ **Vaccination and postexposure care:** isolated anti-HBs indicates vaccine immunity; postvaccination anti-HBs testing is useful in high-risk adults, dialysis, immunosuppression, and occupational exposure decisions. HBIG provides immediate anti-HBs, while vaccine provides durable active immunity.
- ▶ **Blood and organ safety:** screening of donated blood for HBsAg and anti-HBc has markedly reduced transfusion-associated HBV; isolated anti-HBc or occult HBV can still be clinically relevant in donors and immunosuppressed recipients.

High-yield exam pointers

- ▶ HBsAg first, anti-HBs last is the simplest acute HBV chronology.
- ▶ IgM anti-HBc = acute/recent HBV and is the marker of the **window period**.
- ▶ IgG anti-HBc = natural exposure, not vaccination.
- ▶ Anti-HBs alone = vaccination; anti-HBs plus IgG anti-HBc = recovered natural infection.
- ▶ HBsAg >6 months = chronic HBV; HBeAg >3 months after acute infection predicts chronicity.
- ▶ HBeAg = replication/infectivity, but HBV DNA is the best quantitative replication marker.
- ▶ HBeAg-negative does not mean inactive; check HBV DNA and ALT for precore/core promoter mutant disease.
- ▶ **Inactive carrier:** HBsAg positive, anti-HBe positive, normal ALT, low/undetectable HBV DNA, usually <2000 IU/mL.
- ▶ **Isolated anti-HBc** needs interpretation: remote infection, false-positive, window period, or occult/low-level HBV.

SOURCE & COVERAGE

Harrison 22e — “Acute Viral Hepatitis”; Harrison 22e — “Chronic Hepatitis”; Sleisenger & Fordtran’s Gastrointestinal and Liver Disease — “Hepatitis B”; CMDT 2026 — “Liver, Biliary Tract, & Pancreas Disorders”.



Tropical Sprue

Asked in: Paper II Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Tropical sprue (TS) is a **primary, acquired malabsorption syndrome** affecting residents of, or visitors to, endemic tropical regions, characterised by chronic diarrhoea, steatorrhoea, weight loss and multiple nutrient deficiencies (classically **both folate and vitamin B12**). The term “primary” implies that all other recognised causes of malabsorption have been excluded. By the **Baker–Klipstein definition (1970)**, diagnosis requires malabsorption of **at least two unrelated nutrient groups** (e.g. fat, carbohydrate, vitamins), an abnormal small-bowel mucosal biopsy, and exclusion of celiac disease, parasitic infection, SIBO and pancreatic insufficiency. It is regarded by many as a **post-infectious complication** of acute enteritis and responds to broad-spectrum antibiotics plus folic acid.

Historical note & epidemiology

- ▶ **History:** Malabsorption in the tropics is described in the *Charaka Samhita* as “**Grahani**” (loss of “digestive fire”). First English description by **William Hillary (1759, Barbados)** as *aphthoides chronica*; the word “sprue” derives from the Dutch *sprouw* (aphthous mouth ulceration); **Manson** coined “sprue” in 1880.
- ▶ **Geography:** Endemic in **South & South-East Asia** (southern India, Pakistan), **the Philippines**, **the Caribbean** (Puerto Rico, Haiti, Cuba), **Central/South America** and **parts of tropical Africa/Australia**. **Notably rare in Africa, Jamaica and parts of South-East Asia** — distribution is patchy, suggesting different aetiologies in different regions.
- ▶ **Burden:** Occurs in **8–20%** of people after an attack of infectious gastroenteritis in India. **Adults > children** (opposite to celiac disease). **Epidemic TS** occurred in WWII soldiers/POWs and in South India in the 1960s–70s (responsible for **30,000–40,000 deaths**); epidemic disease is **no longer reported**, but **sporadic TS** remains a leading cause of adult malabsorption in South Asia. Seasonal clustering was noted in Puerto Rico (first 3 months of the year).
- ▶ **Declining incidence** over recent decades — attributed to improved sanitation and wider antibiotic use in acute diarrhoea.

Aetiopathogenesis

- ▶ The aetiology is **uncertain**; no single causative agent has ever been isolated despite extensive search. Because TS **responds to antibiotics**, an **infectious/post-infectious basis** is favoured.
- ▶ **Post-infectious trigger:** In travellers/expatriates, an antecedent gastroenteritis (enteropathogenic *E. coli*, *Giardia*, *Cyclospora*) greatly raises risk — in US military personnel, prior infectious gastroenteritis increased the odds of TS **~36.6-fold** and of intestinal malabsorption **~3.9-fold**.
- ▶ **Small-intestinal bacterial overgrowth (SIBO):** Overgrowth of **enterotoxigenic coliforms** (*Klebsiella*, *Enterobacter cloacae*, *E. coli*) in the upper small bowel. Unabsorbed luminal fat activates the “**ileal brake**” (peptide YY, neurotensin) → slowed small-bowel transit → perpetuation of SIBO.

- ▶ **Other agents:** Coronavirus-like viral particles seen in jejunal enterocytes in some series (inconsistent).
- ▶ **Mucosal injury model:** Microbial toxins damage **intestinal crypt stem cells** → immature enterocytes, villous shortening and increased permeability → mucosal inflammation with a marked rise in **intraepithelial lymphocytes (IELs)** (predominantly CD8+ $\alpha\beta$ -T cells; innate signalling via NOD-2/TLR-2, IL-15, T-bet). The difference between symptomatic TS and asymptomatic tropical enteropathy may reflect host innate immune response.

Clinical features

- ▶ **Cardinal triad:** chronic diarrhoea, **sore red tongue (glossitis)** and weight loss; stools are **pale, bulky, frothy, foul-smelling (steatorrhoea)** with abdominal distension and borborygmi; nocturia.
- ▶ **Onset:** In southern India often follows an **acute enteritis**; in expatriates/epidemics begins with fever and watery (rarely bloody) diarrhoea, then lingering diarrhoea with weight loss. Course shows **exacerbations and remissions**.
- ▶ **Deficiency signs:** pallor (iron, folate, B12 anaemia); **angular stomatitis, cheilitis, glossitis** (B-complex); **hyperpigmentation of palms, knuckles and buccal mucosa** (attributed to B12 deficiency — may be the only presenting sign); pedal oedema, leukonychia, koilonychia and hair/skin changes (hypoproteinaemia/iron).
- ▶ **Late/severe:** gross emaciation with proximal muscle weakness; **night blindness, Bitot spots, corneal xerosis** (vitamin A); tetany/carpopedal spasm (Ca/Mg); haemorrhagic diathesis (vitamin K); metabolic bone disease (vitamin D); peripheral neuropathy. *Subacute combined degeneration of the cord* (historical) and “**sprue coma**” (apathy/listlessness from magnesium depletion) are now rare. A rare **Ogilvie-like colonic pseudo-obstruction** may occur.
- ▶ **Clubbing is NOT a feature** — its presence should suggest an alternative (e.g. IPSID/lymphoma).

Histopathology & pathophysiology

- ▶ Biopsy from distal duodenum/proximal jejunum (now standard at upper GI endoscopy) shows **partial villous atrophy with crypt elongation/hyperplasia**; villi may appear fused; lamina propria infiltrated by lymphocytes/plasma cells with **markedly increased IELs** (reported mean ~77 IELs/100 enterocytes); an eosinophilic infiltrate may be seen.
- ▶ The normal **villous-to-crypt ratio of 4:1–5:1 falls to ~2:1 or 1:1**. *Complete/flat (total) villous atrophy as in celiac disease is NOT seen in TS*.
- ▶ **Whole small-bowel involvement** (ileum often more affected than duodenum) — distinguishing it from the proximal-predominant celiac disease. Changes are of **similar severity throughout** the small bowel, and a **gluten-free diet does NOT improve TS**.

- ▶ **Electron microscopy:** degenerating/dead cells in the **basal crypt region** (a feature resembling radiation/chemotherapy enteritis) — supports a **primary stem-cell lesion**; *this differs from celiac disease*.
- ▶ **Functional consequences:** ↓ absorptive surface → ↓ **D-xylose** absorption; **fat malabsorption** with secondary *functional* pancreatic insufficiency (abnormal Lundh/pancreolauryl test, but **normal secretin response**); **B12 and bile-acid malabsorption** from terminal-ileal involvement; folate/iron malabsorption from proximal involvement → **combined folate + B12 deficiency** is characteristic.

Feature	Tropical sprue	Celiac disease
Distribution in small bowel	Entire small bowel (ileum ≥ duodenum)	Proximal (duodenum/jejunum) predominant
Villous atrophy	Partial; ratio 2:1–1:1; never totally flat	May be total/flat (Marsh III)
Vitamin pattern	Folate AND B12 both low	Folate low, B12 usually normal
Serology (anti-tTG/EMA)	Negative	Positive
Response to gluten-free diet	None	Clinical & histologic improvement
Response to antibiotics + folate	Curative	No response
EM crypt change	Degenerating basal crypt (stem-cell) cells	Absent

Diagnosis

- ▶ **No single diagnostic test** — diagnosis rests on **multiple nutrient deficiencies + abnormal small-bowel biopsy + exclusion** of other causes (Baker–Klipstein).
- ▶ **Mandatory exclusions:** *Giardia* and other parasites (≥3 stool samples with modified acid-fast stains — TS should not be entertained until cysts/trophozoites excluded), **celiac disease** (negative anti-tTG/EMA serology), SIBO and chronic pancreatitis.
- ▶ **Malabsorption tests (endemic-area data):** abnormal **D-xylose** ~99%, **steatorrhoea** ~90%, **B12 malabsorption** 60–90%; a 5-g (rather than 25-g) D-xylose dose is used in the tropics to avoid vomiting/diarrhoea. Serum **folate and B12 both low**; raised methylmalonic acid confirms B12 deficiency.
- ▶ **Endoscopy:** **scalloping** of duodenal folds and **mosaic/”mosaiform”** mucosa of the terminal ileum (better seen with narrow-band/magnification imaging); jejunal aspirate culture >10⁵ organisms/mL indicates SIBO.

- ▶ **Imaging:** barium follow-through shows **thickened mucosal folds, loss of the feathery jejunal pattern, dilated atonic loops and delayed transit**; CT mainly excludes mesenteric masses/lymphadenopathy (TB, lymphoma).

Treatment

- ▶ **Specific therapy:** Tetracycline 250 mg QID (or doxycycline 100 mg OD) for 3–6 months *plus* folic acid — usually **curative**, with clinical improvement often within 1–2 weeks; leaving the endemic area improves outcome.
- ▶ **Vitamin/mineral repletion:** parenteral **vitamin B12**, oral **folic acid** (alone induces haematologic remission, weight gain and partial histologic recovery), plus vitamin A (IM if night blindness/Bitot spots), vitamin K (if prolonged PT), vitamin D and calcium.
- ▶ **Supportive:** correct dehydration and electrolytes (**K, Mg, Ca, phosphate**) — severe hypokalaemia may need ECG-monitored replacement; high-protein, **fat-restricted, lactose-free** diet with **medium-chain triglycerides** to reduce steatorrhea; guard against **refeeding syndrome** in the severely malnourished (start ~10 kcal/kg/day, escalate over 4–7 days, give thiamine).
- ▶ **Prognosis:** relapses uncommon, especially if the patient leaves the tropics; **recurrent symptoms warrant re-investigation to exclude small-bowel lymphoma**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Comparative small-intestinal villous histology (three panels):** label (A) *Normal* — tall finger-like villi, villous:crypt ratio 4–5:1; (B) *Tropical sprue* — partial villous atrophy/blunting + fusion, **crypt elongation**, ratio 2:1–1:1, **increased intraepithelial lymphocytes**, lamina-propria lymphocytic infiltrate (ileum ≥ duodenum); (C) *Celiac disease* — flat/total villous atrophy (Marsh III). Add an inset labelling **EM: degenerating basal crypt stem cells** (TS-specific).
- ▶ **Aetiopathogenesis flow diagram:** *Acute enteric infection / bacterial toxins* → *crypt stem-cell injury* → *villous atrophy & ↑ permeability* → *mucosal inflammation (↑ IELs)* → *fat malabsorption* → *ileal brake (↑ peptide YY)* → *slow transit* → *SIBO (coliform overgrowth)* → *perpetuation of malabsorption*.

Clinical / Diagnostic significance

- ▶ Suspect TS in any patient with **chronic diarrhoea + steatorrhea + macrocytic anaemia** who lives in or has travelled to the tropics, once Giardia and celiac disease are excluded.
- ▶ The **folate + B12 deficiency** combination is a key clinical clue — distinguishes TS (whole-bowel disease) from celiac disease (proximal, folate-deficient, B12-normal).
- ▶ A **therapeutic response to tetracycline + folate** is itself supportive of the diagnosis; **failure to respond** mandates a search for lymphoma, TB or other mimics.

- ▶ Differentiate from **tropical (environmental) enteropathy** — the *asymptomatic* subclinical mucosal abnormality of tropical residents (shorter villi, ↑ permeability, abnormal lactulose:mannitol ratio) which causes no overt malabsorption and is linked to childhood stunting and reduced oral-vaccine immunogenicity.

High-yield exam pointers

- ▶ **Baker–Klipstein criteria:** malabsorption of ≥ 2 unrelated nutrients + abnormal biopsy + exclusion of other causes.
- ▶ **TS = whole small bowel; celiac = proximal.** TS: **partial** villous atrophy (never totally flat); celiac: may be **total** flat mucosa.
- ▶ **Both folate and B12 deficient** in TS (combined megaloblastic anaemia); celiac usually B12-normal.
- ▶ **No response to gluten-free diet; responds to antibiotics + folate** (tetracycline/doxycycline 3–6 months).
- ▶ **Hyperpigmentation of palms/knuckles/buccal mucosa** and **glossitis** are classic; **clubbing** is **NOT** (suggests IPSID/lymphoma).
- ▶ **EM hallmark:** degenerating cells in basal crypts (stem-cell lesion) — absent in celiac.
- ▶ **Exclude Giardia** (≥ 3 stools) before diagnosing TS; D-xylose abnormal in ~99%.
- ▶ Epidemic TS (South India 1960s, tens of thousands of deaths) now extinct; **sporadic TS persists.**
- ▶ Watch for **refeeding syndrome** and **magnesium-related “sprue coma”**; recurrence → rule out lymphoma.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Disorders of Absorption” (tropical sprue, environmental enteric dysfunction).
- ▶ **Sleisenger & Fordtran’s Gastrointestinal and Liver Disease, 11e** — “Tropical Diarrhea and Malabsorption” (definition, history, epidemiology, aetiopathogenesis, clinical features, Baker–Mathan histologic grading, pathophysiology, diagnosis and treatment) — primary depth source.
- ▶ **CMDT 2026** — Gastrointestinal Disorders (malabsorption/celiac differential) and Infectious Diseases (traveller’s diarrhoea, chronic watery diarrhoea) for current management context.
- ▶ Coverage note: CMDT 2026 mentions tropical sprue only briefly (within the celiac/traveller’s-diarrhoea differential), so management specifics (tetracycline/doxycycline ± folate) are grounded chiefly in Harrison and Sleisenger.



Autoimmune Hepatitis — Clinical Features, Extra-hepatic Associations and Autoantibodies

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Autoimmune hepatitis (AIH) is a chronic, immune-mediated inflammatory disorder characterised by continuing hepatocellular necrosis and inflammation, usually with fibrosis, that can progress to cirrhosis and liver failure. It is defined serologically by circulating **autoantibodies**, biochemically by **polyclonal hypergammaglobulinaemia** (raised IgG), and histologically by **interface hepatitis** with a plasma-cell-rich infiltrate, in the absence of viral, drug, metabolic or alcoholic causes. The prominence of *extra-hepatic autoimmune features* and seroimmunological abnormalities — reflected in the old labels “**lupoid**” and “**plasma-cell**” hepatitis — underpins its autoimmune pathogenesis. It shows a strong female predominance (~75% of cases) and a characteristic responsiveness to glucocorticoid/immunosuppressive therapy.

Epidemiology & immunopathogenesis (context)

- ▶ **Incidence** 2–4/100,000 and **prevalence** 26–31/100,000 (rising); risk increased in first-degree relatives.
- ▶ **Female predominance** ~75%; **bimodal age distribution** — one peak in early decades (age <30) and a second in middle-to-late years (often >60).
- ▶ Injury is a **cell-mediated (cytotoxic T-cell) attack** on hepatocytes following loss of immune tolerance to self-liver antigens; predisposition is inherited and the trigger is environmental (drugs e.g. **minocycline**, viruses such as hepatitis A/B/C, EBV, measles; reported after **COVID-19** and **COVID-19 vaccination**).
- ▶ **HLA associations:** HLA-B1, B8, DR3, DR4; extended haplotypes *DRB1\0301 and DRB1\0401; *polymorphisms in CTLA-4 and TNFA\2*. **Histology shows cytotoxic T cells and plasma cells;** regulatory CD4+CD25+ T-cell **dysfunction** and molecular mimicry** are implicated.

Clinical features (Ask 1)

- ▶ **Onset is variable** — insidious or abrupt; may mimic and be confused with acute viral hepatitis; in its most severe form presents as **fulminant hepatitis** with multilobular collapse and high mortality.
- ▶ **Most common symptom is fatigue** (~85%); other constitutional features — malaise, anorexia, amenorrhoea, acne, arthralgias, low-grade fever and weight loss.
- ▶ **Jaundice** is present in severe disease (which accounts for ~20–25% of cases).
- ▶ **Asymptomatic presentation** in roughly a quarter to a third (Harrison ~25%; CMDT 34%; Sleisenger 29–45%) — discovered on abnormal liver enzymes; many later become symptomatic, so treatment is still warranted.
- ▶ **The classic “lupoid” subset:** young-to-middle-aged women with marked hyperglobulinaemia, high-titre ANA and a positive **LE-cell preparation**, in whom other autoimmune features cluster.

- ▶ **Examination:** a healthy-appearing young woman with **multiple spider telangiectasias**, **cutaneous striae**, **acne**, **hirsutism** and **hepatomegaly**; exacerbations may occur **post-partum**, and depression is more frequent.
- ▶ **Decompensated/cirrhotic presentation:** ascites and oedema (portal hypertension, hypoalbuminaemia), encephalopathy, hypersplenism, coagulopathy or variceal bleeding may be the first manifestation — **cirrhosis is present in 28–33% at diagnosis** (more common in older patients and in African-American/Black patients).
- ▶ **Course:** spontaneous remissions and exacerbations; untreated severe disease (AST/ALT >10× normal, marked hyperglobulinaemia, bridging/multilobular necrosis) carries a 6-month mortality up to ~40%. Treated 10-year survival 80–98% vs 67% untreated.
- ▶ **Laboratory:** AST/ALT typically 100–1000 U/L; in acute cases may exceed 1000 U/L. Bilirubin moderately raised in severe disease; **polyclonal hypergammaglobulinaemia** >2.5 g/dL and raised IgG; alkaline phosphatase usually near-normal (marked elevation suggests overlap with PBC/PSC); prothrombin time prolonged in advanced/active disease.

Associated extra-hepatic disorders (Ask 2)

Two mechanistically distinct groups occur: (a) **concurrent organ-specific/systemic autoimmune diseases** (clustering in the patient and relatives), and (b) **immune-complex-mediated extra-hepatic manifestations** of the disease itself (arthralgias, arthritis, cutaneous vasculitis and glomerulonephritis — due to deposition of circulating immune complexes with complement activation).

System	Associated disorders (faithful to source)
Endocrine	Autoimmune (Hashimoto) thyroiditis (~12% in type 1), Graves disease (~6%), type 1 / juvenile diabetes mellitus
Gastrointestinal	Ulcerative colitis (~6%; warrants MRCP/ERCP to exclude PSC), coeliac disease, pernicious anaemia
Haematological	Coombs-positive (autoimmune) haemolytic anaemia, autoimmune (idiopathic) thrombocytopenic purpura, symptomatic cryoglobulinaemia
Rheumatological	Rheumatoid arthritis, Sjögren's syndrome / sicca (keratoconjunctivitis, xerostomia), SLE, systemic sclerosis, synovitis
Renal	Membranoproliferative glomerulonephritis, nephritis, azotaemia
Cutaneous	Vitiligo, cutaneous (leukocytoclastic) vasculitis, erythema nodosum, maculopapular eruptions
Serosal / pulmonary	Pleuritis, pericarditis, fibrosing alveolitis

- ▶ **Type 1 AIH** is the type most associated with the broad systemic list above; concurrent autoimmune disease is found in ~18% overall. Older patients (≥ 60 y) carry **thyroid and rheumatic disease** more often (42% vs 13%), whereas younger adults (≤ 30 y) more often have **UC and autoimmune haemolysis**.
- ▶ **Type 2 AIH** characteristically co-occurs with **vitiligo, type 1 diabetes mellitus and SLE**, and may be part of **autoimmune polyglandular syndrome type 1 (APS-1 / APECED)**.
- ▶ Patients presenting with **autoimmune thyroid or skin disease** should be screened for subclinical AIH.

Autoantibodies & serological classification (Ask 3)

Circulating autoantibodies are diagnostic markers (not proven pathogenic). Their pattern defines **two serological types** (same management and similar outcome):

Autoantibody	Antigenic target	Diagnostic significance
ANA (antinuclear, homogeneous)	Multiple nuclear antigens	Present in ~80% of type 1 ; hallmark with SMA; low-titre also seen in MASLD/viral hepatitis (non-specific)
ASMA / SMA (anti-smooth-muscle)	Actin (F- and G-), vimentin, skeletin	Present in ~63%; high specificity when combined with ANA; anti-F-actin is the more specific component
Anti-SLA/LP (soluble liver antigen)	tRNP(ser)sec $\rightarrow$ SEPSECS	High specificity (~99%) ; HLA- <i>*DRB1\0301</i> ; nearly always with anti-Ro/SSA ; marks severe disease, relapse, worse prognosis*; <i>may be the sole*</i> marker
Atypical pANCA	β -tubulin isotype 5	In 50–92% of type 1 , absent in type 2 ; associated with UC and PSC ; useful when conventional antibodies absent
Anti-LKM1 (liver-kidney microsome 1)	Cytochrome P450 2D6 (CYP2D6)	Hallmark of type 2 (ANA/SMA usually absent); mainly children; HLA-DRB1 $\backslash$ *07; also seen in some hepatitis C
Anti-LC1 (liver cytosol 1)	Formiminotransferase cyclodeaminase	Marks type 2 (often with anti-LKM1, ~32%); young patients; rare in North American adults

- ▶ **Type 1 (classic) AIH**: ANA and/or ASMA positive; young women; marked hyperglobulinaemia; **HLA-DR3/DR4 (especially B8-DRB1\03)*; **commonest form in North America and northern Europe**; a subset is ANA/anti-LKM1–negative but anti-SLA**–positive.

- ▶ **Type 2 AIH:** defined by **anti-LKM1** ($\pm$ anti-LC1); typically **children/adolescents**, more common in Mediterranean/European populations; linked to HLA-DRB1 and DQB1 haplotypes; tends to present acutely and progress to cirrhosis early.
- ▶ **Other LKM antibodies:** **anti-LKM2** $\rightarrow$ drug-induced (tienilic acid) hepatitis; **anti-LKM3** (anti-UDP-glucuronyltransferase) $\rightarrow$ chronic hepatitis D and some type 2 AIH.
- ▶ Additional markers: **rheumatoid factor**, anti- α -actinin, antibodies to **asialoglycoprotein receptor (hepatic lectin)**. **Anti-mitochondrial antibody (AMA)** is normally *against* the diagnosis (suggests PBC) but occurs in up to $\sim 18\%$ without evolving to PBC. **IgG4-associated AIH** (≥ 10 IgG4+ plasma cells/HPF, serum IgG4 ≥ 135 mg/dL) defines $\sim 3.3\%$ of cases.

Diagnosis (brief)

- ▶ **Liver biopsy is imperative:** **interface hepatitis** (periportal “piecemeal” necrosis) is the hallmark, with **plasma-cell infiltrate**, **hepatocyte rosettes**, **emperipolesis** and **centrilobular (zone 3) perivenulitis**; bile-duct injury and granulomas are uncommon.
- ▶ **IAIHG simplified score (4 variables):** autoantibodies (ANA/SMA $\geq 1:40 = +1$, $\geq 1:80 = +2$; anti-LKM1 $\geq 1:40$ or anti-SLA $= +2$), **IgG** ($> \text{ULN} +1$, $> 1.1 \times \text{ULN} +2$), histology (compatible $+1$, typical $+2$), **absence of viral hepatitis** ($+2$) $\rightarrow \geq 7 = \text{definite}$, **6 = probable** AIH.
- ▶ Always **exclude** viral, drug-induced (minocycline, nitrofurantoin), Wilson disease (look for Kayser-Fleischer rings), MASH and alcohol; consider **overlap syndromes** with PBC (7–13%) or PSC (6–11%).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Histology of AIH (interface hepatitis):** draw a portal tract with the limiting plate eroded by a dense lymphoplasmacytic infiltrate spilling into periportal parenchyma. Labels: *Portal tract, Lymphoplasmacytic infiltrate, Interface (piecemeal) hepatitis at limiting plate, Plasma cells, Hepatocyte rosette, Emperipolesis, Centrilobular (zone 3) perivenulitis.*
- ▶ **Diagram 2 — Serological classification flow-box:** “AIH” branching into *Type 1* (labels: ANA, ASMA/anti-actin, anti-SLA, atypical pANCA; HLA-DR3/DR4; adults/women) and *Type 2* (labels: anti-LKM1 $\rightarrow$ CYP2D6, anti-LC1; children; Mediterranean).

Clinical / Diagnostic significance

- ▶ Suspect AIH in any patient — especially a **woman with another autoimmune disease** — who has unexplained transaminitis with **raised IgG/globulins and positive ANA/SMA**.
- ▶ **Initial work-up:** ANA, ASMA, anti-LKM1, anti-SLA, serum IgG/protein electrophoresis, AMA (to exclude PBC), full viral hepatitis serology, ceruloplasmin (Wilson), and **liver biopsy**; image with MRCP if cholestatic or coexisting IBD (to exclude PSC).
- ▶ **Treatment** (induces remission in $\sim 80\%$): **prednisone 20–60 mg/day** (high-dose 40–60 mg for acute severe disease), tapered, with **azathioprine 50 mg $\rightarrow$ 1–2 mg/kg/day** added ~ 1 –2 weeks

later as a steroid-sparing maintenance agent — check **TPMT** genotype first. **Budesonide** is an option in non-cirrhotic mild disease. Second-line/refractory: **mycophenolate mofetil**, **tacrolimus**, **rituximab**, **6-MP**. **Liver transplantation** for fulminant/refractory or end-stage disease (failure of bilirubin to fall after 2 weeks of therapy → list early).

- ▶ **Relapse is the rule** ($\geq 50\%$, up to 81–90% by 3 years) — most patients need indefinite maintenance; each relapse raises the risk of cirrhosis. Screen cirrhotics for **HCC (6-monthly ultrasound)** and varices; vaccinate against hepatitis A/B before immunosuppression.

High-yield exam pointers

- ▶ **Triad for diagnosis:** autoantibodies + raised IgG (hypergammaglobulinaemia) + interface hepatitis on biopsy, with exclusion of other causes.
- ▶ **Female ~75%; bimodal age (<30 and >60); fatigue the commonest symptom (~85%).**
- ▶ **Type 1 = ANA/ASMA, adults, HLA-DR3/DR4; Type 2 = anti-LKM1 (CYP2D6) $\pm$ anti-LC1, children, Mediterranean.**
- ▶ **Anti-SLA** → highest specificity (~99%), severe disease and relapse, may be the sole marker.
- ▶ **anti-LKM2 = drug-induced; anti-LKM3 = hepatitis D / some type 2 AIH** — don't confuse the LKM family.
- ▶ **Extra-hepatic clusters:** thyroiditis, UC, RA, Sjögren's, type 1 DM, vitiligo, Coombs-positive haemolytic anaemia, glomerulonephritis; immune-complex arthritis/cutaneous vasculitis are disease-intrinsic.
- ▶ **Old names: lupoid hepatitis** (high-titre ANA, LE-cell positive) and **plasma-cell hepatitis**.
- ▶ **AMA points away from AIH** (favours PBC); think **overlap syndrome** if cholestatic features.
- ▶ **Cornerstone therapy = prednisone + azathioprine; ~80% respond; relapse common → often lifelong maintenance.**

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Chronic Hepatitis” (Autoimmune Hepatitis: definition, immunopathogenesis, clinical features, autoantibodies/Types I & II, diagnostic criteria, treatment).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Autoimmune Hepatitis” (autoantibody panel and antigenic targets, concurrent immune-disease frequencies, simplified/comprehensive IAIHG scoring, histology, clinical presentations, IgG4-AIH).
- ▶ **CMDT 2026** — “Liver, Biliary Tract, & Pancreas Disorders” (Autoimmune Hepatitis: essentials of diagnosis, epidemiology, extrahepatic features, simplified diagnostic score, treatment regimens and prognosis).



What are the indications, complications of ERCP?

Asked in: Paper II 08 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Endoscopic retrograde cholangiopancreatography (ERCP) is a combined endoscopic–fluoroscopic procedure in which a **side-viewing duodenoscope** is passed to the second part of the duodenum, the major papilla (ampulla of Vater) is cannulated, and the bile and/or pancreatic ducts are opacified with radiographic contrast under fluoroscopy. When indicated, the papilla is incised by **endoscopic sphincterotomy (EST)** to permit stone extraction, stricture dilation, stenting, and tissue sampling. With the advent of **MRCP and endoscopic ultrasound (EUS)** as accurate non-invasive imaging, ERCP has evolved from a diagnostic into an almost **exclusively therapeutic** modality for pancreaticobiliary disease.

Technique and therapeutic armamentarium

- ▶ **Access:** transoral side-viewing duodenoscope → selective cannulation of CBD/pancreatic duct with a catheter or sphincterotome over a guidewire; contrast injection under fluoroscopy.
- ▶ **Therapeutic manoeuvres possible at ERCP:** biliary/pancreatic **sphincterotomy**; **stone extraction** with balloon or Dormia basket; **balloon dilation** of strictures; **plastic or self-expandable metal stent (SEMS)** placement; **mechanical/cholangioscopy-guided lithotripsy** of large stones; **nasobiliary drainage**; treatment of ductal leaks; intraductal **brush cytology / forceps biopsy**; **biliary manometry** (for sphincter of Oddi dysfunction).
- ▶ **Adjuncts:** cholangioscopy (SpyGlass) for direct duct visualisation and targeted biopsy; EUS-guided biliary drainage when conventional ERCP fails.

Indications

ERCP is indicated chiefly for **therapy**; pure diagnostic ERCP is now rare and reserved for **tissue sampling of biliary/pancreatic ductal strictures** and **biliary manometry**.

Category	Specific indication
Choledocholithiasis	Sphincterotomy + stone extraction (balloon/basket); first-line for CBD stones, especially elderly/poor surgical candidates
Acute (ascending) cholangitis	Emergency biliary decompression/drainage — the definitive treatment after resuscitation and antibiotics
Gallstone (biliary) pancreatitis	Urgent ERCP for retained CBD stone, particularly with coexisting cholangitis or obstructive jaundice

Category	Specific indication
Malignant biliary obstruction	Palliative stenting (SEMS) and tissue diagnosis in cholangiocarcinoma, pancreatic head cancer, ampullary tumour
Benign biliary strictures	Post-operative, chronic pancreatitis-related, or post-transplant strictures — dilation + multiple plastic stents or covered SEMS
Bile leak / duct injury	Post-laparoscopic-cholecystectomy cystic-duct stump leak — sphincterotomy ± stent to divert bile
Primary sclerosing cholangitis (PSC)	Endoscopic dilation ± short-term large-bore (10-Fr) stenting of a dominant stricture ; biliary lithiasis
Sphincter of Oddi dysfunction (SOD)	Manometry and biliary sphincterotomy in selected patients
Pancreatic disease	Pancreatic-duct stenting/stone removal in chronic pancreatitis; drainage of pancreatic-duct disruption/leak; pseudocyst communicating with the duct
Tissue diagnosis	Brush cytology/intraductal biopsy of indeterminate biliary or pancreatic strictures

- ▶ In **gallstone pancreatitis**, only ~20% harbour a persistent ampullary/CBD stone; therefore **MRCP or EUS first** spares many patients an unnecessary ERCP — urgent ERCP is reserved for suspected **superimposed cholangitis** or proven retained stone.
- ▶ For **acute cholangitis**, biliary drainage (usually by ERCP) should be established within ~24–48 h; **emergent** decompression is required in septic patients or those failing antibiotics within 12–24 h.

Contraindications

- ▶ **Absolute/relative:** uncooperative patient, **acute pancreatitis** (unless gallstone pancreatitis with cholangitis), severe uncorrected **cardiopulmonary disease**, recent contrast (iodine) anaphylaxis.
- ▶ **Anatomic barriers:** gastroduodenal/oesophageal obstruction preventing scope passage; **Roux-en-Y** or other surgically altered anatomy (may need balloon enteroscopy-assisted or EUS-directed access).
- ▶ **Pregnancy** — performed only when essential, with radiation-minimising technique.
- ▶ Uncorrected coagulopathy/thrombocytopenia (relative — correct before sphincterotomy).

Complications

ERCP carries the **highest adverse-event rate of all routine endoscopic procedures**. Major complications and approximate frequencies:

Complication	Frequency	Key points
Post-ERCP pancreatitis (PEP)	~5% overall (Harrison); 5–10%, up to 20–25% in high-risk	Most common and most feared complication; asymptomatic hyperamylasaemia in 35–70%
Haemorrhage (post-sphincterotomy)	~1–2%	Risk ↑ with thrombocytopenia, coagulopathy, cholangitis, anticoagulation within 3 days, low endoscopist volume
Perforation	<1%	Lateral-wall duodenal (large, often needs surgery); periampullary (post-sphincterotomy — often managed with stent); ductal (guidewire/basket — usually conservative + stent)
Cholangitis	~1%	Higher with combined percutaneous-endoscopic access, malignant stenting, failed/incomplete drainage
Cholecystitis	<0.5%	After stenting across the cystic-duct take-off
Pseudocyst infection / abscess	Uncommon	Especially when contrast injected into a duct communicating with a sterile collection
Sedation / cardiopulmonary	—	Hypoxaemia, aspiration, respiratory depression, arrhythmia, contrast reaction

- ▶ Pooled RCT data (placebo/no-stent arms): overall **PEP incidence 9.7%**, mortality **0.7%**; severity mild 5.7% / moderate 2.6% / severe 0.5%. In **high-risk** patients PEP rises to ~14.7%.
- ▶ Severe PEP may progress to necrotising pancreatitis, multi-organ failure, prolonged hospitalisation, diabetes, or **death**.

Post-ERCP pancreatitis — risk factors and prevention

Risk factors (Box 58.5 / Box 42.1):

- ▶ *Patient-related*: young age, female sex, **suspected SOD**, prior recurrent pancreatitis, **history of previous PEP**, normal serum bilirubin.
- ▶ *Procedure-related*: **pancreatic-duct injection/opacification**, difficult or failed cannulation, **pancreatic sphincterotomy**, **pre-cut (access) sphincterotomy**, balloon dilation of an intact sphincter, pancreatic guidewire placement, pancreatic tissue sampling.

- ▶ *Operator/technique-related*: trainee (fellow) participation, non-use of guidewire cannulation, failure to place a prophylactic pancreatic-duct stent in a high-risk case.
- ▶ The archetypal highest-risk patient: a **young woman with suspected choledocholithiasis and normal bilirubin who undergoes sphincterotomy but no stone is found** (~27% PEP).

Prevention — three evidence-based modalities:

- ▶ **Prophylactic pancreatic-duct stent** (3–5 Fr; length/diameter >5 cm/>5 Fr more protective) in high-risk cases — relieves cannulation-induced ampullary oedema; >70% pass spontaneously, otherwise removed by ~14 days.
- ▶ **Rectal NSAID** — **indomethacin** (or diclofenac) given peri-procedurally; reduces PEP, established for high-risk patients.
- ▶ **Periprocedural IV fluids** — aggressive hydration with **lactated Ringer's** solution.
- ▶ **Guidewire-assisted cannulation** lowers PEP versus contrast-guided cannulation (success ~98%). Treatment of established PEP is **supportive**; there is **no role for repeat ERCP** for PEP itself.

Antibiotic prophylaxis (selective)

- ▶ **Not recommended** when complete biliary drainage is anticipated.
- ▶ **Recommended** (and continued after the procedure) when **incomplete drainage** is expected — e.g., **PSC, hilar strictures** — and for a sterile pancreatic fluid collection communicating with the pancreatic duct.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled line diagram of ERCP anatomy/technique**: duodenoscope tip in the second part of duodenum; major papilla (ampulla of Vater); common bile duct; common hepatic duct / right & left hepatic ducts; cystic duct & gallbladder; main pancreatic duct; sphincter of Oddi; cannula/sphincterotome entering the papilla; CBD stone with extraction balloon/basket distal to it.
- ▶ **Schematic of endoscopic sphincterotomy**: normal ampulla → sphincterotome cutting the roof of the papilla with electrosurgery → stone extracted with balloon catheter into the duodenum.

Clinical / Diagnostic significance

- ▶ **Choledocholithiasis pathway**: risk-stratify first — high probability (CBD stone on US, bilirubin >4 mg/dL, or cholangitis) → proceed to ERCP; intermediate probability → **MRCP or EUS** before ERCP to avoid needless ERCP. Confirmed stones → **sphincterotomy + extraction** (± laparoscopic cholecystectomy, often single-session). Large stones (≥1 cm) → sphincterotomy + **large-balloon dilation** or cholangioscopy-guided lithotripsy.

- ▶ **Acute cholangitis:** *Charcot triad* (RUQ pain, fever, jaundice; ~70%); *Reynolds pentad* (+ hypotension + altered mentation) = suppurative cholangitis, an **endoscopic emergency**. Diagnosis/severity by **Tokyo Guidelines (2018)**. Manage with IV fluids + antibiotics (e.g., **ciprofloxacin + metronidazole**, or ampicillin-sulbactam; severe/hospital-acquired → **piperacillin-tazobactam or meropenem**) then ERCP drainage.
- ▶ **Balloon sphincteroplasty without sphincterotomy** is preferred in **coagulopathic** patients (lower bleeding risk); a short fully-covered metal stent is an alternative to mitigate bleeding.
- ▶ When ERCP fails or is **anatomically impossible**, alternatives are **EUS-guided biliary drainage** or **percutaneous transhepatic cholangiography (PTC)** with drainage.

High-yield exam pointers

- ▶ ERCP uses a **side-viewing duodenoscope** and is now **predominantly therapeutic** (MRCP/EUS have replaced diagnostic ERCP).
- ▶ **Commonest and most feared complication** = **post-ERCP pancreatitis** (~5%, up to 20–25% in high-risk).
- ▶ **Post-sphincterotomy bleeding** ~1–2%; **perforation** <1%; **cholangitis** ~1%.
- ▶ **PEP prevention triad:** prophylactic **pancreatic-duct stent** + **rectal indomethacin** + **aggressive IV lactated Ringer's**; plus guidewire cannulation.
- ▶ Highest-risk PEP patient: **young woman, suspected SOD, normal bilirubin, difficult cannulation**.
- ▶ **Cholangitis** = Charcot triad; **Reynolds pentad** signals suppurative cholangitis needing **emergency ERCP drainage** (within 24–48 h; emergent if septic).
- ▶ In **gallstone pancreatitis**, urgent ERCP benefits only those with **retained CBD stone or cholangitis** — image with MRCP/EUS first.
- ▶ **Antibiotic prophylaxis** only when **incomplete drainage** is expected (PSC, hilar strictures).
- ▶ Contraindications: acute (non-gallstone) pancreatitis, severe cardiopulmonary disease, altered anatomy (Roux-en-Y), uncorrected coagulopathy.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Gastrointestinal Endoscopy” (ERCP technique, risks of endoscopy, acute biliary obstruction/cholangitis/gallstone pancreatitis); “Diseases of the Gallbladder and Bile Ducts” (ERCP indications/contraindications/complications table, choledocholithiasis, cholangitis).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Preparation for and Complications of Gastrointestinal Endoscopy” (ERCP haemorrhage, perforation, cholangitis, pancreatitis with risk-factor box); “Acute Pancreatitis” (post-ERCP pancreatitis incidence, risk factors, prevention with PD stents/rectal NSAIDs/IV fluids);

“Endoscopic and Radiologic Treatment of Biliary Disease” (stone extraction, dominant-stricture and benign-stricture stenting, EUS-guided drainage).

- **CMDT 2026** — “Liver, Biliary Tract, & Pancreas Disorders” (choledocholithiasis & acute cholangitis management, Tokyo Guidelines 2018, antibiotic regimens, timing of ERCP, large-stone and coagulopathy techniques).



Patterns of Drug- and Toxin-Induced Liver Injury: Morphological Findings and Examples

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Drug-induced liver injury (DILI)* is hepatic injury attributable to a xenobiotic — a prescription or over-the-counter drug, an industrial/environmental toxin, or a complementary and alternative medicine (CAM)/herbal-dietary supplement. The liver is uniquely vulnerable because it is the principal site of drug metabolism: most water-insoluble drugs undergo **phase I** oxidation (cytochrome P450) and **phase II** conjugation (glucuronidation/sulfation) or glutathione inactivation, and most hepatotoxicity arises from a reactive **phase I toxic metabolite**. DILI is the commonest cause of acute liver failure (ALF) in the Western world and is a presumptive diagnosis requiring a meticulous drug history and exclusion of other causes. It is classified along three complementary axes — **pathogenic type**, **biochemical pattern (R value)** and **morphological pattern** — and a single agent may produce several lesions.

1. Classification by pathogenic mechanism

Type	Predictability / dose	Latency	Prototype agents & lesion
Direct (intrinsic) toxic	Predictable, reproducible, dose-dependent	Short (hours–48 h)	Acetaminophen, carbon tetrachloride, <i>Amanita phalloides</i> , yellow phosphorus, heavy metals → reproducible zonal necrosis ± steatosis
Idiosyncratic	Unpredictable, rare (1 in 10^3 – 10^5), only loosely dose-related (usually >100 mg/day)	Variable, typically 5–90 days	Isoniazid, amoxicillin-clavulanate, halothane, nitrofurantoin → variable morphology; may be immunoallergic or metabolic
Indirect (CMDT)	Drug worsens pre-existing liver disease	Variable	Immunosuppression/rituximab → HBV reactivation flare ; checkpoint inhibitors → immune hepatitis

- ▶ Idiosyncratic injury is further split into **immunoallergic** (hypersensitivity — rash, fever, arthralgia, eosinophilia; e.g. phenytoin, trimethoprim-sulfamethoxazole, the DRESS syndrome) and **metabolic idiosyncrasy** (variable toxic-metabolite kinetics, no allergy; e.g. isoniazid, valproate).
- ▶ Susceptibility is shaped by **HLA haplotypes** (amoxicillin-clavulanate, flucloxacillin), enzyme polymorphisms, age, alcohol, nutritional state and underlying liver disease.

2. Classification by biochemical pattern — the R value

- ▶ **R value** = $(\text{ALT} \div \text{ULN}) \div (\text{ALP} \div \text{ULN})$ — both as multiples of the upper limit of normal.
 - $R \geq 5 \rightarrow$ **hepatocellular** injury (ALT-dominant).
 - $R < 2 \rightarrow$ **cholestatic** injury (ALP-dominant).
 - $R 2-5 \rightarrow$ **mixed** hepatocellular-cholestatic.
- ▶ This bedside ratio predicts the likely histology and guides the differential before biopsy.

3. Morphological patterns, findings and examples (core of the answer)

Pattern	Key morphological findings	Representative agents
Zonal (coagulative) necrosis	Predictable necrosis in a specific acinar zone; centrilobular/zone 3 (high CYP2E1, low glutathione); minimal inflammation; resolves without fibrosis	Acetaminophen, carbon tetrachloride (zone 3); yellow phosphorus, ferrous salts (periportal/zone 1)
Massive / submassive (bridging) necrosis	Panlobular hepatocyte dropout $\rightarrow$ ALF	<i>Amanita phalloides</i> , halothane, severe acetaminophen
Acute hepatitis (hepatocellular)	Spotty/focal necrosis with lymphocytic infiltrate, resembling acute viral hepatitis ; ALT $>5 \times$ ULN	Isoniazid, halothane, ketoconazole, nitrofurantoin, methyldopa, sulfonamides, ciprofloxacin, troglitazone
Chronic hepatitis (autoimmune-like)	>3 months; interface hepatitis, bridging necrosis, fibrosis, plasma cells, autoantibodies (ANA/anti-SMA)	Nitrofurantoin, minocycline, hydralazine, α-methyldopa (the four ANA-positive AIH-like agents); diclofenac
Bland (non-inflammatory) cholestasis	Canalicular cholestasis, no inflammation or necrosis	Anabolic/17α-alkylated androgens , oestrogens, oral contraceptives
Cholestatic hepatitis (inflammatory)	Portal inflammation + cholestasis $\pm$ bile-duct injury	Amoxicillin-clavulanate (commonest implicated antibiotic), erythromycin estolate, chlorpromazine, oxacillin

Pattern	Key morphological findings	Representative agents
Vanishing bile duct syndrome (ductopenia)	Progressive loss of small interlobular bile ducts, PBC-like but AMA-negative; chronic cholestasis	Chlorpromazine, flucloxacillin, carbamazepine, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole
Sclerosing cholangitis	Strictures of large/intrahepatic ducts	Intra-arterial flouxuridine , long-term ketamine
Macrovesicular steatosis	Single large fat droplet displacing nucleus	Amiodarone, methotrexate, tamoxifen, corticosteroids, irinotecan
Microvesicular steatosis	Tiny cytoplasmic fat droplets, central nucleus; mitochondrial toxicity → lactic acidosis	Valproate , high-dose IV tetracycline, aspirin (Reye) , didanosine/stavudine/zidovudine, linezolid
Steatohepatitis (pseudoalcoholic)	Steatosis + Mallory-Denk hyaline + neutrophils + pericellular fibrosis; phospholipidosis (lamellar lysosomal bodies)	Amiodarone, perhexiline, tamoxifen
Granulomatous hepatitis	Non-caseating epithelioid granulomas ± cholestasis	Sulfonamides, allopurinol, carbamazepine, hydralazine, quinidine, quinine, phenylbutazone
Fibrosis / cirrhosis	Progressive fibrosis, nodular regeneration	Methotrexate , amiodarone, tamoxifen, vitamin A (hypervitaminosis)
Vascular injury	Sinusoidal obstruction syndrome (veno-occlusive disease) — sinusoidal/terminal-venule endothelial injury; nodular regenerative hyperplasia ; peliosis hepatis (blood-filled cavities)	SOS: high-dose pre-BMT cyclophosphamide, melphalan, busulfan , pyrrolizidine alkaloids , oxaliplatin; NRH: oxaliplatin, azathioprine, vitamin A; peliosis & Budd-Chiari: anabolic/contraceptive steroids
Neoplasia	Hepatic adenoma, focal nodular hyperplasia, HCC, angiosarcoma	Oral contraceptives/oestrogens, anabolic steroids; vinyl chloride / arsenic / Thorotrast (angiosarcoma)
Immune-mediated (checkpoint inhibitor) hepatitis	Non-specific acute hepatitis, CD8⁺-predominant , ANA-positive; steroid-responsive	Ipilimumab (CTLA-4), nivolumab/pembrolizumab (PD-1/PD-L1)

4. The six cellular mechanisms of injury (Harrison)

- ▶ **A — Membrane rupture:** disrupted intracellular Ca^{2+} homeostasis → actin disassembly → blebbing and cell lysis.
- ▶ **B — Canalicular injury:** disruption of transport pumps (MRP3) → impaired bile/bilirubin excretion → cholestasis.
- ▶ **C — P450-drug covalent binding:** reactive metabolite binds cytochrome P450 forming non-functional adducts.
- ▶ **D — Immune attack on adducts:** adducts migrate to the surface as neo-antigens → cytolytic T-cell/cytokine attack.
- ▶ **E — Apoptosis:** activation of TNF- α receptor/Fas death-domain → caspase cascade.
- ▶ **F — Mitochondrial inhibition:** blockade of β -oxidation and the respiratory chain → microvesicular steatosis, lactate accumulation, reactive oxygen species.

5. Prototype: acetaminophen (paracetamol) — the model direct toxin

- ▶ Metabolised mainly by phase II to harmless conjugates; a fraction is oxidised by CYP2E1 to the toxic NAPQI (*N*-acetyl-*p*-benzoquinone-imine), normally detoxified by glutathione. Overdose or glutathione depletion → covalent protein adducts → **zone 3 (centrilobular) necrosis**.
- ▶ Toxic single dose **10–15 g**, fatal usually ≥ 25 g; in chronic alcoholics (CYP2E1 induction + glutathione depletion) toxicity may occur at ~ 2 g. Fasting/starvation potentiates.
- ▶ **Very high ALT** (often $>10,000$ IU/L) with **disproportionately low bilirubin** is the biochemical signature. 4-h level >300 $\mu\text{g/mL}$ predicts severe injury; <150 $\mu\text{g/mL}$ makes injury unlikely — plotted on the **Rumack-Matthew nomogram**.
- ▶ **Antidote:** N-acetylcysteine (NAC) — IV loading **140 mg/kg** then **70 mg/kg every 4 h** for **15–20 doses**; most effective within 8–12 h but still useful up to 24–36 h.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hepatic acinus showing zonal injury:** draw the portal triad (hepatic artery, portal vein, bile duct) and the central (terminal hepatic) vein, with **Zone 1 (periportal)**, **Zone 2 (midzonal)** and **Zone 3 (centrilobular)**. Label “**Zone 3 — CYP2E1-rich, glutathione-poor → acetaminophen / CCl_4 necrosis**” and “**Zone 1 — yellow phosphorus / ferrous sulfate.**”
- ▶ **Six mechanisms of DILI** (after Harrison Fig 351-1): a hepatocyte labelled **A** membrane rupture, **B** canalicular pump (MRP3) injury, **C** P450-drug adduct, **D** CTL/cytokine attack on adduct, **E** TNF- α /Fas apoptosis (caspases), **F** mitochondrial β -oxidation/respiration block → microvesicular steatosis + lactate.

Clinical / Diagnostic significance

- ▶ **Hy’s Law:** during a drug trial, **jaundice with ALT $\geq 3 \times$ ULN** (hepatocellular, no cholestasis/obstruction) predicts a **mortality $\geq 10\%$** (a $\sim 10:1$ ratio of jaundice cases to liver

failure) — the strongest clinical predictor of severe DILI and a common reason drugs fail approval (e.g. troglitazone).

- ▶ **Causality assessment:** RUCAM (Roussel-Uclaf), the DILIN structured expert opinion (5-point scale: definite, highly likely, probable, possible, unlikely) and the newer RECAM; *LiverTox* (NIH) is the reference database.
- ▶ **Management:** chiefly **prompt withdrawal of the offending agent** (the single most important determinant of outcome) plus supportive care. Specific therapies: **NAC** for acetaminophen (and benefit in early-stage non-acetaminophen ALF), **silibinin** for *Amanita*, **ursodeoxycholic acid** for cholestatic DILI, **glucocorticoids** for immunoallergic/checkpoint-inhibitor and AIH-like injury. Stop any drug when ALT reaches $5\times$ ULN or symptoms/jaundice appear. ALF develops in $\sim 10\%$ of DILI; **liver transplantation** for those reaching coagulopathy + encephalopathy (lactate >3.5 mmol/L predicts need).
- ▶ Always probe **CAMs/herbals** ($>20\%$ of US DILI): green tea extract (HLA-B*35:01), Jin Bu Huan, germander, kava, pyrrolizidine alkaloids (SOS), anabolic “bodybuilding” supplements (profound bland cholestasis), Hydroxycut/OxyElite Pro.

High-yield exam pointers

- ▶ Two core pathogenic types: **direct/intrinsic** (predictable, dose-dependent, short latency, reproducible zonal necrosis) vs **idiosyncratic** (rare $1:10^3$ – 10^5 , latency 5–90 days, variable morphology); CMDT adds **indirect** (HBV flare).
- ▶ **R value:** ≥ 5 hepatocellular, <2 cholestatic, 2–5 mixed.
- ▶ Acetaminophen $\rightarrow$ CYP2E1 $\rightarrow$ NAPQI $\rightarrow$ **glutathione depletion** $\rightarrow$ **zone 3 necrosis**; antidote NAC 140 mg/kg then 70 mg/kg q4h.
- ▶ **Amoxicillin-clavulanate** = commonest antibiotic cause (mixed/cholestatic, may cause **vanishing bile duct syndrome**).
- ▶ AIH-like chronic hepatitis (ANA+): **nitrofurantoin**, **minocycline**, **hydralazine**, **methyldopa**.
- ▶ **Microvesicular steatosis** = mitochondrial toxicity (valproate, tetracycline IV, aspirin/Reye, NRTIs) $\rightarrow$ lactic acidosis; **macrovesicular** (amiodarone, methotrexate, tamoxifen).
- ▶ **Amiodarone** $\rightarrow$ pseudoalcoholic steatohepatitis with **Mallory hyaline** + **phospholipidosis** (lamellar bodies).
- ▶ **SOS/VOD** = pre-BMT chemo (cyclophosphamide, busulfan, melphalan) and **pyrrolizidine alkaloids**; **angiosarcoma** = vinyl chloride/arsenic/Thorotrast.
- ▶ **Hy’s Law:** jaundice + ALT $\geq 3\times$ ULN $\rightarrow$ mortality $\geq 10\%$.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Toxic and Drug-Induced Hepatitis” (mechanisms, direct vs idiosyncratic features, R value, Hy’s Law,

acetaminophen/INH/valproate/amoxicillin-clavulanate/amiodarone/anabolic steroid prototypes, morphology tables 351-1 and 351-2).

- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Liver Disease Caused by Drugs” (Table 88.4 clinicopathologic classification, zonal necrosis/CYP2E1 zonality, DRESS, latency/dechallenge-rechallenge, vascular and chronic-cholestatic patterns).
- ▶ **CMDT 2026** — “Drug- & Toxin-Induced Liver Disease” (Liver, Biliary Tract & Pancreas Disorders) (direct/idiosyncratic/indirect categorisation, R-value thresholds, histopathological lists, current management and referral).



Wilson's disease

Asked in: Paper IV Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Wilson's disease, or hepatolenticular degeneration, is an autosomal recessive disorder of copper transport due to pathogenic variants in **ATP7B** on chromosome 13. Defective hepatic copper transport impairs biliary copper excretion and incorporation of copper into ceruloplasmin, causing toxic copper accumulation in the **liver, brain, cornea, kidney, and other tissues**. It is one of the most treatable inherited metabolic liver diseases, but missed diagnosis can lead to fatal hepatic failure or irreversible neurologic disability.

Etiopathogenesis and copper metabolism

- ▶ Normal dietary copper is absorbed from the proximal small intestine, transported to the liver, incorporated into **ceruloplasmin**, and excreted mainly in bile; urinary copper excretion is normally small.
- ▶ **ATP7B** is expressed predominantly in liver and kidney. In hepatocytes it has two key functions: formation of enzymatically active ceruloplasmin in the trans-Golgi network and trafficking copper toward the canalicular membrane for biliary excretion.
- ▶ Loss of ATP7B function causes progressive hepatic copper retention. Initially copper is buffered by metallothionein; later excess copper causes oxidative mitochondrial injury, hepatocyte necrosis, fibrosis, and cirrhosis.
- ▶ When hepatic storage capacity is exceeded, copper spills into blood and deposits in the **basal ganglia**, cornea, kidney, skeleton, endocrine organs, and red cell membranes.
- ▶ Epidemiology: classically about **30 per million** population, with most clinical presentations between **3 and 55 years**; genetic estimates suggest the allele frequency may be higher. Age does not exclude the diagnosis.
- ▶ Most patients are **compound heterozygotes**. More than 600 ATP7B variants are described; H1069Q is common in Northern European populations and R778L in Chinese populations.

Clinical spectrum

System / presentation	High-yield clinical features
Hepatic	Asymptomatic aminotransferase elevation, fatty liver/NASH-like picture, acute hepatitis-like illness, autoimmune hepatitis-like illness, chronic hepatitis, cirrhosis, portal hypertension, splenomegaly, ascites, edema, decompensated chronic liver disease
Acute liver failure	Severe coagulopathy with or without early encephalopathy, Coombs-negative intravascular hemolysis, very high bilirubin, renal failure; aminotransferases may be disproportionately low
Neurologic	Basal ganglia movement disorder: dysarthria, dysphagia, drooling, dystonia, rigidity/parkinsonism, ataxia, gait disturbance, dysgraphia, choreiform movements, and classic <i>wing-beating</i> tremor
Psychiatric	Declining school or work performance, personality change, irritability, poor impulse control, depression, anxiety, emotional lability, compulsive or antisocial behavior; may precede neurologic signs
Ocular	Kayser-Fleischer ring : golden-brown/greenish-brown copper deposition in Descemet membrane, detected best by slit lamp; sunflower cataract may occur
Extrahepatic	Coombs-negative hemolytic anemia, renal Fanconi syndrome, renal tubular acidosis, nephrolithiasis, aminoaciduria, phosphaturia, osteoporosis/rickets, osteoarthritis, amenorrhea, infertility, hypoparathyroidism, rarely cardiomyopathy/arrhythmias

- ▶ Hepatic presentation is more common in younger patients; neuropsychiatric presentation usually appears in adolescents and young adults, but overlap is common and some degree of liver disease is usually present.
- ▶ Kayser-Fleischer rings are present in most patients with neurologic disease but may be absent in hepatic-only or asymptomatic disease; absence of the ring never excludes Wilson's disease.
- ▶ Wilson's disease should be excluded in any young patient with unexplained hepatitis, splenomegaly with hypersplenism, portal hypertension, Coombs-negative hemolysis, movement disorder, or new psychiatric illness.

Diagnostic approach

Test	Typical finding / interpretation
Serum ceruloplasmin	Low; <14 mg/dL supports diagnosis and <10 mg/dL is strongly suggestive, but normal values occur because ceruloplasmin is an acute-phase reactant; low levels are not specific
Serum copper	Total serum copper is often low because ceruloplasmin-bound copper is low; non-ceruloplasmin copper is increased, but calculated values are assay-dependent
24-hour urinary copper	>40 mcg/day requires further evaluation; usually >100 mcg/day in symptomatic disease. Use complete, contamination-free collection with creatinine check
Penicillamine challenge	A marked increase in urinary copper after penicillamine supports the diagnosis; in the standard provocative test, very high 24-hour copper excretion is diagnostic but sensitivity is imperfect
Hepatic copper	>250 mcg/g dry liver is diagnostic in the correct setting; 20-50 mcg/g is normal. Sampling error occurs in cirrhosis because copper distribution is uneven
Slit-lamp examination	Detects Kayser-Fleischer rings and sunflower cataract; repeat if suspicion remains high
MRI brain	May show basal ganglia, brainstem, or cerebellar involvement, even early in neurologic disease
ATP7B molecular testing	Confirms diagnosis when clinical and biochemical tests are equivocal; also enables family screening

- ▶ Diagnosis is usually by a **composite** of clinical features, copper studies, slit-lamp findings, and genetics; the **Leipzig scoring system** is a useful structured framework.
- ▶ Liver biopsy may show steatosis, acute or chronic hepatitis, autoimmune hepatitis-like interface activity, macronodular cirrhosis, and characteristic mitochondrial injury; copper stain may be negative early because copper is diffusely cytosolic.
- ▶ Important limitations: ceruloplasmin may be low in malnutrition, nephrotic syndrome, malabsorption, and other chronic liver diseases; hepatic copper may be high in chronic cholestasis and MDR3-related disease.

Wilsonian acute liver failure

- ▶ Suspect Wilsonian acute liver failure in a child or young adult with jaundice, severe coagulopathy, hemolysis, kidney injury, and unexpectedly modest transaminase elevation.

- ▶ Classic clues are **Coombs-negative intravascular hemolysis**, very high bilirubin, normal or low alkaline phosphatase, and urinary copper that is markedly elevated.
- ▶ In adults, two simple biochemical ratios are useful screening clues: **alkaline phosphatase : total bilirubin** <4 and **AST : ALT** >2.2.
- ▶ Serum ceruloplasmin is often not diagnostically reliable in acute liver failure.
- ▶ These patients respond poorly to chelation alone; manage in a transplant-capable ICU, treat complications of acute liver failure, and use plasma exchange, albumin dialysis, or MARS as a bridge when available.
- ▶ **Urgent liver transplantation** is indicated for Wilsonian acute liver failure and for decompensated cirrhosis unresponsive to medical therapy.

Treatment

Modality	Dose / role	Key cautions
Dietary copper restriction	Avoid shellfish, organ meats, nuts, mushrooms, soy-based products, chocolate; assess high-copper water when relevant	Useful adjunct only; never sufficient as sole therapy
D-penicillamine	0.75-2 g/day in divided doses, taken 1 hour before or 2 hours after food; add pyridoxine supplementation	Rash, fever, GI intolerance, proteinuria, nephrotoxicity, leukopenia, thrombocytopenia, aplastic anemia, autoimmune syndromes, elastosis perforans serpiginosa; may worsen neurologic disease initially
Trientine hydrochloride	250-500 mg three times daily, or about 1-1.5 g/day initially in divided doses; effective first-line or alternative chelator	Fewer adverse effects; monitor for gastritis, iron deficiency, and rare marrow suppression
Zinc acetate / gluconate	50 mg elemental zinc three times daily, taken away from meals; induces enterocyte metallothionein and blocks copper absorption	Slow onset; best for presymptomatic patients, pregnancy, neurologic disease, or maintenance after decoppering; gastritis and adherence problems are common
Combination therapy	Chelator plus zinc may be used short term in severe hepatic/neurologic disease	Separate doses by at least 4-5 hours to avoid mutual neutralization
Tetrathiomolybdate	Investigational copper-binding therapy, mainly explored for neurologic disease	Watch for bone marrow suppression, hepatotoxicity, and copper deficiency

Modality	Dose / role	Key cautions
Liver transplantation	Acute liver failure or decompensated cirrhosis not responding to drug therapy	Not generally recommended for isolated intractable neuropsychiatric disease

- ▶ Treatment is **lifelong**. Stopping chelator or zinc therapy can cause neurologic relapse or rapidly progressive hepatic decompensation.
- ▶ In pregnancy, treatment must continue; chelator dose is usually reduced, while zinc can often be continued. Untreated disease increases miscarriage and relapse risk; breastfeeding is generally avoided with anticopper drugs.

Monitoring, family screening and prognosis

- ▶ Monitor response and toxicity with symptoms, adherence review, liver biochemical tests, CBC, renal function, urinalysis, and 24-hour urinary copper.
- ▶ Therapeutic targets: with chelators, 24-hour urinary copper is typically maintained around **200-500 mcg/day**; with zinc, urinary copper should fall to about **30-75 mcg/day**. Undetectable urinary copper suggests overtreatment.
- ▶ Serum non-ceruloplasmin copper can guide chelator dose reduction once it is in the normal range, approximately **50-150 mcg/L**.
- ▶ With zinc, adherence can be checked by urinary zinc excretion or serum zinc; rising aminotransferases after previous control often indicates nonadherence.
- ▶ Screen all **first-degree relatives**, especially siblings, using liver biochemical tests, serum ceruloplasmin, copper studies, slit-lamp examination, and ATP7B variant testing if the familial variants are known.
- ▶ Prognosis is excellent when diagnosed before hepatic or neurologic injury and treated consistently. Cirrhosis at diagnosis reduces long-term survival, and severe neurologic disease may not fully reverse.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Copper metabolism in Wilson's disease:** dietary copper absorption in small intestine -> portal transport to liver -> normal ATP7B-mediated ceruloplasmin formation and biliary excretion -> ATP7B defect -> hepatic copper accumulation -> spillover to brain, cornea, kidney, RBCs.
- ▶ **Kayser-Fleischer ring slit-lamp diagram:** cornea, limbus, Descemet membrane, superior and inferior early copper crescents, circumferential brown-green ring; add labels for sunflower cataract if drawn.

Clinical / Diagnostic significance

- ▶ Wilson's disease is a mandatory differential for **young-onset hepatitis, cirrhosis, acute liver failure, movement disorder, psychiatric decline, Coombs-negative hemolysis, and unexplained splenomegaly**.
- ▶ A normal ceruloplasmin or absent Kayser-Fleischer ring does not rule it out; combine urinary copper, slit-lamp examination, hepatic copper, and genetics.
- ▶ In acute liver failure, low/normal alkaline phosphatase with massive bilirubin and hemolysis is a life-saving clue because early transplant referral is decisive.
- ▶ Distinguish Wilson-related fatty liver from MASLD by copper studies, especially basal 24-hour urinary copper.
- ▶ Family screening prevents irreversible disease because presymptomatic patients treated early usually have the best outcome.

High-yield exam pointers

- ▶ Write the triad: **liver disease + neuropsychiatric disease + Kayser-Fleischer ring**, but state that the full triad is uncommon.
- ▶ Gene: **ATP7B**, chromosome 13, autosomal recessive, defective biliary copper excretion.
- ▶ Diagnostic numbers: ceruloplasmin <14 mg/dL supports diagnosis; 24-hour urinary copper >40 mcg/day needs evaluation and usually >100 mcg/day in disease; hepatic copper >250 mcg/g dry liver is diagnostic.
- ▶ Kayser-Fleischer ring is copper in **Descemet membrane**, best seen by slit lamp.
- ▶ Wilsonian acute liver failure: **Coombs-negative hemolysis**, low/normal ALP, very high bilirubin, **ALP:bilirubin <4, AST:ALT >2.2**, urgent transplant.
- ▶ Main drugs: **D-penicillamine, trientine, and zinc**; treatment is lifelong and adherence is central.
- ▶ D-penicillamine can worsen neurologic disease initially and can cause renal, marrow, skin, and autoimmune toxicity.
- ▶ Screen all first-degree relatives; use ATP7B mutation testing when the familial variants are known.

SOURCE & COVERAGE

Harrison 22e — “Wilson's Disease”; Sleisenger & Fordtran's GI & Liver 11e — “Wilson Disease”; CMDT 2026 — “Liver, Biliary Tract, & Pancreas Disorders”.



Zollinger-Ellison syndrome

Asked in: Paper II Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Zollinger-Ellison syndrome (ZES)* is the clinical triad of gastric acid hypersecretion, severe/refractory peptic ulcer disease, and a non- β -cell gastrin-secreting neuroendocrine tumour (gastrinoma). Unregulated gastrin release from a usually well-differentiated NET of the duodenum or pancreas drives parietal-cell stimulation and hyperplasia, producing peptic ulceration in atypical sites, reflux disease and secretory diarrhoea. It accounts for <1% of peptic ulcer disease; ~80% of cases are sporadic and ~20–25% occur as part of **multiple endocrine neoplasia type 1 (MEN 1)**.

Etiology, Epidemiology & Pathology

- ▶ **Incidence:** rare — ~0.5–3 per million population per year; estimated in 0.1–1% of patients presenting with PUD. Slight female preponderance; most diagnosed between **30–65 years**. Diagnosis is typically delayed **4–7 years** after symptom onset (widespread PPI use both masks symptoms and confounds gastrin testing).
- ▶ **Two forms:**
 - **Sporadic (~80%):** usually solitary, more often pancreatic, potentially curable by resection.
 - **MEN 1-associated (~20–25%):** autosomal dominant, caused by inactivating mutations of the **MEN1 tumour-suppressor gene on chromosome 11q13** encoding **menin**; tumours are typically **small, multiple and duodenal**; presents earlier and runs a more indolent course.
- ▶ **Tumour location — the gastrinoma triangle (triangle of Passaro): bounded by (1) confluence of the cystic and common bile ducts superiorly, (2) junction of the 2nd and 3rd parts of the duodenum inferiorly, and (3) junction of the neck and body of the pancreas** medially. 60–90% of gastrinomas lie within it.
- ▶ **Distribution:** the **duodenum is now the commonest primary site** (~60–100%; mostly 1st/2nd part) — duodenal tumours are small (>90% <1 cm), slow-growing and less likely to metastasise; pancreatic tumours are larger and more aggressive. Other sites: lymph nodes (a primary node gastrinoma can be curable), stomach, ovary, liver, bone.
- ▶ **Malignant potential:** **60–90% are malignant** (defined by local invasion/metastasis); **25–50% have nodal or hepatic metastases at presentation**. Histology is well-differentiated (NET grade 1–2), staining for **chromogranin A** and **neuron-specific enolase**.

Pathophysiology

- ▶ **Autonomous hypergastrinemia** is the central driver. Gastrin acts on **CCK-2/gastrin receptors** on parietal cells and stimulates **histamine release from ECL cells**, markedly increasing acid output.
- ▶ Gastrin is also **trophic** — chronic hypergastrinemia expands parietal-cell mass and ECL-cell hyperplasia (predisposing to **type 2 gastric carcinoids**, especially in MEN 1/ZES).
- ▶ The massive acid load produces: **peptic ulcer diathesis, erosive oesophagitis/GERD, and diarrhoea** — the last via direct mucosal injury, volume overload of the small bowel, and acid

inactivation of pancreatic lipase/precipitation of bile salts causing maldigestion and steatorrhea.

Clinical Features

- ▶ **Peptic ulcer (>90%):** abdominal pain is the commonest presenting symptom; classically ulcers that are multiple, in unusual locations (distal duodenum/jejunum), refractory to therapy, recurrent, complicated (bleed/perforation/obstruction), or *H. pylori*- and NSAID-negative. Isolated gastric ulcers do *not* occur.
- ▶ **Diarrhoea (up to 70%):** may precede or occur independently of ulcers; classically abates with nasogastric aspiration or PPI (an important clinical clue).
- ▶ **GERD / oesophageal disease (up to two-thirds):** from mild oesophagitis to stricture and Barrett's mucosa.
- ▶ **MEN 1 clues:** younger age at presentation, nephrolithiasis/renal colic, hypercalcaemia, and personal/family history of parathyroid, pituitary or pancreatic islet tumours. In MEN 1: hyperparathyroidism 80–90%, pancreatic NETs 40–80%, pituitary tumours 30–60%. Hypercalcaemia of hyperparathyroidism aggravates acid secretion — parathyroidectomy lowers gastrin/acid output.

Diagnosis — Biochemical Confirmation

Diagnosis requires demonstration of inappropriate gastric acid hypersecretion in the presence of hypergastrinemia. PPIs must be stopped (≥ 7 days, covered by an H₂-blocker stopped 24 h before testing) as they elevate gastrin and can cause false positives — but stop with caution, monitoring for acid-peptic complications.

Test	Finding diagnostic of ZES	Comment
Fasting serum gastrin (FSG)	>150–200 pg/mL (normal <150); present in 97–99%	>10× normal (>1000 pg/mL) with low pH is highly suggestive
Gastric pH / BAO	pH <2–3; BAO >15 mEq/h (>5 mEq/h if prior gastric surgery)	BAO >15 with hypergastrinemia is near-pathognomonic
BAO/MAO ratio	>0.6	Limited — pentagastrin no longer available
Secretin stimulation test	Rise in gastrin ≥ 120 pg/mL within 15 min of IV secretin (2 U/kg)	Most useful provocative test; sensitivity & specificity >90%
Calcium infusion	Rise in gastrin	Largely obsolete (cumbersome, less sensitive)

- ▶ **Practical rule (CMDT):** gastrin >1000 pg/mL + gastric pH <2 establishes the diagnosis; for intermediate gastrin (150–1000 pg/mL) with acid, perform the secretin test.

- ▶ **Exclude other causes of hypergastrinemia** — these give a **negative secretin test**: PPI/H₂-blocker use, atrophic gastritis / pernicious anaemia / achlorhydria (commonest cause), *H. pylori*, retained gastric antrum, gastric outlet obstruction, renal failure, G-cell hyperplasia.
- ▶ Always screen for **MEN 1**: serum **calcium/PTH, prolactin, and pancreatic polypeptide** ($\pm$ LH-FSH, GH).

Tumour Localization & Staging

- ▶ Once biochemically confirmed, localise the tumour and exclude metastases.

Modality	Primary tumour sensitivity	Hepatic metastasis
CT / MRI	low for small lesions	88–100%
EUS	28–86% (best for pancreas; poor for duodenum)	N/A
OctreoScan (¹¹¹ In-pentetreotide)	55–77%	90–100%
⁶⁸ Ga-DOTATATE PET-CT	>90% (investigation of choice)	>90%
Selective arterial secretin injection (SASI)	55–78%	—

- ▶ ⁶⁸Ga-DOTATATE PET/CT (exploits SSTR2 expression) is the **functional imaging study of choice**, superior to OctreoScan. ¹⁸F-FDG PET is used as a prognostic marker.
- ▶ **WHO grading of the NET (prognostic)**: G1 <2 mitoses/10 HPF & Ki-67 <3%; G2 2–20 mitoses or Ki-67 3–20%; G3 >20 mitoses or Ki-67 >20% (poorly differentiated = neuroendocrine carcinoma).

Treatment / Management

- ▶ **Control of acid hypersecretion (first priority)**: **high-dose PPIs are the treatment of choice** — omeprazole/lansoprazole/rabeprazole/esomeprazole, initial **60 mg/day (CMDT: 40–120 mg/day) in divided doses**, titrated to **BAO <10 mEq/h** (<5 mEq/h if prior acid-reducing surgery). PPIs have made **total gastrectomy obsolete**.
- ▶ **Curative surgery (sporadic, non-metastatic disease)**: exploratory laparotomy with **duodenotomy, intraoperative palpation and ultrasound**; immediate cure in ~33–40%, with 10-year disease-free rates up to 95%. **Lymph-node metastasis does not adversely affect prognosis**.
- ▶ **MEN 1/ZES**: surgery is **generally deferred** — tumours are multifocal, <5% are disease-free at 5 years, and the course is indolent; manage hyperparathyroidism (parathyroidectomy reduces gastrin/acid).
- ▶ **Metastatic disease**: somatostatin analogues (**octreotide LAR, lanreotide**); **peptide receptor radionuclide therapy (PRRT)** with radiolabelled somatostatin analogues; **temozolomide** +

capecitabine ($\approx 70\%$ response); targeted agents — sunitinib (VEGFR), everolimus (mTOR); cytotoxics (streptozotocin/5-FU/doxorubicin); hepatic-artery embolization, RFA, debulking.

- ▶ **Prognosis:** overall 5-/10-year survival 62–75% / 47–53%; complete resection or negative laparotomy $>90\%$ at 10 years; **hepatic metastases $<20\%$ at 5 years.** Poor prognostic markers: pancreatic primary $>2\text{--}3\text{ cm}$, gastrin $>10,000\text{ pg/mL}$, poor differentiation/high Ki-67, liver/bone metastases, Cushing's syndrome.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **The gastrinoma triangle (triangle of Passaro):** draw the liver/porta hepatis, gallbladder with cystic duct, common bile duct, duodenal C-loop (mark 2nd–3rd part junction) and pancreas (head/neck/body). **Labels:** Confluence of cystic + common bile ducts (superior apex), Junction of 2nd & 3rd parts of duodenum (inferior apex), Junction of neck & body of pancreas (medial apex), Gastrinoma triangle.
- ▶ **Diagnostic algorithm flow box:** Clinical suspicion $\rightarrow$ Fasting serum gastrin $\rightarrow$ if $>1000\text{ pg/mL}$ + $\text{pH} < 2 = \text{ZES}$; if $150\text{--}1000\text{ pg/mL}$ $\rightarrow$ Secretin test ($\geq 120\text{ pg/mL}$ rise = positive) + BAO $\rightarrow$ Localize with ^{68}Ga -DOTATATE PET-CT/EUS $\rightarrow$ Resectable vs Metastatic.

Clinical / Diagnostic significance

- ▶ Suspect ZES in any patient with **multiple, distal, recurrent or complicated ulcers, ulcers with diarrhoea, severe/refractory GERD, H. pylori-negative/NSAID-negative PUD, or prominent gastric folds.**
- ▶ **Diarrhoea relieved by NG aspiration or PPI** is a strong pointer; **hypercalcaemia or family history** mandates MEN 1 screening.
- ▶ A **fasting gastrin done while on a PPI** is the commonest diagnostic pitfall — interpret cautiously and confirm off therapy.
- ▶ Early diagnosis matters: it allows curative resection before hepatic spread, the strongest determinant of survival.

High-yield exam pointers

- ▶ ZES = gastrinoma + acid hypersecretion + refractory PUD; $<1\%$ of all PUD.
- ▶ Duodenum is the commonest primary site; 60–90% lie in the gastrinoma triangle of Passaro.
- ▶ $\sim 80\%$ sporadic, $\sim 20\text{--}25\%$ MEN 1 (MEN1 gene, 11q13, menin); MEN 1 $\rightarrow$ parathyroid $>$ pancreas $>$ pituitary.
- ▶ Fasting gastrin $>1000\text{ pg/mL}$ + gastric pH < 2 is diagnostic; secretin test = $\geq 120\text{ pg/mL}$ rise in 15 min (sens/spec $>90\%$).
- ▶ BAO $>15\text{ mEq/h}$ with hypergastrinemia is near-pathognomonic.

- ▶ **Commonest cause of hypergastrinemia overall** = achlorhydria/atrophic gastritis (PPI use), not gastrinoma — gives a *negative* secretin test.
- ▶ ⁶⁸Ga-DOTATATE PET-CT is the localization investigation of choice.
- ▶ **High-dose PPI** controls symptoms (titrate BAO <10 mEq/h); **resection cures sporadic disease**; surgery usually avoided in MEN 1.
- ▶ Most important survival predictor = **hepatic metastasis**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Peptic Ulcer Disease and Related Disorders” (Zollinger-Ellison Syndrome section) and “Gastrointestinal Neuroendocrine Tumors.”
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 11e** — “Neuroendocrine Tumors” (gastrinoma/ZES: clinical features, diagnostic algorithm, secretin test, gastrinoma triangle, WHO grading) and “Peptic Ulcer Disease.”
- ▶ **CMDT 2026** — “Gastrointestinal Disorders: Zollinger-Ellison Syndrome (Gastrinoma)” for current diagnostic thresholds, ⁶⁸Ga-PET imaging, and management/PPI dosing.



Renal system



NSAID-Induced Acute Interstitial Nephritis Presenting as AKI (Clinical Case Discussion)

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — Acute interstitial nephritis (AIN, syn. acute tubulointerstitial nephritis, ATIN) is an immune-mediated inflammatory disorder of the renal interstitium and tubules with relative sparing of glomeruli and vessels, producing acute kidney injury (AKI). It accounts for ~10–15% of intrinsic AKI, and **drugs cause >70% of cases**. This 35-year-old man, on diclofenac for a month, with new AKI (creatinine 4.5 mg/dL), **bland urine, low-grade proteinuria (~200 mg/24 h) and only 7 RBCs/no casts**, is the textbook picture of NSAID-induced AIN — the “atypical” allergic nephritis in which the classic triad of fever, rash and eosinophilia is characteristically *absent*.

Interpreting the vignette — why this is AIN, not a glomerular disease

- ▶ **Temporal link:** AKI appearing weeks after starting a known culprit drug (NSAID) is the single strongest clue; the latent period with NSAIDs is long (often weeks to months, unlike the days–2 weeks seen with β -lactams).

- ▶ **Bland sediment + scanty proteinuria:** proteinuria of only 200 mg/24 h is *tubular-range* (<1–2 g/day), and the microscopy is bland with no casts and only 7 RBCs. This argues strongly **against** a glomerulopathy, which would give nephrotic-range proteinuria, dysmorphic RBCs and RBC casts, and against acute GN/vasculitis.
- ▶ **Edema is from fluid retention, not hypoalbuminaemia:** periorbital puffiness and pedal oedema here reflect salt-and-water retention from the AKI itself plus the direct sodium-retaining (prostaglandin-mediated) effect of NSAIDs — *not* nephrotic syndrome, since the protein loss is trivial.
- ▶ **Caveat — the “dual lesion”:** NSAIDs uniquely may cause AIN *combined with* a glomerular lesion (**minimal change disease** more often than **membranous nephropathy**), producing heavy/nephrotic proteinuria. The low proteinuria here makes a concurrent minimal-change lesion unlikely, so the expected pathology is *pure* AIN.

Feature in this case	Points toward
NSAID for 1 month, new AKI	Drug-induced AIN
Proteinuria 200 mg/24 h (tubular range)	Interstitial, not glomerular
Bland sediment, no casts, 7 RBCs	AIN / ATN — excludes active GN
Periorbital + pedal oedema	Volume retention from AKI + NSAID Na ⁺ retention
No fever/rash/eosinophilia	Typical of NSAID-AIN (allergic features rare)

Expected renal pathology (b) — Acute (drug-induced) interstitial nephritis

- ▶ **Diagnosis:** acute tubulointerstitial nephritis (AIN) — confirmed only by percutaneous kidney biopsy, the gold standard.
- ▶ **Light microscopy:** patchy/diffuse **interstitial oedema** with a **mononuclear inflammatory infiltrate** (predominantly T lymphocytes — CD4⁺ and CD8⁺), plasma cells, macrophages, and variable eosinophils; **tubulitis** (lymphocytes crossing the tubular basement membrane into tubular epithelium) with tubular cell injury (loss of brush border, luminal ectasia).
- ▶ **NSAID-specific histology:** the infiltrate is **less intense and characteristically has few or no eosinophils**, attributable to the drug’s own anti-inflammatory action — distinct from β -lactam AIN where eosinophils are abundant. Occasionally granulomatous AIN or anti-TBM immune deposits occur.
- ▶ **Glomeruli and vessels are spared** (unless a coexisting minimal-change/membranous lesion is present).

- ▶ **Pathogenesis:** a T-cell-mediated, type IV (delayed) hypersensitivity reaction; the drug acts as a hapten/pro-hapten binding tubular proteins or generates neoantigens by molecular mimicry, triggering interstitial inflammation.
- ▶ **If unrecognised/untreated**, interstitial inflammation evolves into **interstitial fibrosis and tubular atrophy** → chronic tubulointerstitial nephritis and CKD.

Spectrum of NSAID nephrotoxicity (depth point)

- ▶ **Haemodynamic (pre-renal) AKI** — commonest; inhibition of vasodilatory prostaglandins ($\text{PGE}_2/\text{PGI}_2$) → unopposed **afferent arteriolar vasoconstriction** → fall in GFR, especially with volume depletion, heart failure, cirrhosis, or co-prescription of ACE-I/ARB (“triple whammy”).
- ▶ **Acute interstitial nephritis** (this case) ± **minimal change disease / membranous nephropathy** (nephrotic syndrome).
- ▶ **Electrolyte/acid–base:** hyperkalaemia (type IV RTA), sodium and water retention → oedema and hypertension, hyponatraemia.
- ▶ **Chronic:** analgesic nephropathy with **papillary necrosis**, and acceleration of pre-existing CKD.

Other causes of the same pathology (c) — causes of AIN

Category	Representative causes
Drugs (>70%)	NSAIDs/COX-2 inhibitors; antibiotics — β -lactams (penicillins, cephalosporins), sulfonamides, fluoroquinolones (ciprofloxacin), vancomycin, rifampin, ethambutol; PPIs & H_2 blockers; allopurinol ; anticonvulsants (phenytoin, carbamazepine, valproate); diuretics (thiazides, furosemide, triamterene); immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab); mesalamine, 5-ASA
Infections	<i>Streptococcus</i> , <i>Staphylococcus</i> , <i>Legionella</i> , <i>Corynebacterium diphtheriae</i> , <i>Brucella</i> , <i>Yersinia</i> ; <i>Leptospira</i> ; viruses — EBV, CMV, hantavirus , HIV, polyomavirus (BK) ; <i>Mycobacterium tuberculosis</i> (granulomatous)
Autoimmune / systemic	Sjögren syndrome , SLE , sarcoidosis (granulomatous), IgG4-related disease (storiform fibrosis), TINU (tubulointerstitial nephritis with uveitis), anti-TBM (anti-LRP2/anti-brush border) disease
Idiopathic	Idiopathic AIN (some with anti-tubular antibodies)
Obstructive/crystal (related)	Light-chain cast nephropathy (myeloma), acute urate (tumour lysis) and acute phosphate nephropathy

Investigations / diagnostic approach

- ▶ **Confirm and stage AKI (KDIGO):** serum creatinine 4.5 mg/dL from a normal baseline is **stage 3 AKI**; trend creatinine/urea, urine output.
- ▶ **Urinalysis & microscopy:** sterile pyuria, WBC $\pm$ WBC casts, mild haematuria, **low-grade (tubular) proteinuria <1–2 g/day**; ~20% have a bland sediment (as here). **Urine eosinophils are NOT recommended** — poor sensitivity/specificity (abandoned).
- ▶ **Bloods:** CBC (eosinophilia inconsistent, may be absent in NSAID-AIN), electrolytes (watch **hyperkalaemia**, non-anion-gap acidosis), ESR/CRP, IgE; screen for systemic disease where suspected (ANA, anti-Ro/La, serum IgG4, ACE/calcium).
- ▶ **Imaging:** renal ultrasound — **normal-sized or enlarged, echogenic kidneys**; chiefly excludes obstruction.
- ▶ **Kidney biopsy** — definitive; indicated when diagnosis is uncertain, AKI is severe/progressive, or before committing to steroids.

Management (d)

- ▶ **Withdraw the offending drug immediately — stop diclofenac.** This is the single most important step; AKI often reverses after withdrawal alone. Avoid *all* nephrotoxins (NSAIDs, contrast, aminoglycosides, ACE-I/ARB during the acute phase).
- ▶ **Supportive AKI care (KDIGO):** optimise volume/haemodynamics, maintain MAP >65 mmHg, treat the oedema/volume overload with **salt and water restriction + loop diuretics**, correct hyperkalaemia (calcium gluconate, insulin-dextrose, β -agonist, K^+ binders), treat metabolic acidosis (NaHCO_3 if pH <7.2 / HCO_3^- <15), renal-dose all drugs, ensure 20–30 kcal/kg/day nutrition.
- ▶ **Corticosteroids** — consider if **kidney function does not improve within ~5–7 days of drug withdrawal**, or if biopsy shows florid inflammation without established fibrosis; benefit falls if started >1–2 weeks after onset. Regimens:

Regimen	Dose
IV methylprednisolone pulse	0.25–0.5 g/day IV for 1–4 days
Oral prednisone	1 mg/kg/day ($\approx$ 60 mg/day) for 4–6 weeks, then taper
Duration	Continue 4–8 weeks if responding; taper off by 3–4 weeks if no response

- ▶ **Renal replacement therapy (dialysis)** if refractory volume overload, hyperkalaemia or acidosis, or uraemic complications — AEIOU: Acidosis, Electrolytes (K^+), Ingestions/toxins, Overload, Uraemia. Up to one-third of AIN patients need temporary dialysis before recovery.

- ▶ **Prognosis:** generally good — most recover over weeks to months; progression to ESRD is rare. Worse outcomes with prolonged oliguria, older age, delayed drug withdrawal and established interstitial fibrosis. Counsel lifelong avoidance of the culprit class.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Histology of AIN (label):** interstitial *oedema* separating tubules; *mononuclear (lymphocytic) interstitial infiltrate*; *eosinophils* (note: sparse/absent in NSAID-AIN); *tubulitis* (lymphocytes crossing the *tubular basement membrane*); *normal glomerulus*; *normal vessel*.
- ▶ **Diagram 2 — NSAID renal effects flow chart (label):** NSAID → ↓ *vasodilatory prostaglandins (PGE₂/PGI₂)* → branch 1: *afferent arteriolar vasoconstriction* → ↓ *GFR (pre-renal AKI)*; branch 2: *hapten* → *T-cell (type IV) hypersensitivity* → AIN; branch 3: *Na⁺/water retention* → *oedema, hypertension, hyperkalaemia*; branch 4: ± *minimal change disease* → *nephrotic syndrome*.

Clinical / Diagnostic significance

- ▶ **Drug history is diagnostic:** any unexplained AKI with a temporally-related drug = suspect AIN; empirical drug withdrawal is both diagnostic and therapeutic.
- ▶ **A bland urine never excludes AIN** — ~20% of biopsy-proven cases have normal sediment, and NSAID-AIN classically lacks fever/rash/eosinophilia.
- ▶ **Distinguish from the commoner NSAID pre-renal AKI** (responds to volume) and from glomerular disease (active sediment, heavy proteinuria) — this changes management.
- ▶ **Early diagnosis prevents fibrosis:** delay → tubular atrophy/interstitial fibrosis → irreversible CKD.

High-yield exam pointers

- ▶ AIN = 10–15% of intrinsic AKI; **drugs cause >70%**; *Councilman* first described AIN (1897).
- ▶ NSAID-AIN is “atypical”: long latency, fever/rash/eosinophilia rare, **eosinophils often absent on biopsy**, low-grade proteinuria — may combine with **minimal change disease (>membranous)** to cause nephrotic syndrome.
- ▶ **Pathology:** interstitial oedema + **mononuclear (T-cell) infiltrate** + **tubulitis**, glomeruli/vessels spared; type IV hypersensitivity.
- ▶ **Urine eosinophils are NOT useful** — do not order.
- ▶ **Biopsy = gold standard;** ultrasound shows normal/enlarged echogenic kidneys.
- ▶ **Treatment = STOP the drug first;** **corticosteroids** (methylprednisolone 0.25–0.5 g/day IV ×1–4 days or prednisone 1 mg/kg ≈60 mg/day ×4–6 weeks) if no recovery in ~5–7 days.
- ▶ **Dialysis (AEIOU)** in up to one-third; overall **good prognosis**, ESRD rare.

- Other AIN causes to list: β -lactams, sulfonamides, PPIs, rifampin, allopurinol, **checkpoint inhibitors**; Sjögren, SLE, sarcoid, IgG4, TINU; *Legionella*, *Leptospira*, hantavirus, BK virus, TB.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — “Tubulointerstitial Diseases of the Kidney” (acute interstitial nephritis: causes, pathology, treatment; Table 328-1 classification; Table 328-2 steroid indications) and “Acute Kidney Injury” (AKI classification, management Table 321-3, dialysis indications).
- **Brenner & Rector's The Kidney** — “Tubulointerstitial Diseases” (Perazella & Rosner): pathogenesis as T-cell type IV hypersensitivity, clinical/laboratory features (Table 35.4), drug list (Table 35.6), NSAID-AIN features and dual minimal-change lesion, differential diagnosis (Table 35.5), corticosteroid regimens (Table 35.7).
- **CMDT 2026** — “Kidney Disease”: Interstitial Nephritis (essentials, Table 25-4 causes, steroid dosing) and AKI management.



Acute Interstitial Nephritis

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — **Acute interstitial nephritis (AIN)** is an acute tubulointerstitial disorder characterised by inflammation and oedema of the renal *interstitium* with secondary tubular injury, while the **glomeruli and renal vessels are relatively spared**. *Councilman* (1897) originally described it as “an acute inflammation of the kidney characterised by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependent on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal.” Today AIN is most often an **allergic (immune-mediated) reaction to a drug** and is an important, frequently reversible cause of acute kidney injury (AKI).

Etiology / Classification

AIN is conveniently grouped into **drug-induced (allergic)**, **infection-associated**, and **autoimmune/systemic** causes (Harrison Table 328-1):

Category	Representative causes
Antibiotics	β -lactams, sulfonamides, quinolones, vancomycin, erythromycin, linezolid, minocycline, rifampin, ethambutol, acyclovir
NSAIDs / COX-2 inhibitors	All NSAIDs; selective COX-2 inhibitors
Diuretics	Rarely thiazides, loop diuretics, triamterene

Category	Representative causes
Anticonvulsants	Phenytoin, valproate, carbamazepine, phenobarbital
Immune modulators	Immune checkpoint inhibitors, vedolizumab, lenalidomide
Miscellaneous drugs	Proton pump inhibitors (PPIs), H2 blockers, captopril, mesalazine, indinavir, allopurinol
Infection	Bacteria (<i>Streptococcus</i> , <i>Staphylococcus</i> , <i>Legionella</i> , <i>Salmonella</i> , <i>Brucella</i> , <i>Yersinia</i> , <i>C. diphtheriae</i>); Viruses (EBV, CMV, hantavirus, polyomavirus/BK , HIV); <i>Leptospira</i> , <i>Rickettsia</i> , <i>Mycoplasma</i> , <i>Histoplasma</i>
Autoimmune / systemic	TINU, Sjögren's syndrome, SLE, granulomatous interstitial nephritis, IgG4-related disease , checkpoint-inhibitor-related TIN, anti-brush border (anti-LRP2) disease, idiopathic autoimmune IN

- ▶ **Drug-induced AIN is the commonest form** and the reaction is *idiosyncratic* (not dose-dependent) — it may recur on re-exposure. *Particularly severe, rapid-onset AIN follows reintroduction of rifampin after a drug-free period.*
- ▶ NSAIDs, PPIs, mesalazine/sulfasalazine and antiretrovirals characteristically cause a more *insidious* reaction that may progress to chronic tubulointerstitial damage.

Pathogenesis

- ▶ AIN represents an **immune-mediated (hypersensitivity) reaction** rather than direct dose-dependent toxicity; the drug or microbial antigen triggers an inflammatory infiltrate that produces interstitial oedema, tubular-cell injury and compromised tubular flow.
- ▶ In some idiopathic and autoimmune cases, **autoantibodies to a tubular antigen** (e.g. collecting-duct or proximal-tubule brush-border antigens, *anti-LRP2/anti-brush border disease*) have been demonstrated, supporting an autoimmune mechanism.
- ▶ The aggressive inflammatory infiltrate (with **eosinophils, lymphocytes and mononuclear cells**) leading to tissue oedema accounts for the *acute* nature and the occasional **flank pain from distension of the renal capsule**.

Clinical Features

- ▶ **Classic triad/tetrad** (the *exception, not the rule*): **fever, rash (maculopapular), peripheral eosinophilia, and oliguric AKI** occurring 7–10 days after starting methicillin or another β -lactam.
- ▶ More commonly, the patient is found **incidentally to have a rising serum creatinine** or presents with non-specific symptoms of AKI.

- ▶ **NSAID-induced AIN is atypical:** fever, rash and eosinophilia are *rare*, but AKI is often accompanied by **heavy (nephrotic-range) proteinuria** (from coexistent minimal-change disease/secondary FSGS).
- ▶ Features of associated tubular dysfunction may occur — *Fanconi's syndrome*, distal/proximal RTA, type IV RTA and nephrogenic diabetes insipidus, especially when injury is prolonged.

Investigations / Diagnosis

- ▶ **Clinical diagnosis** rests on otherwise-unexplained AKI ($\pm$ oliguria) with **temporally-related exposure to an offending agent**.
- ▶ **Urinalysis:** *pyuria (sterile) with white-blood-cell casts and haematuria*; modest proteinuria. Urinary eosinophils are **neither sensitive nor specific** — **testing is NOT recommended**.
- ▶ **Peripheral blood eosinophilia** supports the diagnosis but is present in only a minority.
- ▶ **Renal ultrasound** may show enlarged, echogenic kidneys (“medical renal disease”).
- ▶ **Kidney biopsy** is *generally not required* but is the gold standard when the diagnosis is uncertain or the course atypical — it shows **extensive interstitial and tubular infiltration by leukocytes, including eosinophils**, interstitial oedema separating tubules, with a *normal glomerulus*. Granulomas suggest granulomatous IN; dense IgG4-plasma-cell infiltrate suggests IgG4 disease.
- ▶ Biopsy-proven AIN accounts for **~15% of cases of unexplained AKI** (likely an underestimate, as drugs are often empirically stopped without biopsy).

Important Non-Drug / Systemic Forms

- ▶ **Tubulointerstitial nephritis with uveitis (TINU):** <5% of AIN; **females 3× > males**, median age **15 years**. Lymphocyte-predominant IN + **painful anterior uveitis** (often bilateral, with blurred vision/photophobia); ocular symptoms coincide with renal disease in only **one-third**. Sterile pyuria, mild proteinuria, Fanconi features, **raised ESR**; a diagnosis of exclusion. Self-limited in children, relapsing in adults.
- ▶ **Sjögren's syndrome:** lymphocytic TIN with distal RTA and nephrogenic DI; **anti-Ro (SS-A)/anti-La (SS-B)** positive, polyclonal hypergammaglobulinaemia.
- ▶ **SLE:** interstitial mononuclear infiltrate accompanies class III/IV lupus nephritis; may present with azotaemia and type IV RTA.
- ▶ **Granulomatous IN:** protracted/relapsing; biopsy shows granulomas and multinucleated giant cells (e.g. *sarcoidosis*); **rule out tuberculosis before steroids**.
- ▶ **IgG4-related systemic disease:** IgG4-plasma-cell infiltrate with autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, sialadenitis; steroid-responsive.
- ▶ **Immune checkpoint-inhibitor AIN:** kidney involved in **2% (monotherapy) up to 5% (dual therapy)**; creatinine usually rises **within ~15 weeks**; treat by holding the drug + steroids.

- ▶ **Infection-associated AIN:** distinct from acute pyelonephritis; seen mainly in immunocompromised/transplant patients (**BK polyomavirus reactivation**); a rise in TIN/TINU in children has followed SARS-CoV-2.

Treatment

- ▶ **Prompt withdrawal of the offending drug** is the cornerstone and often leads to recovery of kidney function. Recovery may be **incomplete** if exposure was prolonged (tubular atrophy/interstitial fibrosis).
- ▶ **Supportive care:** management of AKI, fluid/electrolyte and acid-base correction, and **dialysis** when indicated. *Delay in initiating dialysis worsens long-term outcomes.*
- ▶ **Glucocorticoids** may accelerate recovery but are **not required in most cases**; reserve for severe injury when dialysis is imminent, and start promptly if function continues to deteriorate despite stopping the drug (Harrison Fig. 328-1 algorithm).
- ▶ **Relapsing/refractory or immune-mediated AIN** may need maintenance immunosuppression — azathioprine, mycophenolate mofetil or methotrexate.

Indications for corticosteroids / immunosuppressives (Table 328-2):

Absolute indications	Relative indications
Sjögren's syndrome	Drug-induced or idiopathic AIN with rapid progression of renal failure
Sarcoidosis	Diffuse infiltrates on biopsy
SLE interstitial nephritis	Impending need for dialysis
Adults with TINU	Delayed recovery
IgG4-related interstitial nephritis	Children with TINU
Idiopathic & other granulomatous IN	Post-infectious AIN with delayed recovery (?)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Histology of AIN (PAS-stained section):** label — *interstitial mononuclear-cell infiltrate (eosinophils/lymphocytes), interstitial oedema separating the tubules (T), normal glomerulus (G), tubules with cellular debris.*
- ▶ **Treatment algorithm (Fig. 328-1):** boxes — *AKI with features of AIN → withdraw offending agent + supportive care/close observation → improvement (continue observation) OR no improvement in 1 week / rapid progression → classic allergic AIN (corticosteroids) vs atypical features (renal biopsy) → granulomatous/immune IN (immunosuppressive drugs) vs fibrosis (conservative).*

Clinical / Diagnostic significance

- ▶ AIN is a **potentially reversible cause of AKI** — early recognition and **drug withdrawal** are pivotal; missing it leads to progression to CKD via interstitial fibrosis and secondary FSGS.
- ▶ A **high index of suspicion** is needed because the classic allergic syndrome is uncommon; consider AIN in any unexplained creatinine rise with sterile pyuria/WBC casts and a recent new drug.
- ▶ **Recognise atypical NSAID-induced AIN** (nephrotic proteinuria, no allergic features) and **PPI-associated** insidious AIN, given how widely these drugs are used.
- ▶ Distinguish AIN from **acute pyelonephritis** (which causes AKI only if bilateral or with septic shock) and from **crystal/obstructive tubulopathies** (sulfadiazine, indinavir/atazanavir, acyclovir, urate, oxalate).

High-yield exam pointers

- ▶ **Most common cause = drugs**; classic offenders are β -lactams, NSAIDs, PPIs, rifampin, sulfonamides, allopurinol.
- ▶ **Reaction is idiosyncratic, not dose-related**; rifampin re-exposure causes severe rapid AIN.
- ▶ **Classic tetrad** — fever, rash, eosinophilia, AKI 7–10 days post- β -lactam — is the *exception*.
- ▶ **Urine**: sterile pyuria + **WBC casts** + haematuria; **urinary eosinophils not recommended** (poor sensitivity/specificity).
- ▶ **Biopsy** = interstitial leukocyte infiltrate with eosinophils, oedema, **normal glomeruli**.
- ▶ **TINU** = young female, anterior uveitis, raised ESR; **Sjögren's** = anti-Ro/anti-La, distal RTA.
- ▶ **Treatment** = stop the drug first; **steroids not routine**, reserved for severe/immune-mediated disease; maintenance with azathioprine/MMF for relapsers.
- ▶ AIN explains ~15% of unexplained AKI cases.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 328 "Tubulointerstitial Diseases of the Kidney"** (Beck & Salant), including Tables 328-1 (causes) and 328-2 (steroid indications) and Figs 328-1/328-2. *Coverage note:* The provided chapter frames AIN as an "allergic/immune-mediated" reaction with autoantibodies to tubular antigens but does not explicitly classify the mechanism as *type-IV (delayed/cell-mediated) hypersensitivity*; the dose-independent idiosyncratic framing in the Pathogenesis section is standard, universally-accepted internal medicine and is consistent with the chapter's wording.



Acute Kidney Injury

Asked in: Paper IV Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Acute kidney injury (AKI) is the abrupt impairment of kidney filtration and excretory function over hours to days (generally within 7 days), causing retention of nitrogenous and other waste products normally cleared by the kidney. The **KDIGO** definition is a rise in serum creatinine (SCr) of ≥ 0.3 mg/dL within 48 h, OR a rise to ≥ 1.5 times baseline known/presumed within 7 days, OR urine output < 0.5 mL/kg/h for > 6 h. AKI is a *clinical and not a structural* diagnosis — the kidney may have functional impairment with or without parenchymal injury — and ranges from asymptomatic biochemical change to life-threatening failure of volume, electrolyte and acid–base homeostasis. It complicates 5–7% of hospital admissions and up to 30% of ICU admissions, and is an independent risk factor for incident/progressive CKD, cardiovascular disease and death.

Classification and staging

- ▶ Three traditional anatomic-physiological categories: **prerenal azotemia** (commonest), **intrinsic renal disease**, and **postrenal (obstructive) AKI**.
- ▶ Severity is staged by the magnitude of SCr rise and the severity/duration of oliguria. Predecessor consensus systems were **RIFLE** (*Risk, Injury, Failure, Loss, End-stage*) and **AKIN** (Acute Kidney Injury Network); the current unifying system is **KDIGO**.

Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline OR ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) increase	< 0.5 mL/kg/h for 6–12 h
2	2.0–2.9 × baseline	< 0.5 mL/kg/h for ≥ 12 h
3	≥ 3.0 × baseline OR SCr ≥ 4.0 mg/dL OR initiation of RRT OR (age < 18 y) eGFR < 35 mL/min/1.73 m ²	< 0.3 mL/kg/h for ≥ 24 h OR anuria ≥ 12 h

Etiology and pathophysiology

- ▶ **Prerenal azotemia** (~40–80% of community AKI): inadequate renal plasma flow/intraglomerular pressure with *no parenchymal damage* — rapidly reversible once perfusion is restored. Causes: hypovolemia (haemorrhage, GI losses, diuresis, burns, third-spacing), low cardiac output, and reduced effective circulating volume (heart failure, cirrhosis, sepsis). Drugs impair autoregulation: **NSAIDs** block vasodilatory prostaglandins (afferent constriction) and **ACE-inhibitors/ARBs** block efferent constriction — combined use is especially high-risk, as is bilateral renal artery stenosis. *Hepatorenal syndrome* (splanchnic vasodilation in advanced cirrhosis) is a diagnosis of exclusion in this group. Prolonged prerenal ischaemia progresses to **acute tubular necrosis (ATN)**.
- ▶ **Intrinsic AKI** — by site:
 - *Tubular (ATN, ~85% of intrinsic AKI): ischaemia, sepsis, nephrotoxins.* The S3 segment of the proximal tubule in the outer medulla is most vulnerable (dependence on fatty-acid

oxidation/oxidative phosphorylation, venous-derived blood supply, hypoxic medulla).

Ischaemic ATN evolves through **initiation** → **extension (endothelial injury, medullary congestion)** → **maintenance** → **recovery** phases; mechanisms include vasoconstriction, loss of cell polarity (apical mislocalisation of Na^+/K^+ -ATPase → high FeNa), cytoskeletal breakdown, tubular obstruction by casts, and back-leak of filtrate.

- *Nephrotoxic — exogenous*: iodinated **contrast** (CI-AKI; SCr rises 24–48 h, peaks 3–5 d, recovers ~7 d), **aminoglycosides** (nonoliguric AKI in 10–30%, manifests after 5–7 d, hypomagnesaemia), **amphotericin B** (polyuria, hypomagnesaemia, hypocalcaemia, non-gap acidosis), **cisplatin**, vancomycin, tenofovir, **acyclovir/methotrexate/sulfadiazine** (intratubular crystals).
- *Nephrotoxic — endogenous*: **rhabdomyolysis** (myoglobin), haemolysis (haemoglobin), **tumour lysis syndrome** (uric acid often >15 mg/dL, hyperkalaemia, hyperphosphatemia), myeloma light chains, hypercalcaemia.
- *Glomerular (~5%)*: glomerulonephritis/vasculitis — important to recognise early as immunosuppression/plasma exchange may reverse it.
- *Interstitial*: allergic/acute interstitial nephritis (drugs ~75% — antibiotics, PPIs, NSAIDs, immune-checkpoint inhibitors), infection, infiltration.
- *Vascular*: thrombotic microangiopathies (**TTP/HUS**, scleroderma renal crisis, malignant hypertension), atheroembolic disease, renal artery/vein occlusion.
- ▶ **Postrenal AKI (~5–10%)**: obstruction anywhere from renal pelvis to urethra. For significant SCr rise, obstruction must be bilateral (or unilateral in a solitary/CKD kidney). Causes: bladder outlet obstruction (BPH, prostate cancer, neurogenic bladder, blocked catheter), bilateral ureteric stones/clots/papillae, retroperitoneal fibrosis or pelvic malignancy. Early relief usually reverses injury.

Diagnostic evaluation

- ▶ **First steps**: distinguish AKI from CKD (small echogenic kidneys, normocytic anaemia, renal osteodystrophy favour CKD; normal-sized kidneys favour AKI), then localise to prerenal/intrinsic/postrenal. Review every drug; exclude obstruction with bladder catheter and **renal ultrasound/CT** (hydronephrosis).
- ▶ **Urine output**: oliguria = <400 mL/24 h (denotes more severe AKI, worse prognosis). Complete anuria suggests complete obstruction, renal artery occlusion, overwhelming septic shock, cortical necrosis, or severe proliferative GN/vasculitis.
- ▶ **Urine sediment (Fig. 321-6)**: bland/hyaline casts → prerenal or postrenal; **pigmented “muddy-brown” granular and renal tubular epithelial cell casts** → ATN; dysmorphic RBCs/RBC casts → glomerulonephritis; WBC casts/eosinophiluria → interstitial nephritis; uric acid or oxalate crystalluria → tumour lysis or ethylene-glycol toxicity.

► Renal failure (differential) indices:

Index	Prerenal	Intrinsic (ATN)
BUN : creatinine ratio	>20 : 1	<20 : 1
$\text{FeNa} = (\text{UNa} \times \text{PCr}) / (\text{PNa} \times \text{UCr}) \times 100$	<1%	>1–2%
Urine Na^+ (mEq/L)	<20	>20
Urine osmolality (mOsm/kg)	>500	<350 (isosthenuria)
Urine specific gravity	>1.018	~1.010

Caveats: FeNa is most useful in **oliguric, diuretic-free, non-CKD** patients; it may be <1% even in intrinsic AKI from **sepsis (early), contrast, rhabdomyolysis** and glomerulonephritis. After diuretics, **fractional excretion of urea (FeUrea, <35% suggests prerenal)** is more reliable.

- **Blood tests:** hyperkalaemia, hyperphosphatemia, hypocalcaemia, high anion-gap metabolic acidosis; $\uparrow$ CK/uric acid (rhabdomyolysis), low anion gap (myeloma cationic proteins), schistocytes/ $\uparrow$ LDH/low haptoglobin/thrombocytopenia (TMA — check ADAMTS13, Shiga toxin, complement). Immunological panel where indicated: ANA, ANCA, **anti-GBM**, complement, ASO, cryoglobulins, serum free light chains.
- **Novel biomarkers:** NGAL (detectable within 2 h of cardiopulmonary bypass), KIM-1, cystatin C, suPAR, and the FDA-cleared cell-cycle-arrest pair TIMP-2 $\times$ IGFBP7 (**NephroCheck**) for risk of moderate–severe AKI in the critically ill. **Furosemide stress test** (1.0–1.5 mg/kg IV; urine <200 mL over 2 h) predicts progression/need for RRT.
- **Kidney biopsy:** reserved for when prerenal, postrenal and ischaemic/nephrotoxic ATN are unlikely and treatable diagnoses (GN, vasculitis, AIN, myeloma, TTP/HUS) are considered.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Classification flow-chart of AKI** — central box “Acute Kidney Injury” branching to three columns: *Prerenal* (hypovolemia, low cardiac output, low effective circulating volume — CHF/cirrhosis, impaired autoregulation — NSAIDs/ACE-I/ARB); *Intrinsic* (Glomerular: acute GN; Vascular: vasculitis, malignant HTN, TTP-HUS; Tubular/interstitial: ischaemia, sepsis, nephrotoxins — exogenous contrast/aminoglycoside/cisplatin, endogenous haemolysis/rhabdomyolysis/myeloma); *Postrenal* (bladder-outlet obstruction, bilateral pelviureteric obstruction). Label arrows.
- **Pathophysiology of ischaemic AKI** — interacting *Microvascular* limb (vasoconstriction: endothelin, adenosine, angiotensin II, thromboxane A_2 ; $\downarrow$ vasodilators: NO, PGE_2 ; endothelial damage; leukocyte–endothelial adhesion) and *Tubular* limb (cytoskeletal

breakdown, loss of polarity, apoptosis/necrosis, desquamation → **tubular obstruction + back-leak** → fall in GFR. Mark the vulnerable **S3 segment/outer medulla**.

Clinical / Diagnostic significance

- **Complications (mnemonic of the kidney's homeostatic roles):** volume overload/pulmonary oedema, **hyperkalaemia** (most dangerous — arrhythmia; worst in rhabdomyolysis/haemolysis/tumour lysis), high-anion-gap metabolic acidosis, hyperphosphatemia with hypocalcaemia, hyponatremia, **uremia** (encephalopathy, asterixis, pericarditis, platelet dysfunction/bleeding), anaemia, infection and malnutrition (hypercatabolic state).
- **General management (Table 321-3):** optimise systemic/renal haemodynamics with volume resuscitation (**crystalloids preferred**; 0.9% saline or balanced solutions; packed cells for haemorrhage) and judicious vasopressors to keep **MAP >65 mmHg**; **stop/avoid nephrotoxins** (NSAIDs, ACE-I/ARB, aminoglycosides, contrast, checkpoint inhibitors) and **renally dose all drugs**; nutrition **20–30 kcal/kg/day**, protein 0.8–1.0 g/kg/day (non-catabolic), 1.0–1.5 (on dialysis), up to 1.7 (hypercatabolic on CRRT).
- **Cause-specific:** *rhabdomyolysis* — aggressive IV fluids (may need up to 10 L/day), consider alkaline diuresis (risk hypocalcaemia); *tumour lysis* — IV fluids + **allopurinol or rasburicase**; *hepatorenal syndrome* — albumin + **terlipressin** (or noradrenaline, or octreotide + midodrine), definitive treatment **liver transplant**; *scleroderma renal crisis* — **ACE inhibitors**; *idiopathic TTP* — urgent plasma exchange; *atypical HUS* — complement blockade (eculizumab); *postrenal* — prompt catheter/stent/nephrostomy (watch for post-obstructive diuresis).
- **Hyperkalaemia ladder:** calcium gluconate (membrane stabilisation) → insulin–glucose and inhaled β -agonist (intracellular shift) → loop diuretic, K^+ -binders (sodium zirconium cyclosilicate, patiromer, SPS) → dialysis.
- **Renal replacement therapy — indications “AEIOU”:** Acid–base disturbance (refractory acidosis), Electrolyte disturbance (refractory hyperkalaemia), Intoxication (dialysable poison), Overload (volume, diuretic-unresponsive), Uremic complications (encephalopathy, pericarditis, bleeding). Modalities: intermittent haemodialysis; **CRRT** (CVVH/CVVHD/CVVHDF — preferred in haemodynamic instability, cerebral oedema, marked volume overload); SLED/EDD; peritoneal dialysis. Trials (e.g. **STARRT-AKI**) show no survival benefit from earlier/more-intensive RRT — initiate for indications, not arbitrary timing.

High-yield exam pointers

- KDIGO triad: $SCr \uparrow \geq 0.3 \text{ mg/dL/48 h}$ OR $\geq 1.5 \times$ baseline/7 d OR $UO < 0.5 \text{ mL/kg/h} > 6 \text{ h}$.
- Prerenal is commonest; $FeNa < 1\%$, $BUN:Cr > 20$, urine osm > 500 , bland/hyaline casts; ATN — $FeNa > 1\text{--}2\%$, **muddy-brown granular casts**.

- ▶ $\text{FeNa} = (\text{UNa} \times \text{PCr}) / (\text{PNa} \times \text{UCr}) \times 100$; unreliable on diuretics → use **FeUrea** (<35% = prerenal).
- ▶ **S3 proximal tubule / outer medulla** is the most ischaemia-susceptible segment; ATN phases = initiation–extension–maintenance–recovery.
- ▶ NSAID + ACE-I/ARB combination and bilateral renal artery stenosis are classic precipitants of prerenal AKI.
- ▶ Anuria differential: complete obstruction, renal artery occlusion, septic shock, cortical necrosis, severe proliferative GN/vasculitis.
- ▶ Most dangerous complication = **hyperkalaemia**; commonest dialysis indication categories = AEIOU.
- ▶ Low-dose dopamine, fenoldopam, ANP, loop diuretics do **not** prevent or hasten recovery from established ATN.
- ▶ Biomarkers: NGAL, KIM-1, cystatin C, **TIMP-2 × IGFBP7 (NephroCheck)**; furosemide stress test predicts progression.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Acute Kidney Injury” (Waikar & Bonventre): KDIGO definition/staging, etiologic classification, pathophysiology, diagnostic indices, complications, and management (Tables 321-1, 321-2, 321-3; Figs 321-1 to 321-6).
- ▶ **Brenner & Rector's The Kidney** — “Pathophysiology of Acute Kidney Injury”: RIFLE/AKIN/KDIGO context, S3-segment vulnerability, extension-phase microvascular/endothelial injury, Na^+/K^+ -ATPase mislocalisation and high FeNa in ATN.
- ▶ **CMDT 2026** — “Kidney Disease” (AKI / Acute Tubular Necrosis): prerenal/intrinsic/postrenal percentages, FeNa formula and caveats, FeUrea, furosemide stress test, AEIOU dialysis indications, three-phase ATN course and prognosis.



Acute renal failure in Tropics

Asked in: Paper IV May 2022 — RGUHS MD General Medicine

Definition / Introduction — Acute renal failure (now termed **acute kidney injury, AKI**) is an abrupt (hours–days) decline in glomerular filtration rate with retention of nitrogenous wastes and dysregulation of fluid, electrolyte and acid–base balance. *Tropical AKI* is not a separate disease but a distinct **epidemiological pattern**: in the developing world many etiologies are region-specific — **envenomations** (snakes, spiders, caterpillars, bees), **infections** such as **malaria** and **leptospirosis**, and **crush injury/rhabdomyolysis** — and resources to diagnose and treat AKI are often limited. It is typically

community-acquired, affects young previously healthy patients, is frequently single-cause and potentially fully reversible, but carries high mortality where dialysis is unavailable.

Why tropical AKI is distinct (epidemiology)

- ▶ AKI is a **major medical complication in the developing world**; its epidemiology differs from developed countries because of **differences in demographics, economics, environmental factors and the comorbid disease burden**.
- ▶ As urban centres of developing countries increasingly resemble those of the developed world, **hospital-acquired AKI** (sepsis, major surgery, critical illness, nephrotoxins) is rising and now coexists with the classic community-acquired tropical pattern.
- ▶ Region-specific etiologies explicitly named by Harrison: **envenomations from snakes, spiders, caterpillars and bees; infectious causes such as malaria and leptospirosis; and crush injuries with rhabdomyolysis** (e.g., after earthquakes).
- ▶ **Resources to diagnose and manage AKI are often limited**, so prevention, early recognition and timely renal replacement are the principal determinants of outcome.

Classification of causes (anatomical framework applied to the tropics)

The standard three-tier classification (Fig. 321-1) maps neatly onto tropical disease:

Category	General mechanism	Tropical examples (mapped)
Prerenal azotemia	Reduced renal perfusion, no parenchymal damage, rapidly reversible	Acute gastroenteritis/cholera, vomiting/diarrhoea, haemorrhage, sepsis, dehydration
Intrinsic (parenchymal)	Sepsis, ischaemia, endogenous/exogenous nephrotoxins	Sepsis-associated AKI , malaria, leptospirosis, snakebite, pigment nephropathy (rhabdomyolysis, haemolysis), viral infection, acute interstitial nephritis from traditional/herbal remedies
Postrenal (obstructive)	Obstruction to urine flow	Stone disease, schistosomal/genitourinary obstruction, retroperitoneal pathology

- ▶ **Prerenal azotemia is the commonest form of AKI overall**; prolonged hypoperfusion (common with diarrhoeal dehydration) progresses to **ischaemic acute tubular necrosis (ATN)**.
- ▶ **Sepsis complicates >50% of severe sepsis cases** and “is also a very important cause of AKI in the developing world”; reduced urine output is common and GFR can fall even without overt hypotension.

Major tropical syndromes and mechanisms

Syndrome	Renal injury mechanism	Renal lesion / clue
Severe malaria (<i>P. falciparum</i>)	Microvascular sequestration, intravascular haemolysis → haemoglobinuria (pigment nephropathy), volume depletion, sepsis-like cytokine state	ATN; <i>blackwater fever</i> with dark urine; often oliguric
Leptospirosis (<i>Weil's disease</i>)	Direct tubulointerstitial injury, hypovolaemia, jaundice-associated tubular toxicity	Classically non-oliguric , hypokalaemic AKI with jaundice
Snake/other envenomation	Haemolysis, DIC, rhabdomyolysis (myotoxic venom), hypotension, direct nephrotoxicity	ATN; severe cases → renal cortical necrosis
Rhabdomyolysis (crush, exertional, heatstroke, seizures, infections)	Myoglobin release → intrarenal vasoconstriction, direct tubular toxicity, intratubular cast obstruction	Pigmented granular casts; CK and myoglobin elevated ; urine heme-positive with few RBCs; FeNa may be <1%
Sepsis-associated AKI	Arterial vasodilation (inducible NO synthase), inflammation, mitochondrial dysfunction, interstitial oedema	Granular and renal tubular epithelial cell casts; positive cultures
Viral infections	Incompletely understood; pigment/haemodynamic/inflammatory injury	AKI complicates hantavirus, dengue virus, and SARS-CoV-2 ; “typical” diarrhoea-associated HUS from Shiga-toxin <i>E. coli</i>
Obstetric AKI	Septic abortion, haemorrhage, eclampsia, thrombotic microangiopathy	Pregnancy/postpartum TTP-HUS; severe cases → bilateral cortical necrosis

Pathophysiology of pigment (haem) nephropathy — a tropical mainstay

Pigment-induced AKI underlies malaria (haemoglobin), haemolysis (incl. G6PD-related, transfusion reaction) and rhabdomyolysis (myoglobin), and is grounded directly in the chapter:

- ▶ **Myoglobin** is released by injured muscle; **haemoglobin** is released during massive haemolysis — both produce **pigment nephropathy**.
- ▶ Three converging mechanisms: (1) **intrarenal vasoconstriction**; (2) **direct proximal tubular toxicity**; (3) **mechanical obstruction of the distal nephron** when myoglobin/haemoglobin precipitates with **Tamm-Horsfall protein (uromodulin)** — a process favoured by **acidic urine** (rationale for urinary alkalinisation).
- ▶ Causes of rhabdomyolysis listed: traumatic crush injuries, muscle ischaemia, compression during coma/immobilisation, prolonged seizures, excessive exercise, **heat stroke or malignant**

hyperthermia, infections, metabolic disorders and myopathies — many of which are common in tropical/field settings.

Clinical approach and investigations

- ▶ **History:** fluid loss (diarrhoea, vomiting, haemorrhage), fever, animal bite, dark/cola-coloured urine, drug/herbal exposure, recent pregnancy/abortion, oliguria/anuria.
- ▶ **Examination of volume status:** tachycardia, postural/absolute hypotension, low JVP, dry mucous membranes (prerenal); features of sepsis, jaundice, bleeding.
- ▶ **Urinalysis** is pivotal:
 - **Pigmented “muddy-brown” granular casts and tubular epithelial cell casts** → ATN/sepsis-associated AKI.
 - **Urine dipstick heme-positive with few RBCs** → rhabdomyolysis or haemolysis (pigment nephropathy).
 - Bland sediment with **FeNa <1%, urine osmolality >500 mOsm/kg, BUN/creatinine >20** → prerenal.
- ▶ **Blood:** serum creatinine/BUN, electrolytes (**hyperkalaemia is particularly common in rhabdomyolysis and haemolysis**), **creatinine kinase and myoglobin** (rhabdomyolysis), uric acid, LDH/haptoglobin (haemolysis), cultures, peripheral smear (malaria parasites, schistocytes).
- ▶ **Imaging/biopsy:** ultrasound to exclude obstruction and assess kidney size; kidney biopsy reserved for suspected glomerulonephritis/vasculitis/cortical necrosis or diagnostic uncertainty.

Management

General principles common to all AKI (Table 321-3): optimise haemodynamics, correct fluid/electrolyte/acid–base disturbances, **stop nephrotoxic drugs**, dose-adjust all renally-cleared drugs, ensure **20–30 kcal/kg per day** nutrition (protein 0.8–1.0 g/kg in non-catabolic, up to ~1.7 g/kg with hypercatabolism on CRRT), and start renal replacement therapy when indicated.

- ▶ **Prerenal / volume depletion (diarrhoeal AKI):** restore perfusion; **intravascular hypovolaemia is the only indication for fluids** (oliguria alone is not). Replace with crystalloid (commonly **0.9% saline**, or buffered solutions — Ringer’s lactate/Hartmann’s/Plasma-Lyte); transfuse **packed RBCs** for severe acute blood loss.
- ▶ **Rhabdomyolysis / pigment nephropathy:** **early and aggressive volume repletion is mandatory** — may require up to **10 L of fluid per day**; **alkaline fluids** (e.g., **75 mmol/L sodium bicarbonate in 0.45% saline**) may reduce tubular injury and cast formation (consider **forced alkaline diuresis**), but watch for **worsening hypocalcaemia**; diuretics only after adequate repletion, targeting urine flow **200–300 mL/h**. There is no specific therapy for established AKI other than supportive care/dialysis; monitor **calcium and phosphate** closely.

- ▶ **Sepsis-associated AKI:** source control, antimicrobials, restore perfusion with vasopressors as needed; no specific therapy once tubular injury is established — meticulous supportive care.
- ▶ **Electrolyte/acid–base emergencies:**
 - **Hyperkalaemia** — calcium gluconate/chloride (1 g) to stabilise the myocardium, **insulin–glucose** and inhaled β -agonist to shift K^+ intracellularly, loop diuretics, K^+ -binders (**sodium zirconium cyclosilicate, patiomer, polystyrene sulfonate**); stop ACEi/ARB/NSAIDs/ K^+ -sparing diuretics.
 - **Metabolic acidosis** — sodium bicarbonate if pH <7.2 / bicarbonate <15 mmol/L, avoiding overcorrection.
 - **Volume overload** — salt/water restriction, **furosemide bolus (200 mg) then 10–40 mg/h** $\pm$ thiazide, ultrafiltration if refractory.
- ▶ **Renal replacement therapy (RRT):** indicated for **refractory volume overload, hyperkalaemia or acidosis, certain toxic ingestions, and severe uraemic complications** (asterixis, pericardial rub/effusion, encephalopathy, uraemic bleeding). Many initiate empirically when **BUN exceeds ~100 mg/dL** without signs of recovery; early-vs-late initiation has not improved survival in RCTs but RRT should not await a life-threatening complication. Modalities: intermittent **haemodialysis** (3–4 h, 3–4 $\times$ /week), **continuous (CRRT)** for haemodynamically unstable patients, and **peritoneal dialysis** — the latter especially valuable in resource-limited tropical settings.
- ▶ **Postrenal:** prompt relief of obstruction (bladder catheter, ureteric stent or percutaneous nephrostomy); anticipate post-obstructive diuresis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Classification of AKI mapped to tropical causes (flowchart).** Top box: *Acute Kidney Injury*. Three branches: **Prerenal** (labels: *Hypovolaemia — diarrhoea/cholera, haemorrhage; decreased effective circulating volume; sepsis*), **Intrinsic** (labels: *Sepsis/infection; Ischaemic ATN; Endogenous nephrotoxins — myoglobin, haemoglobin; Glomerular — GN/vasculitis; Vascular — TTP-HUS, cortical necrosis; Tropical: malaria, leptospirosis, snakebite, dengue/hantavirus*), **Postrenal** (labels: *Bladder outlet / bilateral ureteric obstruction*).
- ▶ **Diagram 2 — Pathophysiology of pigment nephropathy.** Labels: *Muscle injury / haemolysis $\rightarrow$ myoglobin / haemoglobin $\rightarrow$ (1) intrarenal vasoconstriction, (2) direct proximal tubular toxicity, (3) precipitation with Tamm-Horsfall protein (uromodulin) in acidic urine $\rightarrow$ distal tubular obstruction $\rightarrow$ ATN; arrow to “urinary alkalinisation + volume repletion” as the therapeutic interruption point.*

Clinical / Diagnostic significance

- ▶ **Reversibility:** community-acquired tropical AKI in young patients often recovers fully — the kidney has “remarkable capacity to repair itself” even after dialysis-requiring AKI — so aggressive early support is justified.
- ▶ **Urinary sediment + FeNa + CK/myoglobin** rapidly separate prerenal, ATN and pigment nephropathy at the bedside, guiding fluid and alkalinisation decisions.
- ▶ **Pregnancy/obstetric AKI and severe envenomation** carry a risk of **bilateral renal cortical necrosis**, which may leave permanent CKD/ESKD — a recognised tropical pattern.
- ▶ **AKI predisposes to CKD and to sepsis**, and superimposed AKI on CKD often heals by maladaptive repair — flag survivors for nephrology follow-up.
- ▶ **Peritoneal dialysis** is a practical, low-resource RRT modality central to tropical/rural practice.

High-yield exam pointers

- ▶ Tropical AKI = **community-acquired, young, single-cause, reversible, high mortality without dialysis**; Harrison’s named triad — **envenomation, malaria/leptospirosis, crush rhabdomyolysis**.
- ▶ **Prerenal azotaemia is the commonest AKI**; diarrhoeal dehydration is the prototypic tropical prerenal → ATN sequence.
- ▶ **Pigment nephropathy** trio of mechanisms: vasoconstriction, direct tubular toxicity, **Tamm-Horsfall (uromodulin) cast obstruction favoured by acidic urine** → treat with **volume + urinary alkalinisation**.
- ▶ **Leptospirosis** → classically **non-oliguric, hypokalaemic** AKI with jaundice (a favourite distinguishing point).
- ▶ **Rhabdomyolysis**: CK/myoglobin high, **heme-positive urine with few RBCs**, hyperkalaemia/hyperphosphataemia/hypocalcaemia; fluids up to **10 L/day**, alkaline fluid **75 mmol/L NaHCO₃ in 0.45% saline**, urine target **200–300 mL/h**.
- ▶ **Hyperkalaemia first move** = **IV calcium (1 g) to stabilise myocardium**, then insulin-glucose/β-agonist/binders.
- ▶ **Viral tropical AKI**: hantavirus, dengue, SARS-CoV-2; **Shiga-toxin (E. coli) typical HUS** after diarrhoeal prodrome.
- ▶ **Dialysis** for refractory volume/K⁺/acidosis or uraemic complications; empirical when **BUN >~100 mg/dL**; **peritoneal dialysis** is invaluable where resources are scarce.
- ▶ **No proven pharmacotherapy** reverses established ATN (dopamine, ANP, EPO etc. have all failed) — management is supportive + RRT.

SOURCE & COVERAGE

Harrison’s Principles of Internal Medicine, 22e (2025) — Ch 321 “Acute Kidney Injury” (AKI in the developing world; classification; sepsis-, ischaemia- and pigment-associated AKI;

prevention/treatment, supportive measures, RRT indications/modalities). *Coverage note (gap flagged)*: Ch 321 names the **tropical etiologies** (snake/insect envenomation, malaria, leptospirosis, crush rhabdomyolysis, dengue/hantavirus/SARS-CoV-2, diarrhoeal HUS) and grounds the **pathophysiology of pigment nephropathy and all management figures/doses** used above, but it does **not** detail the disease-specific mechanisms (e.g., *blackwater fever* of falciparum malaria, *Weil's disease* non-oliguric hypokalaemic AKI, snake-venom DIC/myotoxicity, obstetric cortical necrosis, G6PD-related haemolysis). Those points are standard, universally-accepted internal medicine drawn from the dedicated infectious-disease/toxicology chapters not provided in this task and should be cross-checked against Harrison's malaria, leptospirosis and envenomation chapters for full marks.



Autosomal Dominant Polycystic Kidney Disease

Asked in: Paper IV Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Autosomal dominant polycystic kidney disease (ADPKD) is a genetically heterogeneous, multisystem disorder characterised by progressive, bilateral formation of epithelial-lined cysts in the kidneys, leading to massive renal enlargement and a leading cause of kidney failure. It is the **most common life-threatening monogenic disease**, affecting an estimated **12 million people worldwide** (prevalence 1:1000 to 1:400). It is caused by germline mutations in **PKD1** (polycystin-1) or **PKD2** (polycystin-2), is inherited as an autosomal dominant trait with *complete penetrance but variable expressivity*, and belongs to the family of **ciliopathies**.

Genetics and Molecular Biology

- ▶ **PKD1** — chromosome **16p13** (localised 1985, near the alpha-globin gene); 46 exons, ~52 kb genomic DNA; ~14 kb transcript encoding **polycystin-1 (PC1)**, a large ~4300-amino-acid, **11-transmembrane** protein that behaves like a **G protein-coupled receptor (GPCR)**. Accounts for ~85% of cases; more severe phenotype, earlier ESRD.
- ▶ **PKD2** — chromosome **4q21-q23** (mapped 1993); single-copy gene, 15 exons; ~5.3 kb mRNA encoding **polycystin-2 (PC2)**, a 968-amino-acid, **six-transmembrane, calcium-permeable** protein of the **transient receptor potential (TRP)** cation channel family. Accounts for ~15% (probably more, as milder disease is under-diagnosed); later onset, slower progression.
- ▶ **Minor genes** — *GANAB* (encodes glucosidase IIα subunit) and *DNAJB11* (a BiP co-chaperone) cause milder, atypical disease and affect PC1 biogenesis/trafficking; found only in a small number of families.
- ▶ PC1 and PC2 bind via their **C-terminal tails** (proposed **1:3 PC1:PC2 stoichiometry**) to form a receptor-channel complex localised to the **primary cilium** (“9+0” axoneme), cell membrane and

cell–cell junctions, acting as a **mechano-/chemosensor** regulating calcium and G-protein signalling.

Feature	PKD1	PKD2
Chromosome locus	16p13	4q21–q23
Protein	Polycystin-1 (PC1)	Polycystin-2 (PC2)
Protein structure	11-TM, GPCR-like, ~4300 aa	6-TM, TRP Ca ²⁺ channel, 968 aa
Proportion of cases	~85%	~15% (often more)
Clinical severity	More severe, earlier ESRD	Milder, later ESRD

Pathogenesis (Cystogenesis)

- ▶ **Two-hit (“second-hit”) mechanism** — every cell carries a germline mutant allele, but cysts arise only from the small fraction of nephrons in which a **somatic mutation** inactivates the *normal* allele; cysts grow **clonally** from single cells. A **“third hit”** (additional genetic/epigenetic event or renal injury reactivating a developmental programme) may accelerate cyst formation.
- ▶ Loss of ciliary PC1/PC2 function → **aberrant calcium signalling** → increased **adenylyl cyclase** and decreased phosphodiesterase activity → raised **intracellular cAMP** → activation of **protein kinase A**, driving **cell proliferation and fluid secretion** via chloride (CFTR) and aquaporin channels into cysts.
- ▶ Implicated downstream pathways: **mTOR, Wnt, STAT3, cMET, PI3K/Akt, GPCR and EGFR** signalling. Cysts involve only ~5% of tubules, yet their enormous growth destroys surrounding parenchyma and renal function.
- ▶ Result: kidneys enlarge up to **fourfold in length** and weigh up to **20 times normal**; *hundreds to thousands* of cysts by the **fifth decade**.

Clinical Manifestations

- ▶ **Renal** — back/flank pain (~60%, from cyst infection, haemorrhage or stones); **gross haematuria** (~40%) from cyst rupture (recurrent); minor proteinuria; **nephrolithiasis** ~20% (>half **uric acid** stones, rest calcium oxalate — driven by low urine pH, hypocitraturia, distal acidification defects); **cyst infection/pyelonephritis** (gram-negatives) — the **second most common cause of death**; progressive enlargement → **ESRD** in late middle age.
- ▶ **Hypertension** — common, occurs **before any fall in GFR**; due to RAAS activation, increased sympathetic activity, and impaired endothelial cilium-dependent vasorelaxation; a major risk factor for cardiovascular and renal progression; LVH may occur even in normotensives.
- ▶ **Extrarenal:**

- **Polycystic liver disease** — most common extrarenal feature (biliary-epithelium-derived); massive disease **almost exclusively in women with multiple pregnancies**; does *not* cause liver failure. (Isolated ADPLD is a distinct disease from *PRKCSH/SEC63* mutations.)
- **Intracranial (berry) aneurysm** — 4–5× more frequent than general population; 20–50% have “warning headaches” before subarachnoid haemorrhage; CT is the first test, **lumbar puncture** confirms; **MR angiography** screening if positive family history.
- **Cardiac/vascular** — **mitral valve prolapse up to 30%**, tricuspid prolapse, aortic/mitral/tricuspid insufficiency; arterial dolichoectasia predisposing to dissection/stroke.
- **Others** — **colonic diverticulae** and **abdominal wall/inguinal hernias** are increased.
- ▶ **Risk factors for rapid progression** — early diagnosis, hypertension, gross haematuria, multiple pregnancies, **large kidney size**, *PKD1* (vs *PKD2*) and male sex.

Diagnosis

- ▶ Based on a **positive autosomal-dominant family history** plus **bilateral multiple renal cysts** on imaging; **renal ultrasonography** is first-line for presymptomatic screening of at-risk relatives and potential living-related donors.
- ▶ **Unified ultrasonographic (age-dependent) criteria** for at-risk individuals:

Age (years)	Cyst criterion for diagnosis	Performance
15–29	≥ 2 renal cysts (unilateral or bilateral)	Sensitivity 96%, specificity 100%
30–59	≥ 2 cysts in each kidney	Sensitivity 100%, specificity 100%
≥ 60	≥ 4 cysts in each kidney	Sensitivity 100%, specificity 100%

- ▶ In subjects aged 30–59, **absence of ≥2 cysts in each kidney** excludes disease (false-negative rate 0%); criteria are **less sensitive for PKD2** (late onset).
- ▶ **CT and T2-weighted MRI** (with/without contrast) are more sensitive and detect smaller cysts; **gadolinium T2-MRI** has minimal renal toxicity and detects cysts of only **2–3 mm**. CT carries radiation and contrast-nephrotoxicity risk.
- ▶ **Genetic testing** (linkage/mutational analysis, next-generation sequencing) for ambiguous cases; *PKD1* analysis is difficult/costly owing to its large size and multiple homologous pseudogenes.

Treatment

- ▶ **No FDA-approved therapy reverses cyst growth**; management slows progression and lowers cardiovascular risk.
- ▶ **Blood pressure control** — first-line by **inhibiting the RAAS** (ACE inhibitor/ARB); target **140/90 mmHg** (per JNC VIII). The **HALT-PKD** trial showed rigorous BP control slows cyst

growth, but a systolic target of 110 mmHg in moderate/advanced disease may *worsen* renal progression by reducing renal blood flow.

- ▶ **Tolvaptan** — a vasopressin V2-receptor (V2R) antagonist that lowers renal cAMP, slowing functional decline (TEMPO/"TAMPO" programme) and reducing renal pain; **FDA-restricted to patients at risk of rapidly progressing disease**; side effects include hepatotoxicity and polyuria/polydipsia.
- ▶ **Somatostatin analogues** (e.g. octreotide-LAR; ALADIN trial) lower cAMP and slow decline; side effect: cholecystitis. **mTOR inhibitors** (sirolimus, everolimus) have been trialed.
- ▶ **Cyst infection** — **lipid-soluble antibiotics** that penetrate cyst walls: **trimethoprim-sulfamethoxazole, fluoroquinolones, chloramphenicol**, often for 4–6 weeks.
- ▶ **Stones** — analgesia and hydration (standard measures). **Pain** — non-narcotic/narcotic analgesics, TENS, acupuncture, biofeedback, nerve block (DIPAK), occasionally surgical cyst decompression.
- ▶ **ESRD** — **>half eventually need dialysis or transplantation**; peritoneal dialysis may be limited by massively enlarged kidneys; **pre-transplant or bilateral nephrectomy** for very large kidneys or recurrent cyst infection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Primary cilium and the polycystin complex** — label: *primary cilium* ("9+0" axoneme), *ciliary membrane*, *basal body*, *transition zone*, *Polycystin-1 (PC1)*, *Polycystin-2 (PC2/TRP Ca²⁺ channel)*, *kinesin-2 (anterograde)*, *dynein (retrograde)*, and downstream arrows $\text{Ca}^{2+} \rightarrow \uparrow \text{cAMP} \rightarrow \text{PKA} \rightarrow \text{proliferation} + \text{fluid secretion}$.
- ▶ **Cut-section of a polycystic kidney** — label: *grossly enlarged kidney*, *innumerable cortical and medullary cysts of varying size*, *compressed residual parenchyma*, *haemorrhagic cyst*.

Clinical / Diagnostic significance

- ▶ ADPKD is a **systemic disease** — always screen for **hypertension, hepatic cysts and intracranial aneurysm** (MRA if family history of SAH/ICA).
- ▶ Distinguishing a **complex cyst from renal cell carcinoma** needs CT/MRI; RCC is not more frequent but tends to be **bilateral, multicentric and sarcomatoid**.
- ▶ **Cardiovascular complications are the leading cause of mortality**; cyst infection is second — choose cyst-penetrating antibiotics.
- ▶ Pre-symptomatic screening of **potential living-related donors** is mandatory before transplantation.

High-yield exam pointers

- ▶ Most common **life-threatening monogenic** disease; **12 million** affected; prevalence **1:1000–1:400**.
- ▶ **PKD1 (16p13, ~85%, severe)** vs **PKD2 (4q21–q23, ~15%, mild)**; polycystin-1 = GPCR-like 11-TM; polycystin-2 = TRP Ca^{2+} channel.
- ▶ **Two-hit hypothesis**; central effector = **raised cAMP** → **PKA** → **proliferation + fluid secretion**; a **ciliopathy**.
- ▶ Triad to remember — **hypertension (before GFR fall), flank pain/haematuria, palpable enlarged kidneys**.
- ▶ **Berry aneurysm 4–5×**, **MVP up to 30%**, polycystic liver (worse in multiparous women), colonic diverticulae, hernias.
- ▶ **Stones ~20%, mostly uric acid**; gross haematuria ~40%; infection = 2nd commonest cause of death.
- ▶ **Ultrasound diagnostic criteria are age-dependent** (≥ 2 cysts at 15–29; ≥ 2 each kidney at 30–59; ≥ 4 each kidney at ≥ 60).
- ▶ **Tolvaptan (V2R antagonist)** for rapidly progressive disease; **RAAS blockade + BP target 140/90 (JNC VIII)**; **>50% reach ESRD** needing renal replacement.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 327 "Polycystic Kidney Disease and Other Inherited Disorders of Tubule Growth and Development" (Zhou & Pollak). Coverage note: The chapter does not state the specific tolvaptan dosing regimen or named risk-stratification scores (Mayo imaging classification, PROPKD score); the ACE inhibitor/ARB drug names (lisinopril/telmisartan in HALT-PKD) and the "Pei/Ravine" eponym for the unified ultrasound criteria are standard internal-medicine additions — the criterion numbers themselves are verbatim from the chapter.



Bone Manifestations of Chronic Kidney Disease

Asked in: Paper IV Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — The skeletal disturbances of CKD are the bone component of **CKD–Mineral and Bone Disorder (CKD-MBD)**, a *systemic* disorder of mineral metabolism defined by KDIGO (2006) as one or a combination of: (1) abnormalities of **calcium, phosphate, PTH or vitamin D** metabolism; (2) abnormalities of **bone turnover, mineralization, volume, linear growth or strength**; and (3) **vascular or soft-tissue calcification**. *Renal osteodystrophy* is the strictly histological term — an alteration of bone morphology quantifiable only by **bone histomorphometry** — and constitutes the

skeletal arm of CKD-MBD. These derangements begin early (detectable changes in mineral metabolism from CKD stage 2–3, with rising FGF-23) and are nearly universal once GFR falls below 30 mL/min.

Pathophysiology — how uraemia injures bone

- ▶ **Phosphate retention:** Falling GFR reduces phosphate excretion. Retained phosphate is the proximate driver — it stimulates osteocyte synthesis of **FGF-23**, directly stimulates **PTH** secretion, and promotes growth of parathyroid gland mass.
- ▶ **Calcitriol deficiency:** Phosphate retention and high FGF-23 suppress renal **CYP27B1** (1 α -hydroxylase) and accelerate calcitriol degradation (via CYP24), lowering **1,25(OH)₂D₃**. Low calcitriol causes hypocalcaemia (poor gut Ca absorption) and de-represses **PTH gene** transcription.
- ▶ **Hypocalcaemia:** From low calcitriol and phosphate complexing of calcium — a further stimulus to PTH.
- ▶ **FGF-23 / Klotho axis:** FGF-23 (a “phosphatonin”) rises *earliest*. Renal **Klotho** (its obligatory co-receptor) is down-regulated in CKD, so the normal Klotho-dependent inhibitory effect of FGF-23 on the parathyroid is *attenuated*, permitting PTH to climb. High FGF-23 is an independent risk factor for **left ventricular hypertrophy** and mortality.
- ▶ **Net result — secondary hyperparathyroidism:** Hyperphosphataemia + hypocalcaemia + calcitriol deficiency + Klotho loss → sustained PTH excess → high-turnover bone disease. Persistent stimulation can produce autonomous, hypercalcaemic **tertiary hyperparathyroidism**. PTH itself behaves as a uraemic toxin (muscle weakness, myocardial fibrosis, ESA-resistant anaemia from marrow fibrosis).

Spectrum of renal osteodystrophy (KDIGO TMV classification)

KDIGO classifies bone lesions on three histomorphometric axes — Turnover, Mineralization, Volume — replacing older eponymic categories.

Lesion	Turnover	PTH	Histology / hallmark
Osteitis fibrosa cystica (2° hyperparathyroidism)	High	High	Giant multinucleated osteoclasts in Howship’s lacunae , peritrabecular/marrow fibrosis, woven bone, cysts/ brown tumours
Adynamic (low-turnover) bone disease	Low	Low/normal	Absent osteoblast & osteoclast activity, little osteoid, no fibrosis; ↓bone volume & mineralization

Lesion	Turnover	PTH	Histology / hallmark
Osteomalacia	Low	Variable	Excess unmineralized osteoid , wide osteoid seams, markedly reduced mineralization rate
Mixed uraemic osteodystrophy	High + defect	High	Features of 2° HPT <i>plus</i> a mineralization defect on tetracycline labelling

- ▶ **Osteitis fibrosa cystica** is the *classic* high-turnover lesion of secondary hyperparathyroidism — bone pain, fragility, **brown tumours** (haemorrhagic cysts that appear brown) with compression syndromes, and ESA-resistant anaemia.
- ▶ **Adynamic bone disease** is now *increasingly prevalent*, especially in diabetics and older patients. It results from **over-suppression of PTH** — by vitamin D preparations, calcium-based binders or high-calcium dialysate — chronic inflammation, or both. Despite low turnover, patients suffer severe musculoskeletal pain (inability to repair microfractures), increased fractures, and a strong association with **vascular/cardiac calcification** (ingested calcium cannot enter low-turnover bone and is deposited ectopically).
- ▶ **Osteomalacia** is a distinct mineralization defect from reduced calcitriol; historically linked to **aluminium toxicity** (aluminium-containing binders, contaminated dialysate) — now rare. Aluminium deposits stain at the mineralization front.
- ▶ The historical predominance of osteitis fibrosa has shifted: osteomalacia has been largely “replaced” by adynamic bone disease, and mixed uraemic osteodystrophy has risen.

Extraskkeletal manifestations of CKD-MBD

- ▶ **Vascular calcification:** Hyperphosphataemia and hypercalcaemia drive **medial** calcification of coronaries and valves (orders of magnitude greater than in non-CKD), distinct from intimal atherosclerotic calcification. Phosphate induces an *osteoblast-like phenotypic switch* in vascular smooth-muscle cells (up-regulation of **RUNX-2 / MSX2**), with loss of inhibitors (fetuin-A, matrix Gla protein, pyrophosphate). Linked to LVH and cardiovascular mortality.
- ▶ **Calciphylaxis (calcific uraemic arteriopathy):** Devastating, near-exclusive to advanced CKD. Painful **livedo reticularis** and subcutaneous nodules progress to ischaemic skin necrosis/ulceration (legs, thighs, abdomen, breasts) from small-vessel medial calcification and thrombosis. **Warfarin** is a key risk factor (it blocks vitamin K-dependent activation of matrix Gla protein) and must be stopped.
- ▶ **Tumoral calcinosis:** Periarticular soft-tissue calcified masses in chronically, severely hyperphosphataemic, non-adherent dialysis patients.

Clinical / Diagnostic significance

- ▶ **Biochemistry** (serial trends matter more than single values): serum phosphate, corrected calcium, intact PTH, alkaline phosphatase (bone turnover surrogate), 25-OH vitamin D; FGF-23 and Klotho remain largely research tools.
- ▶ **Bone biopsy** (iliac crest) with **double tetracycline labelling** is the *gold standard* for renal osteodystrophy — tetracycline binds hydroxyapatite and fluoresces, allowing dynamic measurement of bone-formation rate (turnover) plus static mineralization and volume.
- ▶ **Radiology: subperiosteal resorption** (radial side of middle phalanges, distal clavicle), resorption of phalangeal tufts (acro-osteolysis), **brown tumours**, “salt-and-pepper” skull and the *rugger-jersey spine* of secondary hyperparathyroidism; pseudofractures (Looser’s zones) in osteomalacia. DEXA quantifies density but cannot distinguish lesion type.
- ▶ **Clinical clues**: bone pain, proximal myopathy/muscle weakness, fragility fractures, pruritus, periarticular masses, and ESA-hyporesponsive anaemia.
- ▶ **Caution: Bisphosphonates and denosumab** suppress turnover and can *precipitate adynamic bone disease* in CKD/ESKD — avoid unless a high-turnover state is confirmed.

Management (prevention-focused; KDIGO targets)

- ▶ **Control phosphate first** — the foundational step. Dietary phosphate restriction (avoid cola, processed/additive phosphate) + **phosphate binders taken with meals**:
 - *Calcium-based* (calcium acetate, calcium carbonate) — cheap but risk hypercalcaemia and positive calcium balance, especially in low-turnover bone; limit use.
 - *Non-calcium* — **sevelamer, lanthanum carbonate**; *iron-based* — **ferric citrate**, sucroferric oxyhydroxide; reduce vascular calcium loading.
 - **Tenapanor** (NHE3 inhibitor) reduces GI phosphate absorption; **aluminium hydroxide** only short-term (osteomalacia/neurotoxicity risk).
- ▶ **Active vitamin D** for secondary hyperparathyroidism once phosphate is controlled and 25-OH D repleted: **calcitriol** or analogues (**paricalcitol** — less hypercalcaemia). Dose-reduce/stop if hypercalcaemia or hyperphosphataemia develops.
- ▶ **Calcimimetics** — **cinacalcet** (oral), **etelcalcetide** (IV, at dialysis) — sensitize the parathyroid CaSR, lowering PTH *and* calcium; watch for hypocalcaemia. Useful when high Ca/PO₄ prohibit vitamin D analogues.
- ▶ **Target PTH**: KDIGO/KDOQI recommend 2–9 × **upper limit of normal** in ESKD (skeletal PTH resistance means normal levels risk adynamic bone); very low PTH predicts fracture and ectopic calcification.
- ▶ **Parathyroidectomy** for severe refractory/tertiary hyperparathyroidism with persistent hypercalcaemia, intractable pruritus, calciphylaxis or progressive disease.

- ▶ **Calciphylaxis:** stop warfarin, use IV **sodium thiosulfate**, correct Ca/PO_4 , wound care $\pm$ hyperbaric oxygen.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Pathophysiology cascade of CKD-MBD:** Box “ $\downarrow\text{GFR}$ ” $\rightarrow$ “Phosphate retention” branching to “ $\uparrow\text{FGF-23}$ (osteocytes)” and “ $\downarrow\text{Calcitriol}$ (CYP27B1 $\downarrow$)”; arrows converging through “Hypocalcaemia” and “ $\downarrow\text{Klotho}$ ” to a central box “**Secondary hyperparathyroidism** ($\uparrow\text{PTH}$)”, with downstream boxes “**Osteitis fibrosa cystica / high-turnover bone**”, “Vascular calcification”, “LVH/CV mortality”. Labels: *GFR, Phosphate, FGF-23, Klotho, Calcitriol, Calcium, PTH*.
- ▶ **Diagram 2 — Classification by bone turnover:** A horizontal axis “Bone turnover (low $\rightarrow$ high)”; left = **Adynamic bone disease & Osteomalacia** (low PTH); right = **Osteitis fibrosa cystica** (high PTH); centre = **Mixed uraemic osteodystrophy**. Annotate KDIGO TMV axes: *Turnover, Mineralization, Volume*.

High-yield exam pointers

- ▶ **CKD-MBD = triad:** biochemical ($\text{Ca}/\text{PO}_4/\text{PTH}/\text{vit D}$) + bone (renal osteodystrophy) + extraskeletal calcification (KDIGO 2006).
- ▶ **FGF-23 rises earliest**, before measurable $\text{PTH}/\text{Ca}/\text{PO}_4$ change; needs **Klotho** co-receptor (down-regulated in CKD).
- ▶ **Osteitis fibrosa cystica** = high-turnover, secondary HPT; *Howship’s lacunae, brown tumours, subperiosteal resorption, rugger-jersey spine*.
- ▶ **Adynamic bone disease** = low PTH, over-suppressed; commonest emerging lesion; linked to fractures + vascular calcification.
- ▶ **Bone biopsy with double tetracycline labelling** = gold standard; classify by TMV.
- ▶ **Target PTH** 2–9 $\times$ ULN in ESKD; avoid *over-suppression*.
- ▶ **Warfarin** $\rightarrow$ **calciphylaxis** (blocks matrix Gla protein); avoid in dialysis where possible.
- ▶ **Avoid bisphosphonates/denosumab** in CKD unless high-turnover confirmed.
- ▶ **Binder hierarchy:** phosphate control *first*, prefer non-calcium binders to limit vascular calcium loading.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Chronic Kidney Disease” (Bone manifestations of CKD; disorders of calcium and phosphate metabolism; calciphylaxis; treatment) and “Disorders of the Parathyroid Gland and Calcium Homeostasis” (osteitis fibrosa cystica, Howship’s lacunae, subperiosteal resorption).

- ▶ **Brenner & Rector's The Kidney** — “Chronic Kidney Disease–Mineral Bone Disorder” (KDIGO CKD-MBD/renal osteodystrophy definitions, FGF-23/Klotho axis, TMV classification, histomorphometry, vascular calcification/RUNX-2).
- ▶ **CMDT 2026** — “Kidney Disease” (mineral bone disorders: binders, calcitriol/analogues, calcimimetics, PTH targets) and “Disorders of Parathyroid Glands & Bone Metabolism”.
- ▶ *Coverage note:* “Rugger-jersey spine,” “salt-and-pepper skull” and “Looser’s zones” are universally accepted standard radiographic eponyms included for completeness; the corpus explicitly documents subperiosteal resorption, phalangeal tuft resorption and brown tumours.



Counter current multiplier system of the Kidney. Write briefly on Gitelman Syndrome

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — The **countercurrent multiplier** is the renal mechanism that generates and maintains a **hypertonic medullary interstitium**, enabling the kidney to produce urine far more concentrated than plasma. It exploits the hairpin (countercurrent) geometry of the **loop of Henle**, where active NaCl reabsorption by the water-impermeable thick ascending limb is “multiplied” along the cortico-medullary axis by the opposing flow in the two limbs. The medullary gradient, in concert with vasopressin-driven water reabsorption in the collecting duct, determines final urine concentration. **Gitelman syndrome** is a contrasting *distal* tubulopathy — an inherited salt-wasting disorder of the distal convoluted tubule (DCT) caused by loss of the thiazide-sensitive Na^+/Cl^- cotransporter.

Anatomical and functional basis of the countercurrent apparatus

- ▶ The loop of Henle has three segments: **descending thin limb**, **ascending thin limb**, and **ascending thick limb (TAL)**; the loop reabsorbs ~15–25% of filtered NaCl, mainly in the TAL.
- ▶ **Descending thin limb** — highly **water-permeable** owing to dense, constitutively active **aquaporin-1** channels; relatively solute-impermeable. Tubular fluid equilibrates osmotically with the interstitium and becomes progressively *concentrated* as it descends.
- ▶ **Ascending thin and thick limbs** — water permeability is **negligible** (“diluting segment”).
- ▶ **Thick ascending limb** — high-capacity secondary-active NaCl transport by the apical $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter (NKCC2) in series with basolateral Cl^- channels and the Na^+/K^+ -ATPase. Tubular K^+ (~4 meq/L) is the limiting substrate, so activity is sustained by K^+ **recycling** through an apical potassium channel (ROMK). NKCC2 is the molecular target of **loop diuretics**.
- ▶ K^+ recycling renders the lumen **electropositive**, driving **paracellular reabsorption** of Mg^{2+} and Ca^{2+} in the TAL.

Mechanism — the “single effect” and its multiplication

- ▶ **Step 1 — the single effect:** Active NaCl reabsorption by the *water-impermeable* TAL moves solute (without water) into the interstitium, **diluting tubular fluid** and **adding new osmoles** to medullary interstitial fluid. At any horizontal level this creates a modest osmotic gradient between lumen and interstitium (classically ~200 mOsm/kg).
- ▶ **Step 2 — countercurrent multiplication:** Because flow in the **descending and ascending limbs runs in opposite directions** (a hairpin), the small transverse single effect is repeatedly summed along the length of the loop, multiplying into a **large axial (cortico-medullary) gradient**.
- ▶ **Step 3 — solute trapping:** As water leaves the permeable descending limb to equilibrate with the hypertonic interstitium, solute is **progressively trapped** in the inner medulla, steepening the gradient from iso-osmotic at the cortex to maximally hypertonic at the papillary tip.
- ▶ **Net result:** A standing medullary osmotic gradient (in humans rising to ~1200 mOsm/kg at the papilla) against which the collecting duct can extract water. *NaCl reabsorption by the TAL is the primary initiating event of the whole process.*

Role of urea recycling and the vasa recta (countercurrent exchanger)

- ▶ **Urea recycling** — the **inner medullary collecting duct** transports urea (via urea transporters) out of the lumen into the interstitium, where it diffuses into the descending and ascending limbs and is recycled. Urea contributes substantially to **maximum medullary interstitial osmolality**.
- ▶ **Vasa recta** — the medullary peritubular capillaries that envelop the loop form the **second countercurrent system**. Their hairpin geometry allows passive **countercurrent exchange**: solutes and water are shunted between descending and ascending vessels so that blood flow nourishes the medulla **without washing out** the gradient. (The loop is an *active* countercurrent **multiplier**; the vasa recta is a *passive* countercurrent **exchanger** that preserves the gradient.)

Using the gradient — vasopressin and the collecting duct

- ▶ Collecting duct cells express vasopressin-regulated aquaporin-2 (apical) and aquaporin-3/-4 (basolateral) water channels.
- ▶ **Vasopressin (ADH)** binds the basolateral **V2 receptor** → G-protein activation of **adenylyl cyclase** → rise in **cyclic AMP** → insertion of aquaporin-2 into the apical membrane → water reabsorption and **concentrated urine**.
- ▶ Without vasopressin, the collecting duct is water-impermeable and urine stays **dilute**. *Vaptans* (nonpeptide V2 antagonists) block this effect to produce a water diuresis (e.g., for hyponatremia).

Feature	Countercurrent multiplier	Countercurrent exchanger
Structure	Loop of Henle (descending + ascending limbs)	Vasa recta (medullary capillaries)

Feature	Countercurrent multiplier	Countercurrent exchanger
Energy	Active (NKCC2 in TAL)	Passive (diffusion only)
Function	Generates the medullary gradient	Preserves the gradient (prevents washout)
Key requirement	Water-impermeable TAL + water-permeable thin descending limb	Hairpin geometry with slow blood flow

Gitelman syndrome

- **Definition / genetics:** An autosomal-recessive **salt-wasting tubulopathy** caused by **loss-of-function mutations of SLC12A3**, which encodes the apical thiazide-sensitive Na^+/Cl^- cotransporter (NCC) of the distal convoluted tubule** — effectively a lifelong “thiazide-like” state. The DCT normally reabsorbs ~5% of filtered NaCl.
- **Mechanism of electrolyte disturbance:**
 - Impaired distal NaCl reabsorption → mild **volume contraction** → activation of renin–angiotensin–aldosterone → enhanced distal Na^+ reabsorption with K^+ and H^+ secretion → **hypokalaemia and metabolic alkalosis**.
 - Blocking apical Na^+/Cl^- cotransport lowers intracellular Na^+ , favouring basolateral $\text{Na}^+/\text{Ca}^{2+}$ exchange and passive apical Ca^{2+} entry (TRPV5) → increased Ca^{2+} reabsorption → **hypocalciuria** (the hallmark distinguishing it from loop pathology).
 - **Hypomagnesaemia** — impaired Mg^{2+} handling in the DCT (the TRPM6/TRPM7 channel complex is critical for DCT Mg^{2+} reabsorption).
- **Clinical features (standard medicine):** Usually presents **later (adolescence/adulthood)** and is **milder** than Bartter syndrome — muscle cramps/weakness, tetany and carpopedal spasm (from hypomagnesaemia), fatigue, salt craving, **normal-to-low blood pressure**, and occasionally chondrocalcinosis.
- **Biochemistry:** Hypokalaemia, metabolic alkalosis, **hypomagnesaemia**, **hypocalciuria**, with high plasma renin/aldosterone and normal/low BP.
- **Management (standard medicine):** Liberal **sodium**, oral **potassium and magnesium** supplementation, and **potassium-sparing agents** (spironolactone/eplerenone or amiloride); magnesium repletion is central because it is needed to correct the hypokalaemia.

Feature	Bartter syndrome	Gitelman syndrome
Tubular site	Thick ascending limb	Distal convoluted tubule
Gene / transporter	NKCC2 (SLC12A2), ROMK (KCNJ1), CLCNKB/BSND, CASR	*NCC (SLC12A3)*

Feature	Bartter syndrome	Gitelman syndrome
Diuretic mimicked	Loop diuretic (furosemide)	Thiazide
K ⁺ / acid-base	Hypokalaemia + metabolic alkalosis	Hypokalaemia + metabolic alkalosis
Urinary calcium	Hypercalciuria ± nephrocalcinosis	Hypocalciuria
Magnesium	Usually normal	Hypomagnesaemia
Typical onset / severity	Neonatal/childhood, severe	Adolescent/adult, milder

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Nephron loop with the medullary gradient:** Draw the U-shaped loop in the medulla. Label *descending thin limb (aquaporin-1, water-permeable)*, *ascending thin limb, thick ascending limb (NKCC2 + ROMK + Na⁺/K⁺-ATPase, water-impermeable)*, *vasa recta (countercurrent exchanger)*, and the *inner medullary collecting duct (urea recycling, ADH/AQP2)*. Add a vertical osmolality scale on the right reading ~300 mOsm/kg (cortex) → ~1200 mOsm/kg (papilla) with horizontal arrows for the “single effect.”
- ▶ **DCT cell for Gitelman:** Apical *thiazide-sensitive Na⁺/Cl⁻ cotransporter (NCC, SLC12A3)* with a red cross (mutated), apical *TRPV5 (Ca²⁺)*, basolateral *Na⁺/K⁺-ATPase*, *Cl⁻ channel*, and *Na⁺/Ca²⁺ exchanger*.

Clinical / Diagnostic significance

- ▶ The medullary gradient is the physiological substrate for the **urine-concentrating/diluting** capacity; its disruption underlies **nephrogenic diabetes insipidus** (AQP2/V2 defects) and the polyuria of medullary disease.
- ▶ **Loop diuretics** abolish the single effect (block NKCC2) → impaired concentration and brisk natriuresis; **thiazides** act at the DCT NCC — the same target lost in Gitelman.
- ▶ **Differentiating hypokalaemic metabolic alkalosis with normal BP:** Gitelman (hypocalciuria + hypomagnesaemia, adult, thiazide-like) vs Bartter (hypercalciuria, neonatal, loop-like) vs surreptitious **vomiting/diuretic abuse** (check urine chloride/diuretic screen).
- ▶ Recognising the volume-contracted, **normal/low-BP** picture separates these salt-wasting tubulopathies from **Liddle syndrome** (ENaC gain-of-function: hypertension + hypokalaemic alkalosis with low renin/aldosterone).

High-yield exam pointers

- ▶ Two countercurrent systems: **loop of Henle = active multiplier**; **vasa recta = passive exchanger** (prevents washout).

- ▶ The **water-impermeable** TAL with NKCC2 is the engine (“single effect”); the **water-permeable descending limb** (AQP1) enables solute trapping.
- ▶ **Urea recycling** from the inner medullary collecting duct is essential for **maximal** medullary hypertonicity.
- ▶ ADH → V2 → cAMP → AQP2 insertion converts the gradient into concentrated urine.
- ▶ Gitelman = *DCT, SLC12A3/NCC, thiazide-like: hypokalaemic metabolic alkalosis + hypocalciuria + hypomagnesaemia*, normal/low BP.
- ▶ Mnemonic contrast — Gitelman = hypocalciuria (Goes low calcium in urine) vs Bartter = hypercalciuria.
- ▶ Treat Gitelman with Na, K, Mg replacement ± K⁺-sparing diuretic; correct Mg to fix the K⁺.

SOURCE & COVERAGE

Harrison 22e — Ch 320 “Cell Biology and Physiology of the Kidney” (countercurrent multiplication, loop/vasa recta, TAL/NKCC2, urea recycling, ADH/AQP2, DCT/NCC and the SLC12A3 Gitelman mention; Bartter genes). Ch 432 “Inherited Defects of Membrane Transport” was provided but covers cystinuria/lysine intolerance only and does **not** address Gitelman syndrome. *Coverage note:* The provided text grounds the countercurrent mechanism fully and names Gitelman syndrome with its core triad (salt-wasting, hypokalaemic alkalosis, hypocalciuria), the SLC12A3/NCC defect, and the DCT calcium/magnesium handling. The expanded Gitelman details — autosomal-recessive inheritance, secondary hyperaldosteronism, clinical presentation (age/severity, tetany, chondrocalcinosis), and treatment — plus the classic ~200 and ~1200 mOsm/kg figures and Bartter hypercalciuria are universally accepted standard internal medicine added for exam completeness, not verbatim from the supplied chapters.



Crescentic Glomerulonephritis

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Crescentic glomerulonephritis* (CrGN) is the histological correlate of the clinical syndrome of **rapidly progressive glomerulonephritis (RPGN)** — a nephritic illness with loss of kidney function over days to weeks, accompanied by dysmorphic (glomerular) haematuria, red-cell casts and sub-nephrotic to nephritic-range proteinuria. It is defined pathologically by **extracapillary proliferation forming crescents in Bowman’s space in >50% of glomeruli**, and represents the most aggressive structural phenotype in the continuum of glomerular inflammatory injury. The terms RPGN (clinical) and crescentic GN (pathological) are used almost interchangeably because aggressive GN that causes RPGN nearly always shows extensive crescents. It is a nephrological emergency: untreated, it

progresses to irreversible scarring and end-stage kidney disease (ESKD), so urgent biopsy and immunosuppression are mandatory.

The crescent — morphology and pathogenesis

- ▶ A **crescent** is a collection of cells and matrix that fills part or all of Bowman's (urinary) space, compressing the glomerular tuft into a half-moon shape (*Fig. — cellular crescent, PAS ×500*).
- ▶ **Pathogenesis (final common pathway):** severe glomerular injury causes **focal rupture of glomerular capillary walls and breaks in the GBM/Bowman's capsule** → leakage of fibrin, plasma proteins and inflammatory mediators into Bowman's space → proliferation of parietal/visceral epithelial cells with influx and maturation of **macrophages**, producing the crescent. Fibrin (seen as *fibrin tactoids* on EM) is a potent stimulus.
- ▶ **Evolution:** *cellular* crescent → *fibrocellular* → *fibrous (fibrotic)* crescent. Cellular crescents are potentially reversible with treatment; fibrous crescents and Bowman's capsule rupture signify irreversibility.
- ▶ Associated features: **segmental fibrinoid necrosis** of the tuft, periglomerular inflammation, and in chronic stages, glomerulosclerosis, tubular atrophy and **interstitial fibrosis** (an ominous sign of irreversibility).
- ▶ Crescents are a marker of severity across many GNs — they are seen in ~97% of anti-GBM, ~90% of ANCA, ~56% of immune-complex and ~61% of proliferative lupus (class III/IV) biopsies (UNC Nephropathology data).

Immunopathologic classification (the three categories / Type I–III)

The precise category requires integrating immunofluorescence (IF) pattern, serology, light and electron microscopy. Three immunopathologic groups account for almost all cases:

Feature	Type I — Anti-GBM	Type II — Immune-complex	Type III — Pauci-immune (ANCA)
IF pattern	Linear IgG along GBM	Granular ("lumpy-bumpy") Ig + C3	Pauci-immune (little/no Ig or complement)
Antigen / serology	Anti-GBM Ab to $\alpha 3$ -NC1 domain of type IV collagen	Circulating/in-situ immune complexes; $\pm$ low complement	ANCA — PR3 (c-ANCA) or MPO (p-ANCA)
Frequency (all ages)	~15%	~24%	~60% (~90% ANCA-positive)
Typical age	Bimodal (20s; 60s–70s)	Children/young adults	Older adults (~79% of CrGN >60 yr)
Representative diseases	Goodpasture syndrome; renal-limited anti-GBM	Post-infectious GN, IgA nephropathy/IgA vasculitis, lupus	GPA, MPA, EGPA, renal-limited (ANCA) vasculitis

Feature	Type I — Anti-GBM	Type II — Immune-complex	Type III — Pauci-immune (ANCA)
		nephritis (III/IV), MPGN, cryoglobulinaemia, C3 glomerulopathy	

- ▶ **Type I (anti-GBM):** autoantibody against the *Goodpasture antigen* — the $\alpha 3$ chain NC1 domain of collagen IV (an autoimmune “conformeropathy”). Genetic link to *HLA-DR2 (DRB1\1501, DQB1\0602). *Bimodal age: young men (more often full Goodpasture syndrome with lung haemorrhage) and elderly (more often renal-limited, female predominance).* 25–33% are also ANCA (usually MPO)-positive* (“double-positive”).
- ▶ **Type II (immune-complex):** the underlying disease shapes the picture — e.g. mesangial IgA (IgA nephropathy), coarse granular capillary-wall deposits and sub-epithelial “humps” (post-streptococcal), C3-dominant with double contours (MPGN/C3GN), “full-house” with tubuloreticular inclusions (lupus). Intact glomeruli show **endocapillary hypercellularity and capillary-wall thickening**.
- ▶ **Type III (pauci-immune/ANCA):** most common cause of CrGN in adults; segmental necrotising GN with crescents but minimal deposits. Part of ANCA-associated small-vessel vasculitis (GPA = PR3 predominant; MPA/EGPA = MPO predominant) or renal-limited. A 4th category — **monoclonal Ig-mediated (MGRS)** — and rare “double/triple antibody-negative” cases are now also recognised.

Clinical features and investigations

- ▶ **Presentation:** rapidly rising serum creatinine over days–weeks, oliguria/anuria, **smoky/cola-coloured urine**, hypertension, oedema and uraemic symptoms (nausea, malaise, fatigue).
- ▶ **Urinalysis (the key bedside clue):** active nephritic sediment — **dysmorphic RBCs, red-cell casts**, pyuria, and proteinuria typically 1–3.5 g/day (rarely nephrotic).
- ▶ **Systemic clues:** haemoptysis/pulmonary haemorrhage (anti-GBM/Goodpasture, ANCA “pulmonary-renal syndrome”); sinusitis, nasal crusting, cavitating lung nodules, mononeuritis multiplex, palpable purpura (ANCA vasculitis); malar rash, arthralgia, serositis (lupus).
- ▶ **Serology panel (send before/at biopsy):** anti-GBM antibody; ANCA (anti-PR3, anti-MPO); ANA, anti-dsDNA, C3/C4 (low in lupus, post-infectious, MPGN, cryoglobulinaemia; normal in anti-GBM and ANCA); ASO/anti-DNase, cryoglobulins, hepatitis B/C and HIV serology, blood cultures.
- ▶ **Kidney biopsy = diagnostic cornerstone:** light microscopy (crescents, % involvement, necrosis, chronicity), **immunofluorescence** (linear vs granular vs pauci-immune — defines the category) and electron microscopy (location of deposits; linear staining has no deposits).

- **Mimics of RPGN to exclude:** thrombotic microangiopathy/HUS (MAHA, thrombocytopenia), atheroembolic disease, acute interstitial nephritis and ATN — these typically lack dysmorphic haematuria and RBC casts.

Management

- **Principle:** treat *urgently and empirically* — outcome depends on how early therapy is started relative to the degree of scarring; oliguria/dialysis-dependence at presentation predicts a poor renal outcome.
- **General:** supportive care — control BP (RAAS blockade once stable), manage volume, treat hyperkalaemia/uraemia, dialysis as needed.

Category	Induction	Adjunct / maintenance
Anti-GBM (Type I)	Daily plasma exchange × ~2 weeks (until antibody negative) + high-dose corticosteroids + cyclophosphamide	Rituximab in refractory cases; transplant deferred ~6 months until antibodies undetectable
ANCA / pauci-immune (Type III)	Corticosteroids + cyclophosphamide or rituximab (3–6 months)	Maintenance rituximab (preferred) or azathioprine 1–2 yr; avacopan (oral C5a-receptor inhibitor) can spare steroids; plasma exchange for Cr >3.4 mg/dL, diffuse alveolar haemorrhage, or double-positive disease
Immune-complex (Type II)	Treat the underlying disease; for severe/idiopathic — pulse methylprednisolone then prednisone 1 mg/kg/day, ± cyclophosphamide ± plasma exchange	Lupus: induction (steroid + MMF or cyclophosphamide ± belimumab) then MMF/azathioprine maintenance

- **Plasma exchange:** standard in anti-GBM and in pulmonary haemorrhage; in ANCA it is reserved (PEXIVAS-era) for severe renal failure or alveolar haemorrhage. It is **mandatory when anti-GBM and ANCA coexist**.
- **Outcomes:** ANCA — remission in 75–90%, but relapse in 25–50% (commonest in GPA). Post-infectious crescentic GN is usually supportive (no immunosuppression even with crescents).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled glomerulus with a cellular crescent:** label *Bowman's capsule, Bowman's (urinary) space, cellular crescent (proliferating parietal epithelial cells + macrophages), compressed glomerular tuft, segmental fibrinoid necrosis, break in GBM/capillary wall, fibrin in Bowman's space*.

- ▶ **Immunofluorescence comparison (three boxes):** *Linear* GBM IgG (anti-GBM / Type I) — *Granular* “lumpy-bumpy” IgG + C3 (immune-complex / Type II) — *Pauci-immune* / *negative IF with ANCA in serum* (Type III).

Clinical / Diagnostic significance

- ▶ **RPGN is a medical emergency** — the single most important determinant of renal recovery is *time to immunosuppression*; never wait for full results if anti-GBM/Goodpasture is strongly suspected.
- ▶ The IF pattern instantly triages therapy and prognosis: linear → plasma exchange + cyclophosphamide; pauci-immune → steroid + rituximab/cyclophosphamide ± avacopan; granular → treat the underlying immune-complex disease.
- ▶ **Percentage of crescents and degree of interstitial fibrosis** on biopsy are the strongest prognostic markers; >50% crescents, serum creatinine >5–6 mg/dL, oliguria or dialysis need at presentation portend a poor outcome.
- ▶ Always test **anti-GBM and ANCA together** — “double-positive” patients exist and require both plasma exchange and prolonged immunosuppression with closer relapse surveillance.

High-yield exam pointers

- ▶ **Crescentic GN = RPGN**; crescents in >50% of glomeruli defines it; crescent = extracapillary proliferation in Bowman’s space.
- ▶ **Three immunopathologic types:** Type I anti-GBM (linear IF), Type II immune-complex (granular IF), Type III pauci-immune/ANCA (negative IF) — remember frequencies ≈15% : 24% : 60%.
- ▶ **Pauci-immune/ANCA is the commonest** cause of CrGN overall and in older adults; **immune-complex** predominates in children.
- ▶ **Goodpasture antigen** = $\alpha 3$ chain NC1 domain of type IV collagen; HLA-DR2 association; lung + kidney = pulmonary-renal syndrome.
- ▶ **C3/C4 low** in lupus, post-infectious, MPGN, cryoglobulinaemia; **normal** in anti-GBM and ANCA vasculitis.
- ▶ **Anti-GBM treatment** = plasma exchange + steroids + cyclophosphamide; ANCA = steroids + rituximab/cyclophosphamide, maintenance rituximab/azathioprine, avacopan steroid-sparing.
- ▶ **Double-positive (anti-GBM + ANCA)** seen in 25–33% of anti-GBM cases — give both plasma exchange and full immunosuppression.
- ▶ **Crescent frequency hierarchy:** anti-GBM (97%) > ANCA (90%) > lupus III/IV (61%) > immune-complex (56%).

- ▶ Poor prognostic signs: oliguria, dialysis-dependence, creatinine >5–6 mg/dL, fibrous crescents and interstitial fibrosis.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Glomerular Diseases*” (acute nephritic syndromes; anti-GBM disease/Goodpasture's; ANCA small-vessel vasculitis; lupus nephritis classification).
- ▶ **Brenner & Rector's The Kidney** — “*Primary Glomerular Disease*” (Rapidly Progressive and Crescentic Glomerulonephritis: nomenclature, immunopathologic categories and frequency Tables 31.8–31.10, the diagnostic IF algorithm, anti-GBM pathogenesis and pathology, treatment).
- ▶ **CMDT 2026** — “*Kidney Disease*” (nephritic spectrum; pauci-immune/ANCA, anti-GBM and immune-complex GN — current induction/maintenance regimens, avacopan, plasma-exchange indications).



Diabetic nephropathy: pathological stages, investigations and management

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — **Diabetic nephropathy (DN)** is a chronic, progressive microvascular complication of diabetes mellitus characterised clinically by persistent **albuminuria**, a relentless **fall in GFR**, and rising blood pressure, and pathologically by **glomerular basement membrane (GBM) thickening**, **mesangial expansion** and **nodular (Kimmelstiel–Wilson) glomerulosclerosis**. It is the single most common cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) worldwide. Approximately **20–40% of all diabetics develop nephropathy**; because type 2 DM is far commoner, most DN patients have type 2 disease. The term *diabetic kidney disease (DKD)* is preferred for the broader clinical entity (including normoalbuminuric GFR loss), reserving *diabetic nephropathy* for biopsy-proven classical glomerulopathy.

Pathogenesis (basis of the lesions)

- ▶ **Chronic hyperglycaemia** is the prime driver, acting through: non-enzymatic **advanced glycation end-products (AGEs)**, activation of **protein kinase C (PKC)** and the **hexosamine pathway**, and excess **reactive oxygen species**.
- ▶ **Haemodynamic injury** — hyperglycaemia activates the **renin–angiotensin–aldosterone system (RAAS)** and up-regulates proximal-tubular **SGLT1/SGLT2**, reducing distal Na^+ delivery to the *macula densa*, **inhibiting tubuloglomerular feedback** → afferent vasodilatation, **glomerular hyperfiltration** and **intraglomerular hypertension**.

- ▶ **Soluble mediators** — angiotensin II, **endothelin-1**, growth hormone, IGF-1, **connective tissue growth factor** and TGF- β , plus dyslipidaemia, drive matrix production and mesangial sclerosis.
- ▶ **Structural** — GBM thickening with **loss of heparan-sulfate (negative-charge) barrier** → increased filtration of albumin; mesangial matrix accumulation → mesangial sclerosis; **podocyte injury/depletion** (podocyturia, nephrinuria) precedes overt sclerosis.

Pathological (histological) stages — Renal Pathology Society (Tervaert) classification

DN evolves through reproducible glomerular lesions; the internationally used **RPS (Tervaert et al., 2010)** scheme grades glomerular damage I→IV with a separate tubulointerstitial/vascular score.

Class	Glomerular lesion	Defining (inclusion) criterion
I	Isolated GBM thickening; mild/non-specific light-microscopy change	EM-proven GBM >395 nm (female), >430 nm (male) ≥9 yrs; no class II–IV features
IIa	Mild mesangial expansion	Mild expansion in >25% of mesangium; not meeting III/IV
IIb	Severe mesangial expansion	Severe expansion in >25% of mesangium; not meeting III/IV
III	Nodular sclerosis (<i>Kimmelstiel-Wilson lesion</i>)	At least one convincing K–W nodule; not meeting IV
IV	Advanced diabetic glomerulosclerosis	Global glomerulosclerosis in >50% of glomeruli, with class I–III lesions

- ▶ **Interstitial / vascular score (separate):** IFTA (interstitial fibrosis & tubular atrophy, 0–3), interstitial inflammation (0–2), **arteriolar hyalinosis** (0–2) and arteriosclerosis (0–2). Higher cumulative scores (a “D-score”) predict worse renal outcome.
- ▶ **Key morphology:** GBM thickening is the earliest and most *sensitive* change but correlates poorly with clinical disease; **mesangial expansion correlates best with clinical DN**; K–W **nodules** are PAS-positive, eosinophilic acellular nodules and are essentially pathognomonic; **afferent and efferent arteriolar hyalinosis** is characteristic. Lesions of type 1 and type 2 DN with albuminuria are largely **indistinguishable**.

Clinical (functional) stages — Mogensen staging

The natural history was first defined in type 1 DM (similar in type 2) and is classically described in **five** Mogensen stages:

Stage	Designation	GFR / albuminuria	Approx. timing
1	Hyperfunction / hypertrophy	GFR ↑ (hyperfiltration), kidneys enlarged; normoalbuminuria	At diagnosis
2	Silent / latent	Structural change (GBM thickening, mesangial expansion); normoalbuminuria; GFR high-normal	First ~2–5 yrs
3	Incipient nephropathy	Microalbuminuria (UACR 30–300 mg/g); GFR begins to fall; BP rising	~5–10 yrs
4	Overt / clinical nephropathy	Macroalbuminuria (>300 mg/g), declining GFR, hypertension	~10–20 yrs
5	End-stage kidney disease	GFR <15; uraemia, requires KRT	~20–25 yrs

- Caveat (contemporary data): the classical sequence is now heterogeneous — **up to 24% of type 1 and ~50% of type 2 DKD are normoalbuminuric**, and microalbuminuria may regress.

Albuminuria remains the strongest single predictor of GFR decline; its regression on treatment is a good prognostic sign.

Investigations

- **Urinary albumin-to-creatinine ratio (UACR)** on an early-morning spot sample — screening/staging cornerstone. ADA/KDIGO categories: **A1 <30 mg/g (normal)**, **A2 30–300 mg/g (moderately increased)**, **A3 >300 mg/g (severely increased)**. Confirm on **2–3 samples over 3–6 months** (exclude transient causes: exercise, fever, UTI, heart failure, marked hyperglycaemia/hypertension).
- **Estimated GFR (eGFR)** from serum creatinine ($\pm$ cystatin C) — stage CKD G1–G5; assess both UACR *and* eGFR because GFR can fall without albuminuria.
- **Screening schedule:** type 1 DM — **5 years after diagnosis, then annually**; type 2 DM — **at diagnosis, then annually**.
- **Fundoscopy/retinal screening:** **>90% of type 1 (only ~60% of type 2) DN patients have diabetic retinopathy**; absence of retinopathy in a type 1 patient with proteinuria should prompt search for non-diabetic kidney disease. Retinopathy correlates with K–W nodules.
- **Supportive:** quantified proteinuria (24-h or PCR; ranges 0.5–25 g/day), serum K^+/HCO_3^- (type IV RTA / hyporeninaemic hypoaldosteronism $\rightarrow$ hyperkalaemia), lipids, HbA1c, renal ultrasound (kidneys remain enlarged even in advanced DN).

- **Renal biopsy** is *not* routinely required — diagnosis is clinical (long-standing DM + albuminuria + retinopathy). **Biopsy is indicated when non-diabetic disease is suspected:** proteinuria <5 yrs after type 1 onset, absence of retinopathy, active urinary sediment / haematuria / red-cell casts, rapid GFR decline or **acute kidney injury**, nephrotic syndrome of abrupt onset, or immunologic features.

Management

Modern care rests on **four to five pillars** of risk-factor and “renoprotective” therapy plus prevention.

Pillar	Agent / target	Key points
Glycaemic control	Individualised HbA1c ($\approx 7\%$)	Prevents/slows DN, strongest in type 1; reassess agents as GFR falls (avoid metformin & sulfonylureas in advanced CKD)
Blood pressure	<130/80 mmHg	Most patients need ≥ 3 drugs; lifestyle + DASH, Na ⁺ restriction, smoking cessation
RAAS blockade	ACE inhibitor or ARB (max tolerated dose)	First-line with albuminuria/HTN; slows progression at micro- and macro-albuminuric stages independent of BP. Do not combine ACEi + ARB. Accept creatinine rise up to 30%; aim to ↓UACR by 30%. Monitor K ⁺ /creatinine
SGLT2 inhibitor	e.g. empagliflozin, canagliflozin, dapagliflozin	Add to ACEi/ARB in type 2 DKD with eGFR >20; reduces ESKD, creatinine doubling and CV events; not effective <20 mL/min ; caution re euglycaemic DKA
Non-steroidal MRA	Finerenone	Added to ACEi/ARB improves renal & CV outcomes in type 2 DKD; monitor serum potassium
GLP-1 receptor agonist	Semaglutide (FLOW trial)	Improves kidney outcomes and lowers CV death in type 2 DM + CKD

- **Adjuncts:** treat dyslipidaemia (statins; LDL-C <55 mg/dL if established ASCVD), modest dietary protein ~ 0.8 g/kg/day, avoid nephrotoxins, hydrate around **iodinated contrast** (hold metformin peri-procedure), manage CKD–mineral bone disease, anaemia and acidosis.
- **End-stage care:** kidney transplantation gives better survival than dialysis (dialysis survival is worse in diabetics); **simultaneous pancreas–kidney transplant** in selected type 1 patients —

sustained normoglycaemia (≈ 10 yrs) can even reverse glomerular lesions including dissolution of K–W nodules.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Stage/natural-history graph:** x-axis *Years from onset of diabetes* (0→25); two curves — GFR (rising in hyperfiltration → returning to normal → progressive decline to <15) and Albuminuria (normo → micro 30–300 → macro >300). Label the five stages (Hyperfiltration, Silent, Incipient/microalbuminuria, Overt/macroalbuminuria, ESKD).
- ▶ **Glomerular histology schematic:** label *thickened GBM*, *mesangial matrix expansion*, *Kimmelstiel–Wilson nodule (PAS+)*, *afferent & efferent arteriolar hyalinosis*, *podocyte effacement*, *capillary microaneurysm*.

Clinical / Diagnostic significance

- ▶ Albuminuria and reduced GFR are potent independent predictors of cardiovascular death — many DN patients die of CVD before reaching ESKD.
- ▶ Retinopathy–nephropathy concordance is a practical bedside diagnostic tool: its absence in type 1 DM argues for an alternative renal diagnosis and biopsy.
- ▶ Distinguishing DN from **non-diabetic kidney disease** (FSGS, IgA nephropathy, membranous, hypertensive nephrosclerosis, acute tubular injury) changes treatment — hence the importance of the biopsy indications above.
- ▶ DN drives the global ESKD burden; **early UACR screening + the renoprotective pillars** measurably delay dialysis.

High-yield exam pointers

- ▶ Kimmelstiel–Wilson nodules = nodular glomerulosclerosis, PAS-positive, classic for DN; correlate with retinopathy.
- ▶ RPS/Tervaert classes I (GBM thickening) → IIa/IIb (mesangial expansion) → III (K–W nodule) → IV ($>50\%$ global sclerosis) + separate IFTA/vascular score.
- ▶ Mesangial expansion correlates best with clinical DN; GBM thickening is earliest/most sensitive.
- ▶ Microalbuminuria = UACR 30–300 mg/g (incipient); macroalbuminuria >300 mg/g (overt).
- ▶ Screen type 1 at 5 yrs, type 2 at diagnosis, then yearly; confirm on 2–3 samples.
- ▶ Kidneys stay enlarged even in advanced DN — a useful clue.
- ▶ Renoprotection pillars: glycaemia + BP $<130/80$ + ACEi/ARB + SGLT2i (eGFR >20) + finerenone ($\pm$ GLP-1 RA semaglutide).
- ▶ SGLT2 inhibitors cut ESKD/creatinine-doubling/renal death; ineffective below eGFR 20; risk of euglycaemic DKA.

- ▶ **Type IV RTA (hyporeninaemic hypoaldosteronism)** → hyperkalaemia, worsened by ACEi/ARB/MRA.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Glomerular Diseases” (diabetic nephropathy pathology, K–W nodules, hyperfiltration, albuminuria thresholds, RAAS/SGLT2/finerenone) and “Diabetes Mellitus: Complications” (natural history, UACR screening, treatment pillars).
- ▶ **Brenner & Rector's The Kidney** — “Epidemiology of Diabetic Kidney Disease” (RPS/Tervaert pathologic classification Tables 39.4/39.5, structure–function relationships, podocyte injury, reversibility, biopsy indications).
- ▶ **CMDT 2026** — “Diabetes Mellitus & Hypoglycemia” (albumin–creatinine cut-offs, ~0.8 g/kg/day protein, ACEi/SGLT2 sequencing, BP targets).

Coverage note: The **five-stage Mogensen functional staging** with approximate timings is standard internal medicine and is referenced in Brenner (Mogensen, *Diabetes* 1983) but the corpus does not tabulate stage-by-stage cut-offs verbatim; Harrison gives the equivalent natural-history sequence (hyperfiltration → silent structural change → albuminuria → GFR decline → ESKD), which is reproduced here.



Diabetic nephropathy

Asked in: Paper IV Dec 2023 · Paper IV Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Diabetic nephropathy, better termed **diabetic kidney disease (DKD)** in clinical practice, is chronic kidney disease attributable to diabetes mellitus, usually recognized by persistent albuminuria and/or falling eGFR in a patient with compatible diabetes duration and other microvascular disease. It is the commonest cause of CKD and ESKD worldwide. The lesion is a combined **metabolic, hemodynamic, glomerular, vascular, podocyte, and tubulointerstitial** injury pattern rather than isolated proteinuria.

Epidemiology and risk factors

- ▶ DKD develops in approximately **20–40%** of patients with diabetes; because type 2 diabetes is much more prevalent, most patients with DKD have type 2 diabetes.
- ▶ It is a major cause of **stage 5 CKD/ESKD** requiring dialysis or transplantation, and CKD in diabetes markedly increases cardiovascular morbidity and mortality.
- ▶ **Type 1 diabetes:** clinically significant DKD usually appears after several years of diabetes; CKD after **10 years or more** of type 1 diabetes is very likely to be DKD if the clinical picture is typical.

- ▶ **Type 2 diabetes:** onset of diabetes is often insidious, so albuminuria or low eGFR may already be present at diagnosis; lesions are more heterogeneous because hypertension, obesity, atherosclerosis, and aging often coexist.
- ▶ Important risk factors are **duration of diabetes, chronic hyperglycemia, hypertension, family history/genetic susceptibility, smoking, obesity, dyslipidemia, ethnicity**, and established cardiovascular disease.
- ▶ Diabetic retinopathy is strongly concordant with DKD, especially in type 1 diabetes; absence of retinopathy in type 1 diabetes with proteinuria should trigger a search for non-diabetic kidney disease.

Pathogenesis

- ▶ **Chronic hyperglycemia** drives advanced glycation end-products, oxidative stress, inflammatory and profibrotic signaling, epigenetic or “metabolic memory” changes, and activation of growth factors such as **TGF-beta** and VEGF.
- ▶ **Hemodynamic injury:** diabetes causes renal hypertrophy, glomerular hyperperfusion, increased intraglomerular pressure, and hyperfiltration. Upregulated proximal tubular **SGLT2** increases sodium-glucose reabsorption, lowers sodium delivery to the macula densa, and perpetuates glomerular hyperfiltration.
- ▶ **RAAS/endothelin axis:** angiotensin II, aldosterone, and endothelin promote efferent arteriolar tone, mesangial matrix production, podocyte injury, and interstitial fibrosis.
- ▶ **Structural glomerular injury:** glomerular basement membrane (GBM) thickening, mesangial matrix expansion, reduced filtration surface area, and later diffuse or nodular glomerulosclerosis.
- ▶ **Podocyte injury** begins early: foot-process widening, podocyte detachment, nephrin loss, and podocytopenia contribute to albuminuria and secondary focal segmental sclerosis.
- ▶ **Tubulointerstitial injury** with tubular basement membrane thickening, tubular dysfunction, inflammation, and fibrosis correlates with progressive eGFR decline.

Natural history and classification

- ▶ Classical sequence: **glomerular hyperfiltration and renal hypertrophy -> moderate albuminuria -> severe albuminuria/overt proteinuria -> declining GFR -> ESKD.**
- ▶ In type 1 diabetes, hyperfiltration and renal hypertrophy occur in the first years; GBM thickening and mesangial expansion appear early; albuminuria often appears after **5-10 years**. In type 2 diabetes, patients may present at any point in this sequence.
- ▶ Atypical but important pattern: DKD may present with **reduced eGFR without albuminuria**, particularly in type 2 diabetes and in contemporary treated cohorts.

Parameter	Category	Exam value
Urine albumin-creatinine ratio (UACR)	Normal	<30 mg/g
UACR	Moderate albuminuria, formerly microalbuminuria	30-299 mg/g
UACR	Severe albuminuria, overt nephropathy	≥300 mg/g
eGFR	G1/G2	≥90 / 60-89 mL/min/1.73 m ²
eGFR	G3a/G3b	45-59 / 30-44 mL/min/1.73 m ²
eGFR	G4/G5	15-29 / <15 mL/min/1.73 m ²

- ▶ Albuminuria is continuous risk: higher UACR predicts faster GFR loss, kidney failure, cardiovascular events, and all-cause mortality.
- ▶ Regression from moderate albuminuria to normoalbuminuria can occur, especially with early treatment; regression is a favorable prognostic sign.

Clinical evaluation and diagnosis

- ▶ Screen with **spot UACR plus serum creatinine-based eGFR**; routine urine dipstick misses low-grade albuminuria.
- ▶ Screening schedule: begin 5 years after onset of type 1 diabetes, and at diagnosis of type 2 diabetes; repeat annually if normal.
- ▶ Confirm an elevated UACR on **2-3 occasions over 3-6 months**, because transient albuminuria may follow strenuous exercise, infection, fever, congestive heart failure, marked hyperglycemia, marked hypertension, or prostate disease.
- ▶ Typical clinical picture: long-standing diabetes, persistent albuminuria, bland urine sediment, hypertension, diabetic retinopathy or neuropathy, and often enlarged kidneys until late disease.
- ▶ Kidney biopsy is usually unnecessary when the phenotype is typical, but is indicated or strongly considered for **sudden onset proteinuria, active urine sediment, RBC casts, nephritic features, rapid eGFR fall, massive proteinuria, refractory hypertension, systemic disease clues, absent retinopathy in type 1 diabetes, or >30% eGFR fall after ACE inhibitor/ARB initiation.**
- ▶ Differential diagnoses in a diabetic patient include hypertensive nephrosclerosis, IgA nephropathy, membranous nephropathy, amyloidosis, monoclonal/light-chain deposition disease, FSGS from obesity, renal artery stenosis, chronic interstitial nephritis, and drug/contrast-related kidney injury.

Renal pathology

- ▶ **Light microscopy:** diffuse mesangial expansion and diffuse glomerulosclerosis are common; advanced disease may show **nodular glomerulosclerosis (Kimmelstiel-Wilson nodules)**.

- ▶ **Kimmelstiel-Wilson nodules:** round, hypocellular mesangial matrix nodules, often PAS/silver positive, surrounded by patent capillaries; a classic exam lesion, but nodular glomerulosclerosis has mimics such as amyloid, light-chain deposition disease, and idiopathic nodular glomerulosclerosis.
- ▶ **Electron microscopy:** early and sensitive **GBM thickening**, mesangial matrix increase, podocyte foot-process widening or detachment, and thickened tubular basement membranes.
- ▶ **Immunofluorescence:** may show nonspecific linear IgG or complement accentuation along basement membranes, without immune-complex deposits on electron microscopy.
- ▶ **Vascular lesions:** afferent and efferent arteriolar hyalinosis is characteristic; exudative lesions include hyaline caps/fibrin caps and capsular drops.
- ▶ **Chronic damage:** global glomerulosclerosis, secondary FSGS, interstitial fibrosis, tubular atrophy, and arteriosclerosis determine irreversible kidney function loss.

Management

- ▶ Aim to slow albuminuria progression, preserve eGFR, reduce cardiovascular risk, avoid AKI, and prepare timely kidney replacement therapy when needed.
- ▶ **Glycemic control:** target HbA1c around 7% in many nonpregnant adults, individualized for age, comorbidity, hypoglycemia risk, and CKD stage. Intensive glycemic control clearly prevents or delays albuminuria in type 1 diabetes and helps early DKD; benefit is less dramatic once established albuminuria and GFR decline are present.
- ▶ As GFR falls, reassess diabetes drugs: insulin requirement may decline; sulfonylureas increase hypoglycemia risk; metformin should be stopped when **eGFR <30 mL/min/1.73 m²**.
- ▶ **Blood pressure:** a practical exam target is **<130/80 mm Hg** in diabetes with albuminuria or CKD, individualized lower if tolerated and cardiovascular/CKD risk is high. Use salt restriction, weight loss, exercise, DASH-style diet, and smoking cessation.
- ▶ **ACE inhibitor or ARB:** first-line antiproteinuric therapy in albuminuric DKD and/or hypertension; reduces intraglomerular pressure and fibrosis. Do not use ACE inhibitor plus ARB together, and do not prescribe RAAS blockade solely to prevent DKD in normotensive, normoalbuminuric diabetes.
- ▶ Check **serum creatinine/eGFR and potassium within 1-2 weeks** after starting or uptitrating ACE inhibitor/ARB/MRA. Review therapy if potassium rises significantly or creatinine rises/eGFR falls by **>30%**.
- ▶ **SGLT2 inhibitors:** in type 2 diabetes with CKD, canagliflozin, dapagliflozin, and empagliflozin slow GFR decline, reduce kidney failure risk, and reduce heart failure events; kidney benefit persists despite reduced glucose-lowering at low eGFR. They are generally useful down to about **20-25 mL/min/1.73 m²** depending on drug and guideline, and are stopped at dialysis initiation.

- ▶ **Mineralocorticoid receptor antagonism:** finerenone or other MRAs reduce albuminuria and improve kidney/cardiovascular outcomes in selected type 2 DKD patients already on ACE inhibitor/ARB; monitor carefully for hyperkalemia.
- ▶ **GLP-1 receptor agonists** such as dulaglutide or semaglutide are useful additional agents for glycemic, weight, cardiovascular, and kidney-risk reduction, especially when SGLT2 inhibitors are not tolerated or CKD is advanced.
- ▶ Treat dyslipidemia with statin-based therapy as indicated; manage obesity, avoid NSAIDs and unnecessary iodinated contrast, hydrate around contrast exposure, treat metabolic acidosis and anemia of CKD, vaccinate, and refer to nephrology for eGFR <30, rapid decline, or heavy albuminuria.
- ▶ ESKD management includes education for dialysis modalities and transplantation; **kidney transplantation improves survival**, and simultaneous pancreas-kidney transplantation may be considered in suitable type 1 diabetes patients.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Natural history graph:** x-axis = diabetes duration in years; y-axis left = UACR/albuminuria; y-axis right = GFR; labels = hyperfiltration, moderate albuminuria, severe albuminuria, falling GFR, ESKD, earlier presentation in type 2 diabetes.
- ▶ **Glomerular pathology diagram:** labels = thickened GBM, mesangial expansion, *Kimmelstiel-Wilson nodule*, podocyte foot-process effacement/detachment, afferent and efferent arteriolar hyalinosis, tubulointerstitial fibrosis.

Clinical / Diagnostic significance

- ▶ DKD is both a renal diagnosis and a **cardiovascular risk marker**; albuminuria independently predicts myocardial infarction, stroke, heart failure, and death.
- ▶ Retinopathy supports DKD, especially in type 1 diabetes; its absence, active sediment, or rapid loss of function should prevent blind attribution to diabetes.
- ▶ Diabetics are prone to **type 4 renal tubular acidosis** with hyperkalemia, especially with ACE inhibitors, ARBs, MRAs, NSAIDs, beta-blockers, or advanced CKD.
- ▶ Diabetes plus CKD is a high-risk setting for **contrast-associated AKI**; use the lowest necessary contrast dose, avoid volume depletion and NSAIDs, and monitor creatinine after exposure.
- ▶ Persistent albuminuria despite good BP and glycemic control should prompt adherence review, sodium intake assessment, optimized RAAS/SGLT2/MRA therapy, and exclusion of non-diabetic kidney disease.

High-yield exam pointers

- ▶ Write **UACR plus eGFR**; dipstick alone is inadequate for early disease.
- ▶ Screening: **type 1 after 5 years, type 2 at diagnosis, then annually.**

- ▶ Confirm albuminuria: 2-3 samples over 3-6 months.
- ▶ Albuminuria categories: 30-299 mg/g and ≥ 300 mg/g.
- ▶ Classical sequence: hyperfiltration $\rightarrow$ albuminuria $\rightarrow$ proteinuria $\rightarrow$ falling GFR.
- ▶ Pathology triad: GBM thickening, mesangial expansion, nodular glomerulosclerosis.
- ▶ Treatment triad for albuminuric DKD: BP control + ACE inhibitor/ARB + SGLT2 inhibitor; add finerenone when appropriate.
- ▶ Do **not** combine ACE inhibitor and ARB; monitor creatinine and potassium.
- ▶ Absence of retinopathy in type 1 diabetes with proteinuria means **look for another renal disease**.

SOURCE & COVERAGE

Harrison 22e — “Diabetes Mellitus: Complications”; “Glomerular Diseases”; Brenner & Rector’s The Kidney — “Epidemiology of Diabetic Kidney Disease”; CMDT 2026 — “Kidney Disease” and “Diabetes Mellitus & Hypoglycemia”.



Discuss clinical features and management of Nephrolithiasis

Asked in: Paper IV 17 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Nephrolithiasis (kidney stone disease, urolithiasis) is the formation of crystalline concretions within the upper urinary tract due to supersaturation of lithogenic solutes in urine when the concentration product exceeds the solubility product, combined with deficient crystallisation inhibitors. It is a common, recurrent, costly **systemic disorder** — lifetime risk reaches ~20% in men and ~10% in women, with >50% of first-time formers recurring within 5–10 years. A stone may sit silently in the kidney for years, then migrate into the ureter to produce **renal colic**, often described by patients as the worst pain ever experienced. Identifying the stone type is central, as it dictates prognosis and the targeted, often life-long, preventive regimen.

Classification / Types of stones

Stone type	Approx. frequency	Key urinary risk factors	Radiology	Special features
Calcium oxalate	~75% (most common)	↑urine calcium, ↑oxalate, ↓citrate	Radiopaque	Insensitive to urine pH; grows on Randall’s plaque
Calcium phosphate	~15%	↑calcium, ↓citrate, ↑phosphate, urine pH ≥ 6.5	Radiopaque	Linked to distal RTA & primary hyperparathyroidism

Stone type	Approx. frequency	Key urinary risk factors	Radiology	Special features
Uric acid	~8%	High uric acid excretion, persistent urine pH ≤ 5.5	Radiolucent on KUB; visible on CT	Seen in gout, obesity, T2DM, tumour lysis
Struvite (Mg-ammonium-phosphate, “triple-phosphate”/infection stone)	~1%	Urease-producing UTI, urine pH > 8.0	Faintly opaque	Forms staghorn calculi ; <i>Proteus mirabilis</i> , <i>Klebsiella</i> , <i>Providencia</i>
Cystine	$< 1\%$	Autosomal-recessive cystinuria	Faintly opaque	Hexagonal crystals; staghorn / bilateral; childhood onset

- ▶ Calcium-containing stones together account for ~85% and are radiopaque, which is why most stones are seen on plain radiographs.
- ▶ Many stones are **mixtures** (e.g., calcium oxalate + calcium phosphate) and contain a protein matrix. Rarely stones are **drug-induced** (acyclovir, atazanavir/indinavir, triamterene, sulfadiazine, guaifenesin).

Pathogenesis and risk factors

- ▶ **Supersaturation–inhibition balance:** stones form when urine is supersaturated and protective inhibitors are deficient. **Citrate** is the most important inhibitor of calcium stones (complexes calcium, raising solubility); others include magnesium and pyrophosphate.
- ▶ **Randall’s plaque hypothesis:** interstitial **calcium-phosphate** deposits begin at the thin limb of the loop of Henle, extend to the papillary tip and erode through the urothelium, providing an anchored nidus on which calcium oxalate/phosphate crystals grow — explaining why stone formation begins years before a clinical stone.
- ▶ **Urinary risk factors:** low urine volume (< 1 L/day more than doubles risk), hypercalciuria (> 250 mg/day men, > 200 mg/day women, or > 4 mg/kg/day), hyperoxaluria (> 40 mg/day), hypocitraturia (< 450 mg/day), hyperuricosuria (> 800 mg/day men, > 750 mg/day women) and unfavourable urine pH.
- ▶ **Dietary risk factors:** high animal protein, oxalate, sodium, sucrose/fructose and high-dose vitamin C (raises oxalate). **Protective:** high dietary calcium (binds gut oxalate), potassium, phytate, citrus and high fluid intake. *Low* dietary calcium is harmful — it increases oxalate absorption and bone loss.
- ▶ **Associated/secondary conditions:** primary hyperparathyroidism, distal (type 1) renal tubular acidosis (urolithiasis in up to 75%), GI malabsorption (Crohn’s, gastric bypass → **enteric**

hyperoxaluria via fatty-acid sequestration of calcium), obesity, type 2 diabetes, gout, medullary sponge kidney, and recurrent UTI.

- ▶ **Genetic disorders:** **cystinuria** (AR defect in dibasic amino-acid reabsorption) and **primary hyperoxaluria** (AR hepatic overproduction of oxalate, types I–III) — both cause early, severe, recurrent stones.

Clinical features

- ▶ **Two classic acute presentations:** (1) **renal colic** and (2) painless gross haematuria.
- ▶ **Renal colic:** sudden-onset, severe **unilateral flank pain** that waxes and wanes (a misnomer — pain rarely fully subsides) with no relieving posture; patients are **restless and writhing** (cf. the still patient of peritonitis). Frequently accompanied by **nausea/vomiting** and visible or microscopic haematuria.
- ▶ **Radiation by stone site:** upper-ureteric stone → pain radiates anteriorly; lower-ureteric stone → radiates to ipsilateral **testis/labium**; ureterovesical-junction stone → urinary **urgency, frequency, dysuria** (mimics cystitis but culture-negative).
- ▶ **Differential diagnosis by location:** right UPJ stone mimics acute cholecystitis; right pelvic-brim stone mimics appendicitis; left pelvic-brim mimics diverticulitis. Also consider biliary colic, ectopic pregnancy/ovarian torsion, **leaking abdominal aortic aneurysm**, herpes zoster, musculoskeletal pain, and ureteric obstruction by clot or sloughed papilla.
- ▶ **Red-flag** — “**pus under pressure**”: an obstructing stone with proximal infection (fever, leucocytosis, sepsis) is an **obstructive pyonephrosis / urologic emergency** requiring emergent drainage; antibiotics alone are inadequate.
- ▶ Note: absence of haematuria does **not** exclude a stone (complete obstruction may give a normal urinalysis), and stone size does not correlate with pain severity.

Investigations

- ▶ **Urinalysis:** micro/gross haematuria in ~90%; sediment may show crystals — *bipyramidal (envelope)* calcium oxalate or *hexagonal* cystine crystals; pyuria with culture if infection suspected.
- ▶ **Imaging** — **non-contrast helical CT (KUB) is the gold standard:** highly sensitive, detects stones as small as 1 mm including “radiolucent” uric-acid stones, and shows hydroureteronephrosis and perinephric stranding. Hounsfield units estimate composition (pure uric acid = low HU).
Ultrasound (no radiation) is preferred first-line in pregnancy and for follow-up but is less sensitive and misses most ureteric stones. **KUB radiograph** misses radiolucent/small stones and gives no information on obstruction.
- ▶ **Blood:** serum electrolytes (for hypokalaemia/RTA), creatinine, calcium, phosphate, uric acid; PTH and 25-OH vitamin D if calcium is high/high-normal.

- ▶ **Metabolic work-up: stone analysis** is essential whenever a stone/fragment is retrieved (patients should strain urine). **Two 24-h urine collections** on the usual diet form the cornerstone of prevention — measure volume, calcium, oxalate, citrate, uric acid, sodium, potassium, phosphate, magnesium, pH, creatinine, and calculated supersaturation. Indicated after the first stone in interested/high-risk patients and in all recurrent formers.

Management — acute and surgical

- ▶ **Analgesia:** parenteral NSAIDs (e.g., ketorolac) are at least as effective as opioids with fewer side effects, and are first-line; opioids are adjuncts.
- ▶ **Fluids:** maintain euvolaemia — forced diuresis does not flush stones and worsens pain/obstruction.
- ▶ **Medical expulsive therapy (MET):** α -blocker (tamsulosin 0.4 mg OD) $\pm$ an NSAID (ibuprofen 600 mg TID) $\pm$ short low-dose prednisone increases spontaneous passage, most effective for distal ureteric stones >5 mm. Stones <5 – 6 mm usually pass spontaneously.
- ▶ **Indications for urologic intervention:** UTI/infection behind obstruction, low likelihood of passage (stone ≥ 6 mm, anatomic abnormality, solitary kidney), intractable pain/vomiting, or non-passage after a few weeks.
- ▶ **Emergency drainage** (ureteric stent or percutaneous nephrostomy) for the infected, obstructed kidney — *definitive stone removal is deferred until sepsis is treated.*
- ▶ **Definitive procedures** (chosen by stone size, site, composition, anatomy):
 - Ureteroscopy + laser/basket — mid/distal ureteric stones; outpatient, most reliable.
 - Extracorporeal shock-wave lithotripsy (ESWL) — least invasive; best for stones <1 cm in the lower pole or <2 cm elsewhere; poor for hard stones (cystine, brushite, >1000 – 1200 HU) and obese patients; contraindicated in pregnancy, untreated UTI, coagulopathy/anticoagulation, and discouraged for staghorn/infected stones.
 - Percutaneous nephrolithotomy (PCNL) — for large (>15 – 20 mm) and staghorn calculi; highest stone-free rate. Open ureterolithotomy/pyelolithotomy is now rarely needed.

Prevention by stone type

- ▶ **Universal measure (all types):** high fluid intake to keep urine volume ≥ 2 – 2.5 L/day — proven by RCT to halve recurrence; tailor advice to the measured 24-h volume.

Stone type	Targeted preventive measures
Calcium oxalate	Normal-to-high dietary calcium (~ 1000 – 1200 mg/d), restrict sodium (<2.5 – 3.5 g/d) & animal protein, reduce sucrose/fructose; thiazide (higher dose than for HTN — chlorthalidone/indapamide OD, HCTZ BD) for hypercalciuria; potassium citrate for hypocitraturia; allopurinol if

Stone type	Targeted preventive measures
	hyperuricosuric; avoid high-dose vitamin C; DASH / Mediterranean diet
Calcium phosphate	Thiazide + sodium restriction; potassium citrate (with urine-pH monitoring , as alkali can worsen phosphate stones); reduce dietary phosphate; exclude/treat distal RTA & hyperparathyroidism
Uric acid	Alkalinise urine to pH 6.5 (potassium citrate/bicarbonate) — <i>mainstay</i> ; reduce purine intake; add xanthine-oxidase inhibitor (allopurinol 300 mg/d or febuxostat) if alkalinisation insufficient (lowers urine uric acid 40–50%)
Struvite	Complete surgical clearance (PCNL) + prevent/treat UTI; acetohydroxamic acid (urease inhibitor) for refractory recurrent cases
Cystine	High urine volume (3–4 L/d), low sodium, alkalinise to pH 7.0–7.5 (potassium citrate); thiol drugs that solubilise cystine — tiopronin (preferred) or D-penicillamine
Primary hyperoxaluria (type I)	Pyridoxine (vitamin B6) in selected patients; siRNA agents lumasiran / nedosiran to cut hepatic oxalate production

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled coronal nephron/urinary tract diagram of stone impaction sites:** label *Kidney (calyx, renal pelvis)*, *Randall's plaque at papillary tip*, and the **three ureteric narrowings** — *Pelvi-ureteric (UPJ) junction*, *crossing of iliac vessels / pelvic brim*, *Vesico-ureteric (UVJ) junction* — plus *bladder*; mark *hydronephrosis* proximal to an obstructing stone.
- ▶ **Urine-pH vs stone-type bar/line:** label axis pH 4.5 → 8.5; mark *uric acid* ≤ 5.5 , *calcium oxalate* (pH-independent), *calcium phosphate* ≥ 6.5 , *cystine* (more soluble at high pH), *struvite* > 8.0 .

Clinical / Diagnostic significance

- ▶ Nephrolithiasis is a **marker of systemic disease** — independently associated with hypertension, CKD/ESRD, reduced bone mineral density, gout, type 2 diabetes and cardiovascular disease; evaluate accordingly.
- ▶ A **culture-negative pyuria with haematuria** plus flank pain should prompt CT for an occult ureteric stone before labelling “cystitis”.

- ▶ Unexplained recurrent calcium stones mandate exclusion of **primary hyperparathyroidism** (serum Ca, PTH) and **distal RTA** (hyperchloraemic metabolic acidosis with inappropriately alkaline urine, hypocitraturia, hypokalaemia).
- ▶ **Stone composition and 24-h urine chemistry**, not symptoms, drive long-term prevention — preventive therapy is usually **life-long** with annual 24-h urine monitoring and radiation-sparing follow-up imaging (prefer ultrasound).

High-yield exam pointers

- ▶ Commonest stone = **calcium oxalate** (~75%); calcium-containing stones ~85% and radiopaque; **uric acid** stones are radiolucent on KUB but visible on CT.
- ▶ **Non-contrast helical CT** = investigation of choice (detects 1-mm stones); **ultrasound** in pregnancy/follow-up.
- ▶ Restless writhing patient with colicky flank-to-groin pain + haematuria = ureteric stone; **NSAIDs** first-line analgesia.
- ▶ **Obstructed + infected kidney** = **emergency drainage** (stent/nephrostomy) — “pus under pressure”.
- ▶ Stones <5 mm usually pass; offer **tamsulosin** MET; ≥6 mm or persistent → intervention; staghorn → PCNL.
- ▶ **Citrate** = key inhibitor; **hypocitraturia** → **potassium citrate**; **hypercalciuria** → **thiazide** + low sodium.
- ▶ Do **not** restrict dietary calcium — it raises oxalate absorption and stone risk; restrict **sodium**, **animal protein**, **oxalate**; fluids to ≥2–2.5 L urine/day.
- ▶ **Struvite** = infection stone (urease-positive *Proteus*); **cystine** = AR, hexagonal crystals, treat with tiopronin + alkali; **uric acid** stones managed primarily by **urinary alkalinisation to pH 6.5**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Nephrolithiasis” (Gary C. Curhan): pathogenesis, Randall’s plaque, stone types, risk factors, evaluation, prevention by stone type.
- ▶ **Brenner & Rector’s The Kidney** — “Urolithiasis”: Randall’s-plaque pathophysiology, hypocitraturia/dRTA, enteric & primary hyperoxaluria, pharmacotherapeutic trial evidence (thiazides, potassium citrate, allopurinol, thiol drugs).
- ▶ **CMDT 2026** — “Urologic Disorders: Urinary Stone Disease”: clinical findings, metabolic thresholds, drug doses (tamsulosin, potassium citrate, allopurinol, thiazides), MET, ESWL/ureteroscopy/PCNL selection and contraindications.



Emphysematous Pyelonephritis: Clinical Presentation, Evaluation and Management

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — *Emphysematous pyelonephritis (EPN)* is an acute, severe, **necrotizing** infection of the renal and perinephric tissues characterized by the production of gas within the renal parenchyma, collecting system and/or perirenal space by gas-forming uropathogens. It is a **urological emergency** that occurs *almost exclusively in patients with poorly controlled diabetes mellitus*, frequently with co-existent urinary obstruction, and carries a high mortality if not promptly recognised and aggressively managed. It must be distinguished from the more benign *emphysematous pyelitis* (gas confined to the collecting system, parenchyma spared) and *emphysematous cystitis* (gas in the bladder wall/lumen).

Pathogenesis and predisposing factors

- ▶ **Diabetes mellitus** is the dominant risk factor — 62–100% of patients in case series are diabetic, and serum glucose is often very high at presentation; EPN occurs **almost exclusively in poorly controlled diabetics**.
- ▶ **Mechanism of gas formation:** high urinary and tissue glucose acts as a fermentable substrate for facultative anaerobes, generating large volumes of gas (CO₂, hydrogen, nitrogen) through *fermentation*. In the *non-diabetic minority*, **fermentation of tissue protein** is the proposed gas source.
- ▶ **Contributory factors:** *impaired host immunity and microvascular disease of diabetes*, **urinary tract obstruction** (calculus, papillary necrosis, stricture — a common predisposant), high tissue glucose, and locally **reduced perfusion**, which favours anaerobic metabolism and necrosis.
- ▶ A **female preponderance** is consistently reported (ascending infection, shorter urethra). Most infection is *ascending* from the lower tract.
- ▶ The end result is **acute suppurative necrosis** of parenchyma; a fulminant course is characterised by *tissue necrosis, intravascular thrombosis and microabscess formation*.

Microbiology

- ▶ ***Escherichia coli** is the single most common organism (~45–54% of episodes) — a gas-forming, facultative anaerobic uropathogen*.
- ▶ ***Klebsiella pneumoniae*** is the next most frequent isolate.
- ▶ Less common: *Proteus mirabilis*, *Enterobacter*, *Pseudomonas aeruginosa* and, rarely, *Candida* and *Clostridium* species.
- ▶ **Bacteraemia** is demonstrable in 20–50% of patients in whom blood cultures are obtained — reflecting the invasive, systemic nature of the disease.

Clinical presentation

- ▶ The presentation overlaps with severe acute pyelonephritis — the **classic triad of fever, vomiting and flank pain**.
- ▶ **Severe pyelonephritis** features: *high fever, rigors, nausea, vomiting, flank/costovertebral-angle (CVA) pain and marked CVA tenderness*; symptoms are usually acute in onset and may or may not be preceded by cystitis.
- ▶ **Systemic toxicity is common**: the patient is frequently *acutely ill, dehydrated, tachycardic and may present with septic shock*.
- ▶ **Crepitus** over the flank or a *palpable, tender renal mass* may rarely be appreciated when gas tracks into the retroperitoneum/subcutaneous tissue.
- ▶ **Frequent accompaniments / complications**: *acute kidney injury, diabetic ketoacidosis or hyperglycaemic crisis, thrombocytopenia, disturbance of consciousness, and shock* — these are also **adverse prognostic markers**.
- ▶ **Pneumaturia** suggests gas in the collecting system/bladder (more typical of emphysematous cystitis or pyelitis).
- ▶ A subset present with a **poor response to standard antibiotics for “pyelonephritis”**, or *persistent fever/bacteraemia*, which should prompt imaging to look for gas, abscess or obstruction.

Evaluation / Investigations

- ▶ **Urinalysis & urine culture**: pyuria, bacteriuria, haematuria; culture (with sensitivities) identifies the organism — *obtain before antibiotics where feasible*.
- ▶ **Blood culture**: positive in a substantial minority; identifies bacteraemia and guides therapy.
- ▶ **Blood investigations**: complete blood count (*leukocytosis with left shift; thrombocytopenia is a poor-prognosis marker*), **renal function (urea/creatinine — AKI is common)**, electrolytes, **blood glucose and HbA1c**, **arterial blood gas / serum lactate** (for acidosis and sepsis), and **CRP** (generally elevated). Screen for **DKA** (ketones, anion gap).
- ▶ **Plain abdominal radiograph (KUB)**: may show mottled/streaky or crescentic gas over the renal shadow — but **identifies renal gas in only ~50%** of EPN cases (more sensitive in emphysematous cystitis).
- ▶ **Ultrasonography**: usually shows renal abnormality with high-amplitude echoes and “dirty” shadowing from gas, but is **less accurate than CT** for defining extent.
- ▶ **Contrast-enhanced CT is the imaging modality of choice** — it confirms the diagnosis, maps the distribution and extent of gas, parenchymal destruction, fluid/abscess, obstruction and contralateral kidney, and underpins the radiological classification that drives management.

Radiological classification (CT-based — Huang & Tseng) — directs management & prognosis:

Class	CT findings	Implication
Class 1	Gas confined to the collecting system (emphysematous <i>pyelitis</i>)	Best prognosis
Class 2	Gas confined to the renal parenchyma alone	Good outcome with drainage
Class 3A	Extension of gas/abscess into the perinephric space	Higher risk
Class 3B	Extension of gas/abscess into the pararenal space (beyond Gerota's fascia)	Higher risk
Class 4	Bilateral EPN , or EPN in a solitary functioning kidney	Worst prognosis

An alternative morphological scheme (Wan) divides EPN into Type I — parenchymal destruction with streaky/mottled gas and no fluid (the “dry,” more necrotic, higher-mortality form) — and Type II — renal/perirenal fluid with bubbly/loculated gas (the “wet,” lower-mortality form).

Adverse prognostic factors (≥2 predict failure of conservative management): *thrombocytopenia, acute kidney injury (raised creatinine), disturbance of consciousness, and shock.*

Management

Management is **multidisciplinary** (physician/intensivist, nephrologist, urologist, interventional radiologist) and combines **resuscitation, source control and metabolic control**.

- ▶ **Resuscitation & supportive care:** IV fluids, correction of dehydration and electrolytes, management of sepsis/septic shock, and **aggressive glycaemic control** (treat DKA/hyperglycaemia with insulin).
- ▶ **Empirical broad-spectrum IV antibiotics**, started promptly after cultures and de-escalated by sensitivities:
 - For hospitalised/systemically ill patients, an IV **β-lactam** is preferred — *ceftriaxone* or *cefepime*, *piperacillin-tazobactam*, or a *carbapenem*; an **aminoglycoside** (e.g. with ampicillin) is an effective addition/alternative. **Carbapenems** are used for ESBL-producing organisms.
 - Treatment is *culture-guided*; switch to oral once stable, with a total course typically extending well beyond uncomplicated pyelonephritis given tissue-invasive necrotising disease.
- ▶ **Relief of obstruction:** *ureteric stenting* or *percutaneous nephrostomy* if there is obstructive uropathy (e.g. obstructing calculus, papillary necrosis) — essential for source control.
- ▶ **Percutaneous catheter drainage (PCD)** of gas/abscess, combined with antibiotics, is now the **recommended initial intervention** and the modern “kidney-sparing” standard; it has *similar or lower mortality* than emergency nephrectomy or medical therapy alone.

- ▶ **Nephrectomy** (emergency or delayed/elective) is reserved for **failure of PCD plus medical therapy**, fulminant/extensive disease, or a non-functioning kidney — typically in patients with **≥2 adverse prognostic factors** or extensive (Class 3B/4) disease.
- ▶ **Outcome:** mortality ranges from 7–20% in less severe disease to ~70% in a fulminant course (necrosis, intravascular thrombosis, microabscesses). Comparative case-series mortality: ~50% with medical therapy alone, ~25% with medical therapy plus emergency nephrectomy, and ~13.5% with medical therapy plus initial percutaneous drainage — underscoring the value of early drainage.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled CT cross-section of EPN (axial):** label *renal parenchyma with destruction, intraparenchymal/streaky gas (mottled lucencies), gas tracking into perinephric space, Gerota's fascia, pararenal space, obstructing calculus/collecting-system gas, and normal contralateral kidney*. Annotate the **Huang-Tseng classes 1–4** alongside (gas in collecting system → parenchyma → perinephric → pararenal → bilateral/solitary).
- ▶ **Management flow-diagram:** *Suspected EPN → resuscitate + IV antibiotics + glycaemic control → CT (classify) → relieve obstruction (stent/nephrostomy) → Class 1–2 or <2 risk factors: percutaneous drainage; Class 3–4 with ≥2 risk factors / failure of PCD: nephrectomy.*

Clinical / Diagnostic significance

- ▶ EPN should be suspected in any diabetic with severe/septic pyelonephritis failing to respond promptly, or with gas seen on KUB/USG — CT is **mandatory** to confirm and stage.
- ▶ Early percutaneous drainage with relief of obstruction has shifted practice away from routine emergency nephrectomy, improving renal preservation and survival.
- ▶ **Glycaemic control and treatment of the underlying diabetes** are integral, not adjunctive — high tissue glucose perpetuates gas-forming infection.
- ▶ Differentiate from *xanthogranulomatous pyelonephritis* (chronic, staghorn-calculus-associated, lipid-laden foamy macrophages, usually needs nephrectomy) and from benign **post-instrumentation gas** in the collecting system (gas in *tissue* defines emphysematous infection).

High-yield exam pointers

- ▶ EPN = **gas-forming necrotising infection of renal/perinephric tissue**, *almost exclusively in poorly controlled diabetics*.
- ▶ ***E. coli (commonest) and Klebsiella pneumoniae are the leading pathogens;** bacteraemia in 20–50%*.
- ▶ **Pathogenesis** = fermentation of **high tissue/urinary glucose** by facultative anaerobes → gas; obstruction and impaired immunity contribute.
- ▶ **CT is the investigation of choice;** KUB detects renal gas in only ~50%.

- ▶ **Huang-Tseng Class 1→4** (collecting system → parenchyma → perinephric → pararenal → bilateral/solitary) classifies and prognosticates.
- ▶ **Four poor-prognosis factors:** *thrombocytopenia, AKI, altered sensorium, shock*; ≥ 2 predicts failure of conservative care.
- ▶ **Modern management** = antibiotics + glycaemic/sepsis control + percutaneous drainage + relief of obstruction; nephrectomy only if these fail.
- ▶ Mortality 7–20% (less severe) up to ~70% (fulminant); PCD-based therapy gives the lowest mortality (~13.5%).
- ▶ Distinguish from **emphysematous pyelitis** (collecting-system gas, parenchyma spared, benign) and **emphysematous cystitis** (bladder).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Urinary Tract Infections: Cystitis, Prostatitis, and Pyelonephritis” (definition of EPN, gas-forming *E. coli*, percutaneous drainage ± elective nephrectomy; pyelonephritis antibiotic regimens).
- ▶ **Brenner & Rector's The Kidney** — “Urinary Tract Infection in Adults” (dedicated *Emphysematous Cystitis and Pyelonephritis* section: pathogenesis, microbiology, diabetic/female predominance, CT as modality of choice, mortality figures, and the shift from emergency nephrectomy to percutaneous drainage).
- ▶ **CMDT 2026** — “Urologic Disorders” (acute pyelonephritis evaluation and empirical antibiotic management; EPN as a life-threatening complication in diabetics).

Coverage note: The Huang & Tseng CT classification (Classes 1–4), the Wan Type I/II morphological types, and the four adverse prognostic factors are *universally accepted standard urological/nephrological references* used to stage and triage EPN but were **not present verbatim in the local corpus**; they are included as standard, accurate exam content. All organism frequencies, mortality percentages, imaging yields, pathogenesis and management principles are grounded in Brenner, Harrison and CMDT as cited above.



Focal Segmental Glomerulosclerosis

Asked in: Paper IV Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — *Focal segmental glomerulosclerosis (FSGS)* is not a single disease but a **clinico-pathological pattern of podocyte injury** characterised by segmental (part of the tuft) scars in *some but not all* (focal) glomeruli, with **proteinuria** as its ubiquitous clinical hallmark. It is best regarded as a *podocytopathy* — a final common pathway of glomerular injury with multiple causes (primary/idiopathic, secondary/adaptive, viral and genetic). FSGS is now the **most common cause of**

primary glomerular disease leading to ESKD in the United States and an important cause of steroid-resistant nephrotic syndrome in both children and adults.

Etiological Classification (Primary, Secondary, Genetic)

- ▶ **Primary (idiopathic) FSGS** — driven by a presumed **circulating permeability factor** (yet to be definitively identified); typically presents with abrupt, *full nephrotic syndrome* and diffuse foot-process effacement; the form most likely to respond to immunosuppression and to recur after transplantation.
- ▶ **Secondary / adaptive FSGS** — maladaptive response to nephron loss, glomerular hypertrophy or hyperfiltration; usually sub-nephrotic proteinuria with *preserved serum albumin* and *segmental* foot-process effacement.

Category	Representative causes (from Harrison Table 326-4 / Brenner Box 31.6)
Adaptive (hyperfiltration / ↓ nephron mass)	Obesity, oligomeganephronia, unilateral renal agenesis/post-nephrectomy, reflux nephropathy, sickle cell disease, cyanotic congenital heart disease, hypoxic pulmonary disease, glomerulomegaly
Viral	HIV (collapsing), hepatitis B, parvovirus B19, SARS-CoV-2
Drug-associated	Heroin, analgesics, bisphosphonates (pamidronate) , interferon, anabolic steroids, ecstasy, lithium
Other secondary	Hypertensive nephrosclerosis, cholesterol emboli, radiation nephritis
Genetic / familial podocytopathies	<i>NPHS1</i> (nephrin), <i>NPHS2</i> (podocin), <i>ACTN4</i> (α-actinin-4), <i>TRPC6</i> , <i>INF2</i> (inverted formin 2), <i>WT1</i> , <i>PLCE1</i> , <i>CD2AP</i> ; Fabry disease (α-galactosidase A); nephrosialidosis
High-risk genetic background	APOL1 risk alleles (G1/G2) in those of sub-Saharan African ancestry

Pathology — Columbia Histological Variants

- ▶ **Light microscopy:** segmental glomerular **sclerosis/consolidation** with capillary collapse, hyalinosis (insudated plasma proteins), foam cells and adhesions to Bowman's capsule. Lesions are most prominent at the **cortico-medullary junction**, so a superficial biopsy may miss them and be mislabelled minimal change disease (MCD).
- ▶ **Immunofluorescence:** non-specific **IgM and C3** trapped *in the sclerotic segments only* (not pathogenic immune complexes).
- ▶ **Electron microscopy:** **foot-process effacement** — diffuse in primary, more *segmental/partial* in secondary FSGS; no immune-type dense deposits in non-sclerotic glomeruli.

- The **Columbia classification** recognises *five morphological variants* correlating with cause and prognosis:

Variant	Key features	Demographics / prognosis
NOS (classic)	Segmental sclerosis without distinctive features; commonest (~42%)	Primary or secondary; intermediate outcome
Perihilar	Sclerosis + hyalinosis at the vascular pole; glomerulomegaly	Typical of adaptive/secondary FSGS; often sub-nephrotic
Tip lesion	Consolidation at the tubular (urinary) pole opposite the hilum	Older Caucasian males; steroid-responsive, best prognosis
Cellular	Endocapillary hypercellularity, foam cells; heavy proteinuria	Intermediate remission/ESKD rates
Collapsing (collapsing glomerulopathy)	Global/segmental capillary collapse + podocyte hyperplasia (“pseudocrescents”)	African-American, HIV-associated; massive proteinuria; worst prognosis

Pathogenesis — Podocyte Injury as the Final Common Pathway

- **Circulating permeability factor (primary FSGS)**: plasma factor increasing glomerular albumin permeability; supported by **recurrence within hours–days of transplantation** and response to **plasmapheresis**. Candidate factors include **soluble urokinase receptor (suPAR)** (activates podocyte $\beta 3$ -integrin) and a galactose-binding factor — *neither yet conclusively proven*.
- **Genetic podocytopathies**: mutations disrupt the **slit diaphragm / actin cytoskeleton / GBM**. *NPHS2* (podocin) is the **most frequent genetic cause of steroid-resistant nephrotic syndrome** (the R138Q and R229Q variants are characteristic); *NPHS1* causes congenital (Finnish-type) nephrotic syndrome; *ACTN4*, *TRPC6* and *INF2* cause autosomal-dominant adult FSGS.
- **APOL1 risk variants (G1/G2, chromosome 22)**: explain the ~4-fold excess of FSGS and the 18–50-fold excess of HIV-associated collapsing FSGS in people of African ancestry (the same alleles that confer protection against *Trypanosoma brucei rhodesiense* — analogous to sickle trait and malaria).
- **Adaptive (maladaptive) hyperfiltration**: nephron loss $\rightarrow$ $\uparrow$ single-nephron GFR and intraglomerular hypertension $\rightarrow$ podocyte stretch, dropout and segmental sclerosis (mediated partly by TGF- $\beta 1$). Worsened by high dietary protein; ameliorated by RAAS blockade and protein restriction.
- **Direct injury**: viruses (HIV $\rightarrow$ collapsing variant with endothelial *tubuloreticular inclusions*), drugs (pamidronate, interferon, anabolic steroids).

Clinical Features and Natural History

- ▶ **Proteinuria is the hallmark** — ranges from sub-nephrotic (1–2 g/day) to >10 g/day with full nephrotic syndrome (oedema, hypoalbuminaemia <2 g/dL, hyperlipidaemia).
- ▶ **Microscopic (and frank) haematuria in >50%**, hypertension in ~⅓, and impaired GFR at presentation in ~25–50%.
- ▶ **Collapsing variant** — rapid onset, very heavy proteinuria, low albumin, high creatinine, rapid decline to ESKD; **tip lesion** — abrupt MCD-like nephrosis but favourable, often reversible AKI and good response.
- ▶ **Prognosis:** FSGS *rarely remits spontaneously*. Nephrotic-range proteinuria with kidney injury carries a poor outcome — ~50% **reach ESKD within 10 years**; proteinuria >10 g/day → most reach ESKD within ~3 years. **Achieving remission (spontaneous or treatment-induced) is the single best prognostic indicator**; entry serum creatinine >1.3 mg/dL also predicts poor renal survival.

Diagnosis and Investigations

- ▶ **Kidney biopsy is required** for diagnosis (LM + IF + EM); a deep/cortico-medullary sample is essential to avoid a false MCD label.
- ▶ **Quantify proteinuria** — spot urine protein:creatinine ratio or 24-h protein; urinalysis may show **oval fat bodies** / “Maltese crosses” under polarised light.
- ▶ **Exclude secondary and genetic causes before treating:** HIV serology (especially with collapsing pattern), hepatitis B/C, parvovirus; drug history (bisphosphonates, heroin, anabolic steroids, interferon); assessment for obesity, reflux, sickle cell, reduced nephron mass; **genetic testing** (increasingly in children and steroid-resistant cases).
- ▶ Supportive labs: hypoalbuminaemia, hyperlipidaemia, **normal complement** (helps distinguish from immune-complex GN).

Treatment

- ▶ **Supportive / antiproteinuric (all forms): RAAS blockade** (ACE inhibitor or ARB) ± mineralocorticoid-receptor antagonist; **SGLT2 inhibitor**; statin for dyslipidaemia; salt restriction and diuretics for oedema; anticoagulation for thrombotic complications of nephrotic syndrome.
- ▶ **Primary FSGS with nephrotic syndrome — immunosuppression:**
 - **Corticosteroids first-line** — prednisone 1 mg/kg/day (children 60 mg/m²/day) for 4–16 weeks followed by slow taper; response is *slower and less frequent than in MCD* — remission in only ~20–45%, median time to remission 3–4 months.
 - **Calcineurin inhibitors** for steroid-resistant or steroid-intolerant disease — cyclosporine 5 mg/kg/day (RCTs by Ponticelli and the North American Nephrotic Syndrome Study Group show induction of remission); relapse is common on withdrawal and chronic use risks nephrotoxicity / interstitial fibrosis.

- **Mycophenolate mofetil** and **rituximab** are second-/third-line/steroid-sparing options with limited evidence (FSGS Clinical Trial: MMF + pulse dexamethasone *not* superior to cyclosporine).
- ▶ **Secondary and genetic FSGS: no role for steroids/immunosuppression** — treat the underlying cause (weight loss, stop offending drug, antiretrovirals for HIV) and maximise antiproteinuric therapy.
- ▶ **Transplantation: FSGS recurs in ~30% of allografts** (more with primary, less with secondary, rarely with genetic disease); recurrent post-transplant FSGS from a presumed circulating factor often responds to **plasmapheresis**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Glomerulus with a segmental sclerotic lesion:** label *Bowman's capsule, capillary tuft, segmental sclerosis/hyalinosis, foam cells, adhesion (synechia) to Bowman's capsule, afferent & efferent arterioles (vascular/hilar pole), tubular (urinary) pole, effaced podocyte foot processes*.
- ▶ **Diagram 2 — Columbia variant map (small glomerular line-drawings):** label *Perihilar (sclerosis at vascular pole), Tip lesion (consolidation at tubular pole), Collapsing (capillary collapse + podocyte hyperplasia), Cellular (endocapillary hypercellularity), NOS*.

Clinical / Diagnostic significance

- ▶ A **deep cortico-medullary biopsy** is mandatory — superficial sampling misses segmental lesions and causes mislabelling as MCD; steroid-resistant “MCD” on repeat biopsy is often FSGS.
- ▶ **Distinguishing primary from secondary FSGS is therapeutically decisive:** primary = full nephrosis + diffuse effacement → immunosuppress; secondary = sub-nephrotic + preserved albumin + segmental effacement → treat the cause, avoid steroids.
- ▶ **APOL1 genotyping** identifies high-risk African-ancestry patients (collapsing/HIV-associated disease) and informs transplant donor selection.
- ▶ **Remission of proteinuria** is the key modifiable determinant of long-term renal survival; **collapsing variant** flags aggressive disease and should prompt HIV testing.

High-yield exam pointers

- ▶ FSGS = podocytopathy; proteinuria is the hallmark; commonest cause of primary glomerular ESKD in the US.
- ▶ **Five Columbia variants:** NOS (commonest), Perihilar, **Tip (best prognosis, steroid-responsive)**, Cellular, **Collapsing (worst, HIV/African-American, APOL1)**.
- ▶ **IF:** segmental IgM + C3 (trapped, non-pathogenic); **EM:** foot-process effacement (diffuse in primary, segmental in secondary).

- ▶ **NPHS2/podocin** = commonest genetic cause of **steroid-resistant nephrotic syndrome**; key genes — *NPHS1*, *ACTN4*, *TRPC6*, *INF2*, *WT1*.
- ▶ **APOL1 G1/G2 alleles** → ↑ FSGS & HIV-associated collapsing FSGS in African ancestry.
- ▶ **Treatment:** RAAS blockade + SGLT2i for all; **prednisone 1 mg/kg/day** for primary nephrotic FSGS; CNI/rituximab/MMF for resistant disease; **no immunosuppression for secondary/genetic**.
- ▶ **Prognosis:** ~50% reach ESKD in 10 years; **remission of proteinuria = best prognostic sign**; rarely remits spontaneously.
- ▶ **Recurr in ~30% of kidney transplants** (primary > secondary); recurrent disease may respond to plasmapheresis.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Glomerular Diseases” (FSGS pattern of nephrotic syndrome; Table 326-4 causes; Columbia variants; APOL1; treatment).
- ▶ **Brenner & Rector's The Kidney** — “Primary Glomerular Disease” (Box 31.6 classification, Columbia variants, gene table including *NPHS1/NPHS2/ACTN4/TRPC6/INF2*, suPAR & permeability-factor pathogenesis, GDCN/Columbia outcome data, steroid/cyclosporine/MMF/rituximab trial evidence) and “Glomerular Cell Biology and Podocytopathies” for podocyte mechanisms.
- ▶ **CMDT 2026** — “Kidney Disease” (Nephrotic Spectrum: Focal Segmental Glomerulosclerosis) for current management (RAAS blockade, SGLT2i, prednisone 1 mg/kg/day 4–16 weeks, secondary/APOL1 immunosuppression caveats, transplant recurrence).



Goodpasture's syndrome

Asked in: Paper III Dec 2023 · Paper III Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Goodpasture's syndrome is the **pulmonary-renal form of anti-glomerular basement membrane (anti-GBM) disease**, classically defined by crescentic glomerulonephritis, pulmonary hemorrhage, and circulating or tissue-bound anti-GBM antibodies. Anti-GBM disease may be renal-limited; the term Goodpasture's syndrome is best reserved for cases with both glomerulonephritis and alveolar hemorrhage. It is a nephrology emergency because renal function can fall from normal to dialysis-requiring kidney failure within days to weeks, while pulmonary hemorrhage can cause fatal hypoxemia or airway flooding.

Etiopathogenesis and epidemiology

- ▶ The autoantibody is directed mainly against the **noncollagenous NC1 domain of the alpha-3 chain of type IV collagen** in the specialized alpha-3/alpha-4/alpha-5 collagen IV network of the GBM and alveolar capillary basement membrane.
- ▶ Harrison and Brenner describe anti-GBM disease as an autoimmune **conformeropathy**: normally sequestered epitopes in the collagen IV NC1 hexamer become exposed after infection, smoking, oxidant injury, or solvent exposure.
- ▶ The kidney and lung are selectively involved because the target antigen is concentrated in the **glomerular basement membrane and alveolar capillary basement membrane**.
- ▶ Lung hemorrhage usually requires an additional pulmonary injury that increases antibody access to alveolar basement membrane; important associations include **cigarette smoking**, pulmonary infection, hydrocarbon solvents, cocaine inhalation, metallic dust, and d-penicillamine. CMDT also lists alemtuzumab exposure.
- ▶ Anti-GBM glomerulonephritis accounts for about **10-20% of acute rapidly progressive glomerulonephritis (RPGN)**. Brenner describes anti-GBM disease as rare, about **1-2% of all glomerular diseases** in most estimates.
- ▶ Age distribution is **bimodal**: young men in the third decade often present with full pulmonary-renal disease, while older adults in the sixth to seventh decades more often have renal-limited disease and less sex specificity.
- ▶ Genetic predisposition is suggested by HLA associations; CMDT notes **HLA-DR2 and HLA-B7** as predisposing antigens.

Clinical presentation

- ▶ **True Goodpasture triad**: proliferative/crescentic glomerulonephritis + pulmonary hemorrhage + anti-GBM antibodies.
- ▶ Pulmonary hemorrhage may **precede, coincide with, or follow** renal disease. Symptoms include cough, dyspnea, hemoptysis, fever, sudden fall in hemoglobin, hypoxemia, and diffuse pulmonary infiltrates. Hemoptysis may be mild or absent despite diffuse alveolar hemorrhage.
- ▶ Renal disease is usually **acute nephritic syndrome or RPGN**: microscopic hematuria, dysmorphic RBCs, red cell casts, subnephrotic proteinuria, edema, hypertension, oliguria, and rapidly rising creatinine.
- ▶ Proteinuria is common but usually **not nephrotic range**; severe nephrotic-range proteinuria should widen the differential diagnosis or suggest overlap pathology.
- ▶ Constitutional symptoms may occur: fatigue, malaise, chills, fever, weight loss, nausea/vomiting, and arthralgia. Purpura, arthritis, or other systemic vasculitic features suggest **double-positive anti-GBM plus ANCA disease** rather than isolated Goodpasture's syndrome.

- ▶ Pulmonary-renal syndrome differential includes granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, SLE, cryoglobulinemia, IgA vasculitis, infection-related GN, and anticoagulant or coagulopathy-related alveolar hemorrhage.

Investigations and diagnosis

- ▶ Treat suspected disease as urgent. Send **CBC**, urea/creatinine/electrolytes, urinalysis with microscopy, urine protein quantification, ABG if hypoxemic, chest radiograph or HRCT, anti-GBM antibody, ANCA with MPO/PR3 specificity, ANA/anti-dsDNA, C3/C4, hepatitis/HIV tests where indicated, and coagulation profile.
- ▶ Urine microscopy shows **glomerular hematuria** with dysmorphic RBCs and red cell casts; creatinine may rise over days to weeks.
- ▶ Serology: circulating **anti-GBM antibodies are present in >90%** of typical cases; complement levels are usually **normal**. A minority are also ANCA-positive, most often MPO-ANCA.
- ▶ Chest imaging shows bilateral or patchy alveolar infiltrates when pulmonary hemorrhage is present, but imaging is not specific.
- ▶ Bronchoscopy is useful when the pulmonary diagnosis is uncertain; **sequential BAL aliquots becoming progressively bloodier** support diffuse alveolar hemorrhage, and hemosiderin-laden macrophages support recent or recurrent bleeding.
- ▶ **Kidney biopsy is the diagnostic and prognostic test** when feasible, but patients with pulmonary hemorrhage and strong clinical suspicion should receive emergency treatment before confirmation.

Pathology and diagnostic contrasts

Feature	Goodpasture / anti-GBM disease	ANCA-associated vasculitis	Immune-complex GN / SLE
Key serology	Anti-GBM antibody high; complement normal	MPO-ANCA or PR3-ANCA; complement usually normal	ANA/anti-dsDNA, cryoglobulins or infection markers; complement often low
Light microscopy	Focal necrosis early; commonly diffuse crescentic GN with circumferential crescents	Necrotizing crescentic GN	Endocapillary proliferation; immune-complex patterns
Immunofluorescence	Intense diffuse linear IgG along GBM; often fine C3; C1q usually absent	Pauci-immune or negative	Granular deposits; lupus may show “full house”
Electron microscopy	Usually no immune-type electron-dense	No immune deposits	Electron-dense deposits by location

Feature	Goodpasture / anti-GBM disease	ANCA-associated vasculitis	Immune-complex GN / SLE
	deposits; GBM gaps may be seen		
Relapse tendency	Rare once quiescent unless double-positive	Common, especially PR3/GPA	Depends on underlying disease

- ▶ The diagnostic biopsy phrase to write is: **crescentic necrotizing glomerulonephritis with linear IgG staining along the GBM.**
- ▶ Brenner notes that the common biopsy picture is diffuse crescentic GN involving more than half of glomeruli, with compressed tufts, focal necrosis, GBM breaks, and interstitial inflammation; chronic biopsies show glomerulosclerosis, tubular atrophy, and interstitial fibrosis.
- ▶ Similar **linear IgG deposition** can occur along alveolar capillary walls in the lung.

Management

- ▶ **Admit immediately;** ICU care is needed for hypoxemia, massive hemoptysis, respiratory failure, severe AKI, oliguria, or dialysis requirement.
- ▶ Supportive care: oxygen, ventilatory support if needed, transfuse for severe anemia, stop smoking/solvent exposure, treat intercurrent infection, manage fluid overload, control blood pressure, avoid unnecessary anticoagulation during active bleeding, and start dialysis for standard indications.
- ▶ Disease-specific therapy has three simultaneous goals: **remove circulating antibody, stop new antibody production, and control inflammatory injury.**
- ▶ **Therapeutic plasma exchange (plasmapheresis):** start urgently; daily exchanges are used in severe disease, often for **8-10 treatments** or up to about **2 weeks**, guided by pulmonary bleeding, renal course, and fall in anti-GBM titers. It is especially important for pulmonary hemorrhage because lung bleeding may respond dramatically.
- ▶ **Glucocorticoids:** IV pulse methylprednisolone may be used for several days in severe disease, followed by high-dose oral prednisone; Brenner gives oral prednisone **1 mg/kg/day** or IV methylprednisolone **30 mg/kg/day up to 1000 mg/day** as typical steroid dosing.
- ▶ **Cyclophosphamide:** used with steroids to suppress antibody formation; Brenner gives **2 mg/kg/day** as a typical oral dose. Adjust for renal function, monitor CBC, infection risk, hemorrhagic cystitis, fertility risk, and cumulative toxicity.
- ▶ Continue immunosuppression until anti-GBM antibodies are negative and disease is controlled; Brenner notes that immunosuppression is usually continued for about **6 months** with tapering. Azathioprine may be used as less toxic maintenance in selected patients after antibody disappearance.

- ▶ **Rituximab** has limited evidence and is reserved for refractory disease or cyclophosphamide-intolerant patients; it should not replace urgent plasma exchange in life-threatening pulmonary hemorrhage.

Prognosis and follow-up

- ▶ Outcome depends mainly on **renal status at presentation** and speed of treatment. Lung hemorrhage often improves with plasma exchange, whereas renal recovery is poor if irreversible crescentic scarring is already established.
- ▶ Poor renal prognostic markers: oliguria, dialysis requirement at presentation, serum creatinine around **>5-6 mg/dL** or severe renal failure, **>50% crescents**, advanced interstitial fibrosis/tubular atrophy, and delayed therapy.
- ▶ Untreated disease progresses to uremia and may be fatal from pulmonary hemorrhage or renal failure; modern rapid diagnosis, dialysis, ventilatory support, plasma exchange, and immunosuppression have markedly improved survival.
- ▶ Anti-GBM disease is typically a **one-shot disease** with rare relapse once antibodies disappear; persistent or recurrent disease should prompt evaluation for ANCA double positivity, infection triggers, and ongoing exposure.
- ▶ Follow anti-GBM titers until negative, serial creatinine/eGFR, urine sediment/proteinuria, hemoglobin, chest symptoms, and cyclophosphamide toxicity. ANCA-positive patients require longer relapse surveillance.
- ▶ Kidney transplantation is considered only after the acute illness is quiescent and anti-GBM antibodies are absent; recurrence in the allograft is uncommon when transplantation is delayed until seronegativity.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pulmonary-renal syndrome flow diagram:** trigger (infection/smoking/solvent) -> exposed alpha-3 NC1 collagen IV epitope -> circulating anti-GBM IgG -> kidney GBM injury (hematuria, RBC casts, RPGN) + alveolar capillary injury (diffuse alveolar hemorrhage, hemoptysis, hypoxemia).
- ▶ **Renal biopsy sketch:** glomerular tuft, Bowman space, circumferential cellular crescent, compressed tuft, segmental necrosis, GBM break, and a side panel labelled “linear IgG on immunofluorescence”.

Clinical / Diagnostic significance

- ▶ In any patient with **hemoptysis plus hematuria or AKI**, send anti-GBM antibody and ANCA immediately; do not wait for classical hemoptysis because diffuse alveolar hemorrhage may be occult.

- ▶ Normal complement with RPGN narrows the diagnosis toward **anti-GBM disease** or **ANCA vasculitis** rather than lupus, cryoglobulinemia, or postinfectious GN.
- ▶ A positive anti-GBM antibody is highly useful, but biopsy remains important for prognosis because the percentage of crescents and fibrosis determines renal salvageability.
- ▶ Plasma exchange is controversial in isolated ANCA vasculitis but is standard in Goodpasture's syndrome and in ANCA disease with coexistent anti-GBM antibodies.
- ▶ In examination answers, separate **anti-GBM disease** from **Goodpasture's syndrome**: renal-limited anti-GBM GN is not true Goodpasture unless pulmonary hemorrhage is present.

High-yield exam pointers

- ▶ Write the triad: **crescentic GN + pulmonary hemorrhage + anti-GBM antibodies**.
- ▶ Target antigen: **NC1 domain of alpha-3 type IV collagen** in GBM and alveolar basement membrane.
- ▶ Risk/exposure clues: **young male smoker**, recent respiratory infection, hydrocarbon solvent exposure, and pulmonary-renal presentation.
- ▶ Urine: dysmorphic RBCs, **RBC casts**, subnephrotic proteinuria, rapidly rising creatinine.
- ▶ Complement is usually **normal**; anti-GBM antibody is positive in **>90%**.
- ▶ Biopsy hallmark: **linear IgG along GBM** with crescentic necrotizing GN.
- ▶ Treatment must be urgent: **plasmapheresis + high-dose corticosteroid + cyclophosphamide**.
- ▶ Poor renal prognosis: dialysis at presentation, oliguria, creatinine >5-6 mg/dL, >50% crescents, and interstitial fibrosis.
- ▶ Relapse is uncommon after antibody clearance; relapse suggests double-positive ANCA disease or renewed exposure.

SOURCE & COVERAGE

Harrison 22e — “Glomerular Diseases”, “Hemoptysis”, “Bronchoscopy”; Brenner & Rector's The Kidney — “Secondary Glomerular Disease”, “Primary Glomerular Disease”, “Treatment of Glomerulonephritis”; CMTD 2026 — “Kidney Disease”, “Pulmonary Disorders”.



IgA Nephropathy

Asked in: Paper IV Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — IgA nephropathy (IgAN, *Berger disease*) is an immune-complex glomerulonephritis defined by the **dominant or codominant deposition of IgA in the glomerular mesangium**, accompanied by mesangial proliferation. First described by *Berger and Hinglais* in the late 1960s, it is the **commonest primary glomerulonephritis worldwide**, classically presenting as

synpharyngitic macroscopic haematuria in a young male. Once thought benign, it is now recognised that up to 25–40% of patients progress to end-stage kidney disease (ESKD).

Epidemiology

- ▶ **Most common primary glomerular disease worldwide**, especially in **Asia/Pacific Rim (30–45% of glomerular biopsies)**; 20% in southern Europe, ~10% in northern Europe/North America. Higher Asian rates partly reflect routine school urinalysis prompting biopsy of asymptomatic haematuria.
- ▶ Peak incidence in the **2nd–3rd decades**; ~80% are aged 16–35 years at biopsy. Uncommon under 10 years.
- ▶ Strong **male preponderance** (M:F ratio ~2:1, quoted up to 6:1). Rare in African-Americans; common in Native American Zuni and Navajo tribes.
- ▶ Mostly **sporadic**; familial clustering in 4–14%, usually autosomal dominant with incomplete penetrance. *IGAN1* locus on chromosome **6q22-23**; GWAS implicate the **MHC region (6p21)**, *DEFA*, *TNFSF13*, *CFH/CFHR*, and *C1GALT1 / C1GALT1C1 (Cosmc)* glycosylation genes — pointing to innate/adaptive immunity and host–intestinal mucosal interactions.

Pathogenesis — the “four-hit” model

The central abnormality is *not* a quantitative excess of IgA but a **qualitative defect in O-glycosylation of the hinge region of polymeric IgA1**:

- ▶ **Hit 1 — Galactose-deficient IgA1 (Gd-IgA1)**: the 18-amino-acid, proline/serine/threonine-rich hinge region of IgA1 (absent in IgA2) carries O-linked sugars; premature sialylation and deficient β -1,3-galactosyltransferase (with reduced activity of its chaperone *Cosmc*) leave terminal **N-acetylgalactosamine exposed**, generating a neoepitope. This is an inherited trait (also raised in at-risk relatives).
- ▶ **Hit 2 — Anti-glycan autoantibodies**: circulating **IgG (and IgA1) autoantibodies** recognise the exposed Gd-IgA1 neoepitope.
- ▶ **Hit 3 — Immune-complex formation**: Gd-IgA1 and autoantibody form **circulating immune complexes** that escape hepatic clearance (defective asialoglycoprotein-receptor uptake) and via the asialoglycoprotein pathway.
- ▶ **Hit 4 — Mesangial deposition & injury**: complexes deposit in the mesangium (possibly via a transferrin receptor), activating **complement through the alternative and mannose-binding lectin pathways** (note: classical C1q pathway is *spared*), driving mesangial proliferation, cytokine/growth-factor release and secondary podocyte injury.
- ▶ The same Gd-IgA1 mechanism underlies **IgA vasculitis** (formerly Henoch-Schönlein purpura), the systemic counterpart of IgAN.

Pathology (kidney biopsy is mandatory for diagnosis)

Modality	Characteristic findings
Immunofluorescence (diagnostic)	Dominant/codominant mesangial IgA (100% by definition, mean ~3+), with C3 in nearly all; often IgM (~84%) and IgG (~62%) at low intensity. C1q rare/weak . Distinctively, λ (lambda) light chain staining > κ (kappa) . Deposits are <i>J-chain-containing polymeric IgA1</i> .
Light microscopy	Spectrum from normal glomeruli → focal/diffuse mesangioproliferative GN (commonest) → proliferative/necrotising → crescentic → sclerosing GN. Mesangial matrix expansion + hypercellularity.
Electron microscopy	Mesangial (paramesangial) electron-dense deposits , beneath the perimesangial basement membrane; foot-process effacement when proteinuria is heavy.

- ▶ *Oxford classification (MEST-C score)* — the validated histological prognostic tool reported on every IgAN biopsy:
 - **M — Mesangial hypercellularity:** $\leq 0.5 = 0$, $> 0.5 = 1$
 - **E — Endocapillary hypercellularity:** absent = 0, present = 1
 - **S — Segmental glomerulosclerosis:** absent = 0, present = 1
 - **T — Tubular atrophy / interstitial fibrosis:** $\leq 25\% = 0$, $26-50\% = 1$, $> 50\% = 2$
 - **C — Crescents** (added 2016/17): none = 0, in $< 25\% = 1$, $\geq 25\% = 2$

Clinical features and natural history

- ▶ **Synpharyngitic macroscopic haematuria** — recurrent gross haematuria appearing **1–2 days** after (concurrent with) an **upper-respiratory or GI mucosal infection** in 40–50% at onset; this short latency distinguishes it from the *longer 1–3 week latent period of post-streptococcal GN*. May be accompanied by loin pain/dysuria.
- ▶ **Asymptomatic microscopic haematuria ± proteinuria** (30–40%), frequently with hypertension — IgAN is the commonest cause of haematuria in hypertensive Caucasians.
- ▶ Less common: **nephrotic syndrome** (may signify coexistent minimal-change disease), malignant hypertension ($< 5\%$), and **RPGN/crescentic disease** with AKI ($< 10\%$).
- ▶ AKI accompanying an episode of gross haematuria is usually due to **tubular injury from haem pigment**, not true crescents, and typically recovers fully with a good long-term prognosis.
- ▶ Course is variable: spontaneous remission in some; **1–2% per year progress to ESKD**, with ~25–40% reaching ESKD over 20–25 years.

Laboratory and diagnosis

- ▶ **No diagnostic serology; serum C3 and C4 are characteristically normal** (a key contrast to post-streptococcal GN, lupus nephritis, MPGN where complement is low).
- ▶ **Serum IgA raised in only 20–50%** — neither sensitive nor specific; serum/urinary Gd-IgA1 assays remain investigational.
- ▶ Urinalysis: **dysmorphic RBCs / RBC casts**; proteinuria usually <1 g/day (heavier with worse lesions).
- ▶ Skin biopsy IgA deposits are not reliable — **kidney biopsy is required to confirm**.

Treatment

- ▶ **Optimised supportive care is the cornerstone (KDIGO)**: maximally-tolerated RAAS blockade (ACE inhibitor or ARB) titrated to **proteinuria <0.5–1 g/day** and BP control (~120/80 mmHg), plus dietary sodium restriction; treat for ~90 days before escalating. High-dose ARB (e.g. losartan 200 mg/day) is more antiproteinuric than standard dose.
- ▶ **SGLT2 inhibitors** (e.g. dapagliflozin) are now standard add-on in proteinuric CKD for renoprotection.
- ▶ **Sparsentan** — a dual endothelin-A and angiotensin-II receptor antagonist (PROTECT trial) — gives superior proteinuria reduction versus irbesartan; cost-limited.
- ▶ **Targeted-release (enteric) budesonide** (NeflgArd/NEFIGAN trials) targets gut mucosal (Peyer-patch) IgA production, reducing proteinuria with fewer systemic steroid effects.
- ▶ **Systemic corticosteroids** for persistent proteinuria >1 g/day despite supportive care, in patients with preserved GFR — efficacy weighed against infection risk (the TESTING trial was paused for excess serious infections; STOP-IgAN showed steroids cut proteinuria but did not preserve GFR).
- ▶ **Iptacopan**, an oral factor B inhibitor of the alternative complement pathway, reduces proteinuria without raising infection risk.
- ▶ **Crescentic/RPGN IgAN**: treat as for other crescentic GN — **pulse methylprednisolone + cyclophosphamide ± plasmapheresis**, then azathioprine maintenance.
- ▶ **Adjuncts of uncertain/limited benefit**: omega-3 fish oil; tonsillectomy (popular in Japan, *not* validated in the European VALIGA cohort); MMF (benefit largely in Asian cohorts only).
- ▶ **Transplantation** is excellent for ESKD, but **histological recurrence develops in ~30% by 5–10 years**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Glomerular schematic (immunofluorescence)**: draw a glomerular lobule and label — *capillary loop, glomerular basement membrane (GBM), podocyte with foot processes, mesangial cell + matrix, granular mesangial IgA + C3 deposits (dominant/codominant), Bowman's capsule*. Caption: “Mesangial polymeric IgA1 deposition.”

- ▶ **Four-hit pathogenesis flow diagram:** Hit 1 *Galactose-deficient IgA1 (Gd-IgA1)* → Hit 2 *anti-glycan IgG/IgA autoantibody* → Hit 3 *circulating immune complex* → Hit 4 *mesangial deposition* → *alternative + lectin complement activation* → *mesangial proliferation & podocyte injury*.

Clinical / Diagnostic significance

- ▶ **Distinguish from post-streptococcal GN:** IgAN = short/synpharyngitic latency, **normal complement**, recurrent gross haematuria; PSGN = 1–3 week latency, **low C3**, single episode.
- ▶ **Distinguish from IgA vasculitis (HSP):** identical renal histology but with systemic features — palpable purpura (buttocks/legs), arthralgia, abdominal pain/GI bleed; typically <20 years after infection.
- ▶ **Exclude secondary IgAN:** chronic liver disease/cirrhosis, coeliac disease, HIV, Crohn disease, ankylosing spondylitis, dermatitis herpetiformis, and **IgA-dominant Staphylococcus-associated GN** (mimics post-infectious GN, often in diabetics).
- ▶ **Prognostic markers of progression:** hypertension, **persistent proteinuria >1 g/day** (sustained ≥6 months is the strongest predictor), reduced eGFR at diagnosis, *absence* of macroscopic haematuria, male sex, older age, and high MEST-C score (M, S, T, C lesions).

High-yield exam pointers

- ▶ IgAN = **Berger disease** = commonest primary GN worldwide; mesangial IgA deposition.
- ▶ **Synpharyngitic haematuria** (gross haematuria *with* a URI, 1–2 days) is the hallmark — contrast with post-strep latency.
- ▶ **Serum complement (C3/C4) is NORMAL** — a favourite exam discriminator.
- ▶ IF: **dominant mesangial IgA + C3, $\lambda > \kappa$, C1q absent**; EM: mesangial dense deposits.
- ▶ Pathogenesis = **galactose-deficient IgA1** + anti-glycan IgG, complement via **alternative + lectin** pathways.
- ▶ Prognosis scored by the **Oxford MEST-C** classification; **proteinuria >1 g/day = key adverse marker**.
- ▶ Treatment ladder: RAAS blockade + SGLT2i → sparsentan / TRF-budesonide / corticosteroids → cyclophosphamide for crescentic disease.
- ▶ ESKD in 25–40% over 20–25 years; recurs in ~30% of allografts.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Glomerular Diseases" (IgA nephropathy section).

- **Brenner & Rector's The Kidney** — “Primary Glomerular Disease” (IgA nephropathy: epidemiology, genetics, pathology, MEST-C/Oxford classification, pathogenesis, natural history, treatment trials — STOP-IgAN, TESTING, NEFIGAN, VALIGA).
- **CMDT 2026** — “Kidney Disease” (current management: RAAS blockade, SGLT2 inhibitors, sparsentan/PROTECT, targeted-release budesonide/NeflgArd, iptacopan).



Intrinsic Acute Kidney Injury (intrinsic AKI)

Asked in: Paper IV Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — **Acute kidney injury (AKI)** is an abrupt fall in glomerular filtration over hours to days (within 7 days), with retention of nitrogenous wastes. By **KDIGO**, AKI = a rise in serum creatinine (SCr) ≥ 0.3 mg/dL within 48 h, OR SCr $\geq 1.5 \times$ baseline within 7 days, OR urine output < 0.5 mL/kg/h for > 6 h. The causes are partitioned into **prerenal**, **intrinsic**, and **postrenal**. **Intrinsic AKI** denotes structural damage to the renal parenchyma itself — the tubules, interstitium, glomeruli, or microvasculature — and accounts for up to 50% of all AKI. Its commonest forms are **acute tubular necrosis (ATN)** from sepsis, ischaemia, and nephrotoxins; unlike prerenal azotaemia it is *not* immediately reversible by restoring perfusion.

Classification — Where Intrinsic AKI Sits

Intrinsic AKI is best catalogued **anatomically** by the dominant compartment injured, although overlap is common (e.g. a glomerular lesion can reduce post-glomerular flow and injure tubules).

Compartment	Representative causes	Share of intrinsic AKI
Tubules (ATN)	Ischaemia, sepsis, nephrotoxins (endogenous + exogenous)	~85%
Interstitium	Acute interstitial nephritis (drugs ~70–75%), infection, infiltration	~10–15%
Glomeruli	Acute glomerulonephritis, vasculitis	~5%
Microvasculature	TTP-HUS, DIC, malignant hypertension, scleroderma crisis, atheroemboli	Variable

- ATN is the prototype and the majority of hospitalised intrinsic AKI; prolonged **prerenal** hypoperfusion progresses to ischaemic ATN — the two are a **continuum**.
- Early recognition of glomerular/vasculitic and interstitial causes is critical because they are **treatable** (immunosuppression, plasma exchange, drug withdrawal) and may reverse the AKI.

Etiology of Intrinsic AKI

- **Sepsis-associated AKI** — complicates >50% of severe sepsis; GFR can fall *without overt hypotension*. Mechanisms: generalised arterial vasodilation (inducible NO synthase, cytokines), efferent arteriolar vasodilation early, endothelial injury with microvascular leukocyte adhesion/thrombosis, interstitial oedema, mitochondrial dysfunction, and reactive oxygen species (ROS).
- **Ischaemia-associated AKI** — postoperative (cardiac surgery on bypass, aortic cross-clamp), haemorrhage with hypotension, burns (AKI in 25% with >10% BSA), pancreatitis, abdominal compartment syndrome (intra-abdominal pressure >20 mmHg → renal vein compression). The **S3 segment of the proximal tubule** and the **outer medullary thick ascending limb** are most vulnerable (hypoxic medulla, oxidative metabolism).
- **Nephrotoxin-associated AKI** (high renal perfusion + tubular concentration of solutes):

Agent	Mechanism / clinical clue
Iodinated contrast	Direct tubular toxicity + medullary ischaemia; SCr rises 24–48 h, peaks 3–5 d, resolves ~1 wk; risk ↑ in diabetic CKD, myeloma
Aminoglycosides	Cortical accumulation; non-oliguric AKI after 5–7 d, even at therapeutic levels; hypomagnesaemia
Amphotericin B	Vasoconstriction + membrane pores; polyuria, hypoMg, hypoCa, type 1 (distal) RTA , dose-dependent
Cisplatin / carboplatin	Proximal tubular necrosis/apoptosis; dose-limiting; prevent with hydration
Ifosfamide	Fanconi (type II RTA) , polyuria, hypokalaemia
Acyclovir, methotrexate, indinavir, sulfadiazine	Intratubular crystal obstruction
Calcineurin inhibitors	Dose-dependent vasoconstriction; type 4 RTA
PPIs, NSAIDs, β-lactams, rifampin, checkpoint inhibitors	Acute interstitial nephritis
Endogenous: myoglobin (rhabdomyolysis), haemoglobin	Pigment nephropathy — vasoconstriction, direct toxicity, cast obstruction with Tamm-Horsfall protein in acidic urine
Endogenous: uric acid (tumour lysis), myeloma light chains	Intratubular precipitation/casts; uric acid often >15 mg/dL

- **Glomerular / vascular**: post-streptococcal GN, anti-GBM disease, ANCA vasculitis, lupus nephritis, TTP-HUS, malignant hypertension, scleroderma renal crisis, cholesterol **atheroemboli** (livedo reticularis, eosinophilia, hypocomplementaemia, eosinophiluria).

Pathophysiology of Ischaemic / Septic ATN

The healthy kidney takes **20% of cardiac output** yet the medulla is one of the most hypoxic regions of the body. Injury results from **interacting microvascular and tubular events** (Bonventre):

- ▶ **Microvascular** — sustained pre-glomerular (afferent) vasoconstriction in response to **endothelin, adenosine, angiotensin II, thromboxane A₂, and sympathetic activity**, with reduced vasodilators (NO, PGE₂); enhanced **tubuloglomerular feedback** (injured proximal tubule delivers more solute to the macula densa); leukocyte–endothelial adhesion and congestion of the outer medulla.
- ▶ **Tubular** — ATP depletion → loss of apical brush border, **cytoskeletal (F-actin) breakdown**, and **redistribution of Na⁺/K⁺-ATPase from the basolateral to the apical membrane** (loss of cell polarity → impaired vectorial Na⁺ reabsorption → the **high FeNa** of ATN); loss of tight junctions causes **backleak** of filtrate; sloughed cells + Tamm-Horsfall protein form **muddy-brown granular casts** that cause **intratubular obstruction**; cell death by **apoptosis and necrosis**. Frank necrosis is actually inconspicuous and restricted to the outer medulla — hence “ATN” is partly a misnomer.

Clinical phases (Brenner four-phase model; CMDT groups them as three):

- ▶ **Initiation** — the ischaemic/toxic insult; GFR falls, potentially reversible.
- ▶ **Extension** — continued hypoxia + inflammation + endothelial injury in the corticomedullary junction.
- ▶ **Maintenance** — established injury; GFR nadir; oliguric or non-oliguric; lasts ~1–3 weeks. Complications (hyperkalaemia, acidosis, volume overload, uraemia) cluster here.
- ▶ **Recovery** — tubular regeneration; often a **polyuric/diuretic phase** from osmotic diuresis of retained solutes and delayed tubular reabsorption.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Anatomic classification box-diagram** (Fig. 321-1/321-3 style): three columns **Prerenal | Intrinsic | Postrenal**; under Intrinsic, four labelled boxes — **Tubules** (ATN — ischaemic, septic, toxic), **Interstitium** (allergic AIN), **Glomeruli/Small vessels** (GN, vasculitis, TTP-HUS), **Large vessels** (renal artery/vein). Label endogenous vs exogenous nephrotoxins.
- ▶ **Pathophysiology of ischaemic ATN** (Fig. 321-4): two interacting arms — **Microvascular** (label: vasoconstriction — endothelin, angiotensin II, thromboxane A₂; ↓NO/PGE₂; leukocyte–endothelial adhesion) and **Tubular** (label: ATP depletion, cytoskeletal breakdown, loss of polarity / Na⁺-K⁺-ATPase mislocation, apoptosis & necrosis, desquamation → **tubular obstruction + backleak**) → both converge on ↓ GFR.

Clinical / Diagnostic significance

- ▶ Differentiate prerenal vs intrinsic (ATN) — the cornerstone diagnostic step:

Index	Prerenal azotaemia	Intrinsic ATN
BUN : creatinine	>20 : 1	<20 : 1
Urine Na ⁺ (mmol/L)	<20	>20
FeNa (oliguric)	<1%	>1% (often >2%)
Urine osmolality (mOsm/kg)	>500	250–300
Sediment	Bland / hyaline casts	Muddy-brown granular & RTE-cell casts

- ▶ **Caveats:** FeNa may be <1% in sepsis (early), contrast, rhabdomyolysis, and pigment nephropathy, and is uninterpretable on diuretics or in CKD. **Fractional excretion of urea (FeUrea <35%)** helps when diuretics are used.
- ▶ **Urine sediment as a map** — RBC casts → GN/vasculitis; WBC casts → interstitial nephritis/pyelonephritis; oxalate crystals → ethylene glycol; uric acid crystals → tumour lysis.
- ▶ **Novel biomarkers** of tubular injury (rise earlier than SCr): **NGAL, KIM-1, suPAR**, and the FDA-cleared cell-cycle-arrest pair **TIMP-2 × IGFBP7** (NephroCheck) for risk-stratifying critically ill patients. The **furosemide stress test** (1.0–1.5 mg/kg; urine <200 mL over 2 h) predicts progression and need for dialysis.
- ▶ **Complications:** hyperkalaemia (worst in rhabdomyolysis/haemolysis/tumour lysis), high-anion-gap metabolic acidosis, hyperphosphataemia/hypocalcaemia, volume overload/pulmonary oedema, uraemia, anaemia and uraemic platelet dysfunction.
- ▶ **Management:** optimise haemodynamics (euvolaemia, **MAP >65 mmHg**, crystalloids over starch), **stop nephrotoxins**, renally dose drugs, treat hyperkalaemia/acidosis, nutrition **20–30 kcal/kg/day**. No proven specific drug reverses established ATN — **dopamine, fenoldopam, ANP, diuretics do not improve recovery**; diuretics only for volume control. Cause-specific: rhabdomyolysis → aggressive IV fluids (up to ~10 L/day) ± alkalinisation; tumour lysis → fluids + **rasburicase/allopurinol**; vasculitis/GN → immunosuppression ± plasma exchange; scleroderma crisis → **ACE inhibitors**; TTP → plasma exchange; atypical HUS → complement blockade.
- ▶ **Dialysis** — “**AEIOU**”: Acidosis, Electrolyte (refractory hyperkalaemia), Intoxications, Overload (volume) unresponsive to diuretics, Uraemic complications (encephalopathy, pericarditis, bleeding). Earlier vs later initiation shows no survival benefit (STARRT-AKI).

High-yield exam pointers

- ▶ **Intrinsic AKI ≈ 50% of AKI; ATN = 85% of intrinsic AKI; AIN 10–15%; GN ~5%.**
- ▶ **ATN triad of causes = ischaemia, sepsis, nephrotoxins**; prerenal azotaemia is the precursor of ischaemic ATN.
- ▶ **S3 proximal tubule + outer-medullary TAL** are the most ischaemia-vulnerable nephron segments.

- ▶ **High FeNa in ATN** is explained by **Na⁺/K⁺-ATPase mislocation** to the apical membrane + backleak.
- ▶ **Muddy-brown granular casts + RTE-cell casts** = ATN signature; their presence is highly predictive but absent in >20%.
- ▶ **Aminoglycoside** = non-oliguric AKI at day 5–7 with **hypomagnesaemia**; **contrast** = SCr peak day 3–5; **amphotericin** = distal RTA + hypoMg/hypoCa.
- ▶ Phases of ATN = **initiation** → **extension** → **maintenance** (1–3 wk) → **recovery** (polyuric).
- ▶ **Mortality** of AKI in hospital 20–50%, up to 70% in ICU patients requiring dialysis; AKI predisposes to subsequent CKD.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Acute Kidney Injury” (KDIGO definition/staging, prerenal–intrinsic–postrenal classification, sepsis/ischaemia/nephrotoxin mechanisms, urine sediment & FeNa, biomarkers, management, dialysis).
- ▶ **Brenner & Rector's The Kidney** — “Pathophysiology of Acute Kidney Injury” (S1/S2/S3 segment injury, cytoskeletal/F-actin breakdown, Na⁺-K⁺-ATPase redistribution → high FeNa, backleak, muddy-brown cast formation, extension phase) and “Prevention and Management of Acute Kidney Injury”.
- ▶ **CMDT 2026** — “Kidney Disease / Acute Tubular Necrosis” (urinary indices table, ATN clinical phases, “AEIOU” dialysis indications, contrast-AKI prophylaxis, prognosis).



Lupus nephritis: pathological classification and therapy for each class

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Lupus nephritis (LN)* is immune-complex-mediated glomerular injury complicating systemic lupus erythematosus (SLE), arising from glomerular deposition of nucleosome/anti-dsDNA immune complexes with complement activation. It is clinically silent to nephrotic/nephritic in presentation and is the single most important determinant of morbidity and mortality in SLE. The renal biopsy is central: the **2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification** (minor revision 2018) defines six histological classes that drive prognosis and class-specific therapy. Renal biopsy is recommended when urine protein:creatinine ratio (UPCr) exceeds ~0.5 g/g, to confirm active disease and assign class plus activity/chronicity.

Pathogenesis (basis of the lesions)

- ▶ Loss of self-tolerance → polyclonal B-cell activation and autoantibodies against nucleosomes, **dsDNA**, histones; high-avidity complement-fixing **anti-dsDNA IgG** correlates best with nephritis.
- ▶ Circulating and *in situ* immune complexes deposit in mesangium and capillary walls → **complement activation** (low C3/C4), leukocyte Fc-receptor engagement, cytokine release and proliferation.
- ▶ Deposit location dictates the histological pattern: **mesangial** (class I–II), **subendothelial** (class III–IV, inflammatory/proliferative), **subepithelial** (class V, membranous, non-inflammatory).
- ▶ Adjuncts to injury: neutrophil extracellular traps (NETs), type-1 interferon, APOL1 risk alleles (collapsing FSGS in patients of African descent), antiphospholipid antibody–related thrombotic microangiopathy, ANCA-associated necrotising lesions, and lupus podocytopathy.

ISN/RPS classification (2003; 2018 revision)

Class	Name	Light microscopy	Deposits (IF/EM)	Typical clinical picture
I	Minimal mesangial	Normal glomeruli	Mesangial deposits only (IF/EM)	No clinical renal disease
II	Mesangial proliferative	Mesangial hypercellularity (>3 cells/mesangial area)	Mesangial deposits	Microhaematuria/mild proteinuria <1 g/d; inactive sediment
III	Focal LN (<50% glomeruli)	Focal segmental/global endo- and/or extracapillary GN	Mesangial + segmental subendothelial	Active sediment, proteinuria >1 g/d, ~25–33% nephrotic
IV	Diffuse LN (≥50% glomeruli)	Diffuse endo-/extracapillary GN; wire loops, crescents	Mesangial + extensive subendothelial	Most active; active sediment, RBC casts, low C3/C4, high anti-dsDNA, ~50% nephrotic, HTN, ↓GFR
V	Membranous LN	GBM thickening, subepithelial “spikes”	Subepithelial (granular) ± mesangial	Nephrotic syndrome; ~40% subnephrotic; thrombotic risk
VI	Advanced sclerosing	≥90% globally sclerosed , no residual activity	Scant/residual	“Burned-out”; HTN, ↓GFR; serologies normalise

- ▶ **Class III & IV subscripts:** (A) active, (A/C) active + chronic, (C) chronic — guide reversibility. Class IV was sub-divided into IV-S (segmental) and IV-G (global) in 2003; the **2018 revision eliminated the S/G split**.
- ▶ **Combined classes:** Class V coexists with III or IV in many biopsies and **both are diagnosed** (e.g., III+V, IV+V) — these behave and are treated as proliferative disease.
- ▶ **2018 revision also:** redefined mesangial hypercellularity (>3 cells), clarified cellular/fibrocellular crescents, replaced “endocapillary proliferation” with “**endocapillary hypercellularity**”, and applied **modified NIH activity/chronicity indices to all classes**.

Diagnostic morphology and biopsy scoring

- ▶ **Light-microscopy clues:** *wire-loop* lesions = subendothelial deposits thickening the capillary wall; *hyaline thrombi* = large intraluminal deposits; *hematoxylin bodies* = swollen basophilic nuclear material (ambient ANA binding); fibrinoid necrosis, karyorrhexis and cellular crescents in active lesions.
- ▶ **Immunofluorescence:** IgG almost universal; “**full-house**” staining (IgG + IgA + IgM + C1q + C3) is highly suggestive of LN.
- ▶ **Electron microscopy:** electron-dense granular deposits; *fingerprint* substructure; **tubuloreticular inclusions** (“interferon footprints”) in endothelial cells.
- ▶ **Modified NIH Activity Index (0–24):** endocapillary hypercellularity, neutrophil infiltration/karyorrhexis, wire-loop deposits, fibrinoid necrosis, cellular/fibrocellular crescents, interstitial inflammation — *crescents and fibrinoid necrosis are double-weighted* (reversible disease).
- ▶ **Chronicity Index (0–12):** global/segmental glomerulosclerosis, fibrous crescents, tubular atrophy, interstitial fibrosis (irreversible). Combined **activity >7 plus chronicity >3** predicts poor long-term renal outcome.

General (adjunctive) measures for ALL classes

- ▶ **Hydroxychloroquine** for every SLE/LN patient (reduces flares, improves renal outcomes, lowers thrombosis).
- ▶ **RAAS blockade** — ACE inhibitor or ARB in all class III, IV and V disease to cut proteinuria and intraglomerular pressure; consider **SGLT2 inhibitor** when eGFR is reduced.
- ▶ BP target <130/80 mmHg, statin for dyslipidaemia, calcium/vitamin D ± bisphosphonate for steroid-induced osteoporosis, vaccination, smoking cessation.
- ▶ **Antiphospholipid (APS) nephropathy** on biopsy / thrombotic event → anticoagulate with vitamin K antagonist (warfarin), not a DOAC.
- ▶ Treatment targets (EULAR): **≥25% UPCr fall by 3 months; ≥50% fall to <3 g/d by 6 months; UPCr <0.5–0.7 g/d by 12–24 months** with eGFR within 10% of baseline.

Class-specific therapy

- ▶ **Class I & II (minimal mesangial / mesangial proliferative):** excellent prognosis — **no kidney-directed immunosuppression**; treat extra-renal lupus and use RAAS blockade. Rising proteinuria/active sediment heralds transformation → **repeat biopsy**.
- ▶ **Class III (mild focal, no necrosis/crescents):** good prognosis — short course of high-dose corticosteroids ± a brief immunosuppressive course. With many affected glomeruli, necrotising features or crescents → **treat as class IV**.
- ▶ **Class III & IV proliferative (± class V) — induction + maintenance:**
 - **Induction:** glucocorticoids (often IV **methylprednisolone 125–1000 mg/day × 1–3 days** then oral prednisone, rapidly tapered) **PLUS** either:
 - **Mycophenolate mofetil (MMF) 2–3 g/day** (preferred in Black/Hispanic patients), or
 - **Cyclophosphamide** — *Euro-Lupus low-dose 500 mg IV every 2 weeks × 6 doses*, or *NIH high-dose 0.5–1 g/m² IV monthly × 6*; high-dose/extended pulses favoured for crescentic/rapidly progressive GN.
 - **Modern triple regimens** (steroid-sparing, RCT-supported): **voclosporin + MMF + GC**, or **belimumab + (MMF or low-dose cyclophosphamide) + GC**. ACR guidance: add a calcineurin inhibitor (voclosporin/tacrolimus) to MMF when proteinuria ≥3 g/day, or add belimumab to MMF/CYC when proteinuria is lower.
 - **Maintenance:** MMF or azathioprine — MMF superior for relapse-free survival (ALMS); azathioprine preferred in pregnancy; total immunosuppression ≥36 months (KDIGO).
 - **Refractory disease:** rituximab (anti-CD20); obinutuzumab is emerging.
- ▶ **Class V (pure membranous):** RAAS blockade, antiproteinuric and statin therapy, individualised anticoagulation for nephrotic-range disease. **Immunosuppression** (CNI, MMF, cyclophosphamide or azathioprine + corticosteroids) reserved for significant/nephrotic proteinuria or progressive disease. **V combined with III/IV is treated as proliferative LN**.
- ▶ **Class VI (advanced sclerosing):** immunosuppression futile — supportive CKD care and **renal replacement therapy/transplantation**; allow 3–12 months of disease quiescence before transplant (recurrence in graft <4%).

Drug-safety / monitoring pearls

- ▶ Screen for homozygous **TPMT deficiency** before azathioprine (severe marrow suppression).
- ▶ **MMF and methotrexate are teratogenic** — avoid in pregnancy; **azathioprine and tacrolimus** are pregnancy-compatible.
- ▶ High-dose cyclophosphamide → premature ovarian failure; give a **GnRH agonist** for gonadal protection and **mesna** for bladder protection; *Pneumocystis* prophylaxis with cytotoxics/rituximab.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Glomerular capillary loop — deposit location by class** (schematic, after ISN/RPS): label *podocyte (epithelial cell)*, *GBM*, *endothelial cell*, *mesangial cell/mesangium*, *urinary space*, *capillary lumen*; mark Class I/II = mesangial deposits, Class III/IV = subendothelial deposits + leukocyte infiltration (wire loop), Class V = subepithelial deposits with GBM “spikes”, Class III/IV + V = combined subendothelial + subepithelial deposits.
- ▶ **Therapy algorithm flow-box:** *Renal biopsy* → *ISN/RPS class*; Class I/II → no renal immunosuppression + RAAS/Hcq; Class III/IV (±V) → Induction: GC + MMF or cyclophosphamide ± voclosporin/belimumab → Maintenance: MMF or azathioprine; Class V (pure) → antiproteinuric ± immunosuppression; Class VI → RRT/transplant (all classes share HCQ + ACEi/ARB ± SGLT2i).

Clinical / Diagnostic significance

- ▶ **Serology–biopsy correlation:** low C3/C4 with high anti-dsDNA flags active proliferative (III/IV) disease; serology does **not** reliably predict long-term renal prognosis or replace the biopsy.
- ▶ **Prognostic drivers:** ISN/RPS class, activity/chronicity indices, serum creatinine >3 mg/dL, Black race/socioeconomic factors, cellular crescents + interstitial fibrosis, and renal flares (relapse markedly raises risk of doubling creatinine).
- ▶ A **repeat (6-month) biopsy** can document conversion of active to chronic lesions and guide therapy switching when remission is not achieved.
- ▶ Class V predisposes to **renal-vein thrombosis/PE**; SLE carries accelerated atherosclerosis — aggressive cardiovascular risk reduction is essential.

High-yield exam pointers

- ▶ **Six ISN/RPS classes:** I minimal mesangial, II mesangial proliferative, III focal (<50%), IV diffuse (≥50%), V membranous, VI advanced sclerosing (≥90% sclerosed).
- ▶ **Class IV = most severe/common** for clinical nephritis; **wire-loops**, **hyaline thrombi**, **hematoxylin bodies** = active proliferative lesions.
- ▶ “Full-house” IF (IgG+IgA+IgM+C1q+C3) + **tubuloreticular inclusions** on EM ≈ lupus nephritis.
- ▶ **2018 revision:** dropped IV-S/IV-G, redefined mesangial hypercellularity (>3 cells), “endocapillary hypercellularity,” NIH activity/chronicity to all classes.
- ▶ *Class I/II → no renal immunosuppression; III/IV → induction (GC + MMF or cyclophosphamide) then maintenance (MMF or azathioprine).*
- ▶ **Euro-Lupus cyclophosphamide** = 500 mg IV q2-weekly × 6 = as effective as high-dose with less toxicity.

- ▶ **Voclosporin and belimumab** are the newer add-on agents approved for active LN; **rituximab** for refractory disease.
- ▶ **HCQ + ACEi/ARB** in essentially every patient; **azathioprine/tacrolimus** safe in pregnancy, **MMF/cyclophosphamide** teratogenic.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Systemic Lupus Erythematosus” (ISN/RPS classes, Figure 368-3 ultrastructure, Figure 368-5 lupus nephritis treatment algorithm, EULAR targets, voclosporin/belimumab).
- ▶ **Brenner & Rector's The Kidney** — “Secondary Glomerular Disease” (ISN/RPS Table 32.1, 2018 revision, NIH activity/chronicity indices, full-house IF, wire-loop/hyaline thrombi/hematoxylin bodies, clinico-pathologic correlation, Euro-Lupus/ALMS/MAINTAIN induction–maintenance evidence, class-V management).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic, & Allergic Disorders” (current induction/maintenance regimens, ACR combination-therapy guidance, Euro-Lupus vs NIH cyclophosphamide).



Lupus nephritis

Asked in: Paper IV 17 Apr 2026 · Paper III 09/2025 · Paper IV Dec 2023 · Paper III Nov 2020 · Paper IV Jul 2020 (5×) — RGUHS MD General Medicine

Definition / Introduction — **Lupus nephritis (LN)** is immune-complex–mediated glomerulonephritis occurring as a complication of **systemic lupus erythematosus (SLE)**, the human prototype of chronic immune-complex glomerular disease. It results from glomerular deposition (and *in situ* formation) of immune complexes — principally **DNA/anti-dsDNA** — with complement activation, leukocyte infiltration and cytokine release. Clinically apparent renal disease is present in ~25–50% of patients at SLE onset and develops in up to 60% during the course; it is a major determinant of morbidity and mortality, and ~5–20% progress to **end-stage kidney disease (ESKD)**.

Pathogenesis

- ▶ **Loss of self-tolerance:** defective clearance of apoptotic material, polyclonal B-cell activation and defective B-/T-cell tolerance generate autoantibodies to **nucleosomes, dsDNA, histones and ribonucleoproteins**.
- ▶ **Immune-complex deposition:** circulating and *in situ*-formed complexes localise in the **mesangium, subendothelium and/or subepithelium** (site determines histologic class and clinical picture).

- ▶ **Effector amplification:** complement cascade activation (classical pathway), Fc-receptor-mediated leukocyte recruitment, procoagulant activation and cytokine release; **type I interferon (IFN-α)** signature is prominent.
- ▶ **Neutrophil extracellular traps (NETs):** poorly degraded in SLE — a source of autoantigen and IFN-α induction by plasmacytoid dendritic cells.
- ▶ **Genetic/host factors:** HLA-DR3/DR13, homozygous **C1q/C2/C4 deficiency**, Fcγ-receptor and **APOL1** risk alleles (markedly raise ESKD risk in patients of African descent); female:male ≈ 10:1, peak onset 15–45 yr.
- ▶ **Modifiers:** antiphospholipid antibodies (thrombotic microangiopathy), ANCA-associated pauci-immune necrotising lesions, and a podocytopathy (MCD/FSGS/collapsing) pattern.

ISN/RPS classification (2003, modified 2004; 2018 revision)

Biopsy is the cornerstone — it defines class and **guides therapy**. The International Society of Nephrology / Renal Pathology Society (ISN/RPS) system integrates light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM).

Class	Name	Defining histology	Typical clinical picture
I	Minimal mesangial	Normal LM; mesangial deposits only on IF/EM	Inactive sediment; normal function
II	Mesangial proliferative	Mesangial hypercellularity (>3 cells/mesangial area) + mesangial deposits	Mild; proteinuria <1 g/d; nephrotic syndrome rare
III	Focal	Endocapillary ± extracapillary GN in <50% of glomeruli; focal subendothelial deposits ± fibrinoid necrosis	Haematuria, proteinuria, active sediment; ~25–33% nephrotic
IV	Diffuse	Same lesions in ≥50% of glomeruli; diffuse subendothelial deposits; subdivided IV-S (segmental) / IV-G (global)*	Most active; high anti-dsDNA, low complement, RBC casts; ~50% nephrotic
V	Membranous	Diffuse subepithelial deposits + GBM thickening; may coexist as III+V or IV+V	Nephrotic syndrome; thrombotic risk (RVT, PE)
VI	Advanced sclerosing	≥90% globally sclerosed glomeruli, no residual activity	ESKD, hypertension; serologies often normalise

Indices appended: (A) active, (A/C) active+chronic, (C) chronic. The 2018 revision raised the mesangial cutoff to >3 cells, refined crescent definitions, replaced “endocapillary proliferation” with endocapillary hypercellularity, and applies modified NIH activity/chronicity indices to all classes (eliminating the IV-S/IV-G split).*

Histopathology, immunofluorescence and indices

- ▶ **LM hallmarks of proliferative LN:** endocapillary hypercellularity, leukocyte infiltration, fibrinoid necrosis, karyorrhexis, **cellular/fibrocellular crescents**; “**wire-loop**” lesions (subendothelial deposits thickening capillary walls); “**hyaline thrombi**” (large intraluminal deposits); **hematoxylin bodies** (ANA-bound nuclear debris).
- ▶ **IF — “full-house” staining: IgG + IgA + IgM + C1q + C3** — highly suggestive of LN (IgG near-universal). “Tissue ANA” nuclear staining may be seen.
- ▶ **EM:** electron-dense granular deposits; “**fingerprint**” **substructure** (curvilinear arrays); **tubuloreticular inclusions** (24-nm “interferon footprints” in endothelial cells).
- ▶ **Activity index (0–24):** graded 0–3+ on six features — endocapillary hypercellularity, neutrophils/karyorrhexis, wire-loop deposits, **fibrinoid necrosis** and **crescents** (latter two **double-weighted**), interstitial inflammation; identifies *reversible* lesions.
- ▶ **Chronicity index (0–12):** glomerulosclerosis, **fibrous crescents**, tubular atrophy, interstitial fibrosis (each 0–3+); identifies *irreversible* damage. High activity (>7) **plus** chronicity (>3) predicts poor long-term renal survival.
- ▶ Tubulointerstitial disease, vasculopathy (non-inflammatory necrotising vasculopathy, thrombotic microangiopathy) and lupus podocytopathy carry independent prognostic weight.

Clinical features and investigations

- ▶ **Presentation:** proteinuria (most common), microscopic haematuria, **dysmorphic RBCs and RBC casts**, hypertension, oedema, nephrotic syndrome (esp. class IV/V) and varying GFR loss; rapidly progressive GN with crescents.
- ▶ **Serology:** anti-dsDNA (high-avidity, complement-fixing IgG) correlates best with renal activity; **hypocomplementaemia (C3, C4) in 70–90%** of acute LN — falling C3/C4 and rising anti-dsDNA often **herald a flare**. Anti-Sm is specific but insensitive; ANA is a sensitive screen.
- ▶ **Indication for biopsy:** new/unexplained proteinuria (UPCR >0.5 g/g), active sediment or rising creatinine — to establish class, activity/chronicity and guide/withdraw therapy. **Repeat biopsy** is valuable because classes can **transform** and the 6-month biopsy predicts outcome.
- ▶ **Monitoring:** serial UA, UPCR, eGFR, C3/C4 and anti-dsDNA; quarterly urinary biomarkers where available.

Management

General principle: vigorous **induction** (~6 months) to attain remission, then prolonged **maintenance** (≥3 years) — per KDIGO 2024 and EULAR 2023/24 recommendations.

- ▶ **Background for all classes:** hydroxychloroquine (unless contraindicated); ACE inhibitor / ARB for class III/IV/V to cut proteinuria and intraglomerular pressure; consider SGLT2 inhibitor if eGFR reduced; BP, lipid, bone and infection prophylaxis; VKA/heparin if concomitant antiphospholipid nephropathy.
- ▶ **Class I / II:** no class-specific immunosuppression; antiproteinuric therapy and monitor for transformation.
- ▶ **Class III / IV (proliferative — aggressive Rx):** glucocorticoids (pulse IV methylprednisolone 125–1000 mg/d ×1–3 days for severe disease, then oral GC tapered rapidly to ≤5 mg/day) PLUS one of:
 - Mycophenolate mofetil (MMF) 2–3 g/day — first-line, especially in Black/Hispanic patients;
 - Low-dose IV cyclophosphamide — Euro-Lupus regimen: 500 mg every 2 weeks ×6 doses (then AZA/MMF), as effective as and safer than high-dose;
 - High-dose (“NIH”) IV cyclophosphamide 0.5–1 g/m² monthly ×6 — reserved for crescentic/RPGN, fibrinoid necrosis or reduced eGFR;
 - Triple therapy: add belimumab (anti-BAFF; FDA-approved 2020) or voclosporin (calcineurin inhibitor; FDA-approved 2021, given with MMF) for more severe presentations.
- ▶ **Class V (membranous):** treat if significant nephrotic-range proteinuria or superimposed proliferative lesions (V+III / V+IV → treat as class IV); CNIs especially effective; ACEi/ARB + anticoagulation prophylaxis for thrombotic risk.
- ▶ **Maintenance:** MMF (preferred) or azathioprine for ≥3 years; AZA preferred in pregnancy (cyclophosphamide and MMF are contraindicated/teratogenic). Screen TPMT before azathioprine.
- ▶ **Treatment targets:** ≥25% reduction in UPCR by 3 months; ≥50% reduction (to <3 g/day) by 6 months; UPCR <0.5–0.7 g/day by 12–24 months, with eGFR within 10% of baseline.
- ▶ **Refractory/relapsing:** rituximab (anti-CD20), obinutuzumab + MMF (steroid-sparing) or multi-target regimens; GnRH agonist before cyclophosphamide to preserve ovarian function.
- ▶ **ESKD:** dialysis (lupus activity often quiesces); transplant after ~3–12 months of inactive disease — allograft survival comparable to non-lupus recipients, recurrence low.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Glomerulus showing deposit sites by class:** draw a capillary loop + mesangium and label — *mesangial deposits* (class I/II), *subendothelial deposits* = “wire-loop” (class III/IV),

subepithelial deposits + GBM “spikes” (class V), fibrinoid necrosis + cellular crescent (active class III/IV), and “full-house” IF (IgG, IgA, IgM, C1q, C3).

- ▶ **Induction–maintenance algorithm:** boxes for *Biopsy* → *ISN/RPS class*; *Class III/IV* → *GC + (MMF or low-dose CYC) ± belimumab/voclosporin (induction 6 mo) → MMF/AZA maintenance ≥3 yr*; *Class V* → *CNI/MMF if nephrotic*; with the adjunct rail labelled *HCQ + ACEi/ARB ± SGLT2i*.

Clinical / Diagnostic significance

- ▶ **Biopsy is decisive:** class, activity and chronicity directly determine immunosuppression intensity and prognosis; clinical/serologic activity alone under-stages disease (“silent LN”).
- ▶ **Serologic surveillance** (anti-dsDNA ↑, C3/C4 ↓) gives early warning of flares before creatinine rises.
- ▶ **Prognostic markers of poor outcome:** raised serum creatinine, **crescents/fibrinoid necrosis**, high combined activity+chronicity index, interstitial fibrosis, nephrotic-range proteinuria, hypertension, male sex, African descent/APOL1, and failure to achieve early complete remission.
- ▶ **Pregnancy:** plan for ≥6 months remission; AZA, tacrolimus and HCQ are compatible; anti-Ro antibodies risk **neonatal lupus** and congenital heart block.
- ▶ **Drug-induced lupus** (procainamide, hydralazine, minocycline, anti-TNF) rarely causes nephritis; **anti-histone** antibodies positive, renal involvement uncommon.

High-yield exam pointers

- ▶ ISN/RPS classes I–VI; class III <50% vs class IV ≥50% glomeruli; class VI ≥90% sclerosed.
- ▶ “Full-house” IF = IgG + IgA + IgM + C1q + C3 — pathognomonic clue to LN.
- ▶ Wire-loop = subendothelial; spikes/subepithelial = membranous (class V); hyaline thrombi, hematoxylin bodies, tubuloreticular inclusions (“IFN footprints”).
- ▶ Anti-dsDNA + low C3/C4 correlate with renal activity; **hypocomplementaemia in 70–90% of acute LN**.
- ▶ **Activity index 0–24** (crescents + fibrinoid necrosis double-weighted); **chronicity index 0–12** (irreversible).
- ▶ **Euro-Lupus CYC = 500 mg IV q2wk ×6**; MMF 2–3 g/day first-line, preferred in Black/Hispanic patients.
- ▶ **Triple therapy** = standard + **belimumab** (2020) or **voclosporin** (2021); **rituximab** for refractory disease.
- ▶ **All patients: hydroxychloroquine + ACEi/ARB**; **AZA preferred in pregnancy**; screen TPMT before azathioprine.
- ▶ **Targets:** UPCR ↓25% at 3 mo, ↓50% (<3 g/d) at 6 mo, <0.5–0.7 g/d at 12–24 mo.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Glomerular Diseases” (lupus nephritis section, ISN/RPS classification, Table 326-3) and “Systemic Lupus Erythematosus” (EULAR-based treatment algorithm, Fig. 368-5; belimumab/voclosporin).
- ▶ **Brenner & Rector's The Kidney** — “Secondary Glomerular Disease” (ISN/RPS 2003 classification with 2018 revision, full-house IF, NIH activity 0–24 / chronicity 0–12 indices, induction/maintenance trial evidence — NIH, Euro-Lupus, ALMS, MAINTAIN).
- ▶ **CMDT 2026** — “Kidney Disease” (lupus nephritis; KDIGO 2024 induction/maintenance regimens, obinutuzumab + MMF).



Medullary sponge kidney

Asked in: Paper IV Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Medullary sponge kidney (MSK), also called *precalyceal canalicular ectasia* or *renal tubular ectasia* and eponymously *Lenarduzzi–Cacchi–Ricci disease*, is a developmental malformation characterised by ectasia (dilatation) and cystic transformation of the **terminal (papillary) collecting ducts**, strictly confined to the **medullary pyramids**. It is usually a sporadic, benign, often incidentally-discovered condition, but is clinically important because it predisposes to **recurrent calcium nephrolithiasis, nephrocalcinosis, haematuria and urinary tract infection**. It affects roughly <1% of the general population yet is found in ~13% of patients with calcium urolithiasis, and is typically diagnosed in the **third to fourth decade**.

Etiology, genetics and pathogenesis

- ▶ **Developmental basis** — thought to arise from disruption of the **ureteric bud–metanephric mesenchyme interface** during nephrogenesis, producing malformation and cystic dilatation of the collecting ducts. Although the lesion is present from birth, its rarity in children suggests an **acquired/progressive** component, with documented progression of tubular ectasia and cyst development in some patients.
- ▶ **Inheritance** — classically regarded as **non-hereditary and sporadic**, but **autosomal dominant** inheritance has been demonstrated in several families. Variants of the **GDNF (glial cell–derived neurotrophic factor)** gene cosegregated with disease in five MSK families. A study of family members of 50 MSK patients identified 59 affected first- and second-degree relatives, supporting **familial clustering with autosomal dominant inheritance, reduced penetrance and variable expressivity**.

- ▶ **Tubular/metabolic consequences** — dilated, stagnant precalyceal ducts cause urinary stasis, which together with frequent tubular dysfunction promotes crystal nidus formation and infection.

Pathology and disease associations

- ▶ Despite the name the kidney does **not** truly resemble a sponge; it is usually **normal-sized or slightly enlarged**. On sectioning the medulla shows dilated ducts containing small calculi — gross specimens give a “*Swiss-cheese*” appearance.
- ▶ Ectasia may involve **one or more papillae in one or both kidneys**; lesions are **bilateral in ~70%** of cases (may be asymmetric, occasionally only a single calyx).
- ▶ Dilated ducts communicate proximally with normal-calibre collecting tubules and show a **relative constriction at the calyceal junction**; duct diameter is typically **1–3 mm, occasionally 5 mm, rarely up to 7.5 mm**.

Associated condition	Note
Calcium nephrolithiasis	Strongest association; ~13% of calcium-stone formers have MSK
Primary hyperparathyroidism	“Puzzling association”; possibly via calcium leak / hypercalciuria
Hemihypertrophy	Reported developmental association
Ehlers–Danlos syndrome	Several reported cases
ADPKD	Precalyceal canalicular ectasia frequently seen
Congenital hepatic fibrosis / Caroli (ARPKD)	Medullary ductal ectasia of ARPKD may mimic MSK (different prognosis)

Clinical features

- ▶ **Often asymptomatic** and may remain undetected for life; frequently an **incidental** radiological finding.
- ▶ **Nephrolithiasis** is the commonest presentation — up to **60–70% lifetime stone risk**; stones are **calcium oxalate and calcium phosphate**, forming in the ectatic ducts.
- ▶ **Gross or microscopic haematuria** — may be recurrent.
- ▶ **Recurrent urinary tract infections** — often the first manifestation; patients (especially women) are more susceptible, and infected stones may need long-term antimicrobial suppression.
- ▶ **Tubular dysfunction:**
 - **Mild renal concentrating defect** (impaired urine concentrating ability).
 - **Incomplete distal (type 1) renal tubular acidosis** in **30–40%** — reduced capacity to lower urine pH after an ammonium-chloride load.

- Occasionally a low maximal potassium-excretory capacity.
- ▶ **Metabolic stone risk factors** — chiefly **hypercalciuria** and **hypocitraturia**. Among MSK stone-formers, hypercalciuria is **absorptive** in ~59% and due to a **renal calcium leak** in ~18%.
- ▶ **Prognosis is benign** — MSK **seldom progresses to ESKD**; morbidity stems from recurrent stones, infection, nephrocalcinosis and acidosis. A minority have a poorer course from relapsing urolithiasis and pyelonephritis.

Investigations and diagnosis

- ▶ **Excretory urography (IVU/IVP)** is the historical **gold standard** — early and delayed films (without ureteric compression and without obstruction) show contrast pooling in the dilated terminal collecting ducts:
 - **Parallel brush-like striations** / “**paintbrush**” appearance radiating from the calyceal border.
 - With more severe disease, **grape-like or bead-like** (“**bouquet of flowers**”) clusters.
- ▶ **Plain film / non-contrast CT** — characteristic **medullary nephrocalcinosis** with calculi **clustered fanning away from the calyx**; CT best demonstrates the calculi.
- ▶ **CT urography** (which has largely replaced IVU) is **less sensitive** for the ectasia itself, but shows cystic dilatation of distal collecting tubules with a **striated “papillary brush” pattern** and collecting-system calcification.
- ▶ **Ultrasonography** — **medullary hyperechogenicity** / **nephrocalcinosis**: suggestive but **not diagnostic**.
- ▶ **Metabolic stone work-up** — 24-h urine for calcium, citrate, oxalate, uric acid, volume and pH; serum calcium/PTH to exclude hyperparathyroidism; urinary acidification testing for incomplete dRTA.

Modality	MSK finding
IVU/excretory urography	“Paintbrush” striations / “bouquet of flowers” calyceal blush — most specific
Non-contrast CT	Medullary nephrocalcinosis; stones clustered around papillae
CT urography	Striated papillary brush pattern; less sensitive than IVU
Ultrasound	Medullary hyperechogenicity (non-specific)

Differential diagnosis

Entity	Distinguishing feature
Medullary nephrocalcinosis (1° hyperparathyroidism, dRTA, sarcoid, vit-D excess)	Diffuse calcification without ductal ectasia / brush pattern

Entity	Distinguishing feature
Renal papillary necrosis	Sloughed papillae, ring/club calyx; analgesics, diabetes, sickle cell
Calyceal diverticulum	Single, communicates with calyx; not diffuse papillary ectasia
ARPKD with medullary ductal ectasia	Childhood, congenital hepatic fibrosis, far worse prognosis
Autosomal dominant tubulointerstitial / medullary cystic kidney disease	Progressive CKD, corticomedullary cysts, no stone-clustering

Management

- ▶ **No specific cure** — management is **supportive**, directed at stone prevention and treating complications; incidental asymptomatic MSK warrants **reassurance** (benign, not life-threatening).
- ▶ **High fluid intake** — aim for urine output $\geq 2.5\text{--}3\text{ L/day}$.
- ▶ **Dietary** — low-salt, low-animal-protein diet to reduce calcium excretion and stone risk.
- ▶ **Potassium citrate (oral alkali)** — **first-line** for any metabolic risk factor (hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria): start **~20 mEq citrate/day in two divided doses**, titrate up by **10 mEq** to achieve citraturia **>450 mg/24 h**, while keeping **24-h urine pH <7.5** (to avoid promoting calcium-phosphate stones). This regimen reduced the stone event rate from **0.58 to 0.10 stones/patient/year** and improved bone density (vertebral T-score $-2.82 \rightarrow -1.98$).
- ▶ **Thiazide diuretics** — added/reserved for persistent stone-formation or hypercalciuria despite optimal citrate.
- ▶ **Infection** — prompt treatment of UTIs; preventive measures (especially in women); long-term suppressive antibiotics if infected stones cannot be cleared. Avoid repeated unnecessary investigation of benign recurrent haematuria.
- ▶ **Urological intervention** (ESWL / ureteroscopy) for obstructing or symptomatic stones, as for any stone-former.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled coronal section of the kidney in MSK** — label: *cortex, medullary pyramid, papilla, dilated/ectatic terminal (precalyceal) collecting ducts, small calculi within ducts, minor calyx, normal-calibre proximal collecting tubule with constriction at calyceal junction, renal pelvis*.
- ▶ **IVU schematic of a single calyx** — label: *“paintbrush” parallel striations radiating from the calyx, “bouquet of flowers”/grape-like contrast clusters in ectatic ducts, medullary nephrocalcinosis (clustered stones fanning from calyx)*.

Clinical / Diagnostic significance

- ▶ Consider MSK in any young/middle-aged recurrent calcium-stone former with bilateral medullary nephrocalcinosis and haematuria/recurrent UTI.
- ▶ Always screen for the treatable/contributory associations — **incomplete distal RTA, hypocitraturia, hypercalciuria and primary hyperparathyroidism** — as these guide therapy.
- ▶ IVU's "paintbrush"/"bouquet-of-flowers" sign remains the single most diagnostic feature; CT urography may miss the ectasia, so a high index of suspicion is needed in the post-IVU era.
- ▶ Distinguishing MSK (benign, normal renal function) from **ARPKD-related medullary ductal ectasia** (progressive, hepatic involvement) is prognostically critical.

High-yield exam pointers

- ▶ MSK = ectasia + cystic dilatation of papillary collecting ducts confined to medullary pyramids; eponym *Cacchi-Ricci (Lenarduzzi-Cacchi-Ricci) disease*.
- ▶ **Bilateral in ~70%**; kidneys **normal-sized**; "Swiss-cheese" cut surface.
- ▶ **~60–70% lifetime risk of stones** (calcium oxalate/phosphate); F > M among calcium-stone formers.
- ▶ **Incomplete distal RTA in 30–40%**; with **hypocitraturia + hypercalciuria** (mostly absorptive) and a **urinary concentrating defect**.
- ▶ Diagnostic imaging — "paintbrush" striations and "bouquet of flowers" on IVU; **medullary nephrocalcinosis** on CT.
- ▶ GDNF gene variants; **autosomal dominant, reduced penetrance, variable expressivity** in familial cases; classically sporadic.
- ▶ Associations: **primary hyperparathyroidism, hemihypertrophy, Ehlers–Danlos syndrome, ADPKD**.
- ▶ Treatment — **fluids ≥ 2.5 –3 L/day + potassium citrate (keep urine pH <7.5) $\pm$ thiazide**; rarely progresses to ESKD.

SOURCE & COVERAGE

- ▶ **Brenner & Rector's The Kidney** — "Cystic Diseases of the Kidney" (Medullary Sponge Kidney section: epidemiology, GDNF/autosomal-dominant genetics, pathology, diagnosis, metabolic abnormalities, potassium-citrate regimen) and "Diagnostic Kidney Imaging" (paintbrush/bouquet IVU signs, medullary nephrocalcinosis); "Urolithiasis" (potassium-citrate stone data).
- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Polycystic Kidney Disease and Other Inherited Disorders of Tubule Growth and Development" (MSK as developmental collecting-duct dilatation; stones, concentrating defect, UTI; CT urography less sensitive

than IVP) and “Approach to the Patient with Renal Disease” (MSK among congenital anomalies/nephrocalcinosis).

- **CMDT 2026** — “Kidney Disease” (MSK: <1% prevalence, ureteric-bud–metanephric mesenchyme aetiology, “Swiss-cheese” appearance, up to 70% nephrolithiasis, type 1 dRTA, supportive treatment with alkali/citrate, thiazide, fluids; benign prognosis).

Coverage note: The corpus covers MSK well (Brenner provides full subspecialty depth). Harrison’s dedicated coverage is brief (as flagged in the spec); the depth, genetics (GDNF), imaging eponyms and citrate-regimen detail are drawn from Brenner & Rector and CMDT. The *Lenarduzzi–Cacchi–Ricci* / *Cacchi–Ricci* eponym is documented in the Brenner reference list (Padua Medical School, 1930s).



Nephrotic syndrome

Asked in: Paper IV Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Nephrotic syndrome is a glomerular disorder defined by **heavy proteinuria** (>3.0 g/24 h) together with **hypoalbuminaemia**, **oedema/anasarca**, **hypercholesterolaemia** and **hypertension**, classically accompanied by *minimal (microscopic) haematuria* and an acellular urinary sediment. When large amounts of protein are excreted without the full clinical picture, the term **nephrotic-range proteinuria** is used. It arises from injury to the glomerular filtration barrier (predominantly the **podocyte and its slit-diaphragm**), and may be a *primary* (idiopathic) glomerulopathy or *secondary* to systemic disease. Untreated, persistent heavy proteinuria progressively damages nephrons and lowers GFR — the higher the 24-h protein excretion, the more rapid the decline.

Diagnostic criteria & pathophysiology

- **Nephrotic “pentad”**: heavy proteinuria + hypoalbuminaemia + oedema + hyperlipidaemia (hypercholesterolaemia) + hypertension; haematuria, when present, is minimal/microscopic.
- **Filtration-barrier injury** — loss of the size- and charge-selective barrier (effacement of podocyte foot processes, weakening of slit-pore membranes) allows albumin and larger proteins to escape. In children the loss is predominantly albumin (*selective proteinuria*); in adults it is typically *non-selective*.
- **Oedema** — due to renal **salt and water retention**; intravascular hypoalbuminaemia (low oncotic pressure) contributes. Severe hypoalbuminaemia with intrarenal oedema (*nephrosarca*) can cause a diuretic-responsive fall in GFR that must be distinguished from acute kidney failure due to **hypovolaemia**.
- **Hyperlipidaemia** — hypoalbuminaemia drives hepatic lipoprotein overproduction with reduced catabolism; patients are at increased **cardiovascular risk**.

- ▶ **Hypercoagulable state** — urinary loss of anticoagulant proteins produces a thrombotic tendency; renal vein thrombosis, pulmonary embolism and deep-vein thrombosis are the major venous complications (highest with membranous nephropathy).
- ▶ **Loss of other binding/transport proteins** — e.g. thyroid-binding globulin loss alters thyroid function tests; loss of immunoglobulins predisposes to infection [standard medicine].

Classification — causes by histology

Category	Lesion / disease	Key features (Harrison 22e)
Primary glomerular	Minimal change disease (MCD)	70–90% of childhood, 10–15% of adult nephrotic syndrome; normal light microscopy, IgM ± in mesangium, foot-process effacement on EM; steroid-responsive
	Focal segmental glomerulosclerosis (FSGS)	Most common cause of <i>primary</i> glomerular disease in ESKD (US); segmental scars at the corticomedullary junction ; <i>APOL1</i> risk variants; collapsing variant with HIV (HIVAN)
	Membranous glomerulonephritis (MGN)	~25% of adult nephrotic syndrome; peak 30–50 y, M:F 2:1; subepithelial deposits , silver-stain “spikes” ; anti-PLA2R IgG4 in 70–80% of primary cases
	Membranoproliferative GN / C3 glomerulopathy	May present nephrotic with low complement
Secondary / systemic	Diabetic nephropathy	Single most common cause of CKD worldwide; Kimmelstiel-Wilson nodules , GBM thickening, mesangial expansion
	Amyloidosis (AL primary, AA secondary)	Congo-red positive fibrils; nephrotic syndrome common; AL → ~20% dialysis, AA → ~40–60% dialysis
	Light-chain deposition disease / MGRS	Plasma-cell dyscrasia; non-fibrillar, Congo-red negative light-chain deposits
	Fibrillary-immunotactoid disease; Fabry’s disease	Fabry: α-Gal A deficiency, <i>Maltese-cross</i> lipid bodies, FSGS pattern

Category	Lesion / disease	Key features (Harrison 22e)
	Infection / drug / malignancy / autoimmune (secondary MGN)	HBV, HCV, syphilis, malaria; gold, penicillamine, NSAIDs; solid tumours (breast, lung, colon); SLE (membranous lupus, ISN/RPS class V)

Clinical features & complications

- ▶ **Presentation** — peri-orbital and dependent **oedema**, weight gain, frothy urine, ascites, anasarca; often abrupt in MCD.
- ▶ **Infections** — increased susceptibility (urinary immunoglobulin loss); spontaneous bacterial peritonitis and pneumococcal sepsis are classic in nephrotic children [standard medicine].
- ▶ **Thromboembolism** — renal vein thrombosis (esp. MGN), PE, DVT from the hypercoagulable state.
- ▶ **Acute kidney injury** — from hypovolaemia/over-diuresis, *nephrosarca*, acute tubular necrosis or interstitial inflammation.
- ▶ **Metabolic** — accelerated **atherosclerosis** (dyslipidaemia), protein malnutrition, and altered drug/hormone protein binding.

Investigations / approach

- ▶ **Urinalysis** — heavy proteinuria; *bland/acellular* sediment; **oval fat bodies** and “**Maltese-cross**” lipid-laden casts under polarised light; *selective* (children) vs *non-selective* (adults) proteinuria.
- ▶ **Quantify proteinuria** — 24-h urine protein (nephrotic = >3.0 g/24 h; MCD averages ~10 g) or spot **albumin/protein-to-creatinine ratio** (Table 326-1: albuminuria >300 mg/g).
- ▶ **Blood** — serum albumin, lipid profile, creatinine/eGFR, fasting glucose/HbA1c, complement (C3/C4), serology (ANA, anti-dsDNA, ANCA, hepatitis B/C, HIV, syphilis), and serum/urine **electrophoresis with free light chains** when paraproteinaemia suspected.
- ▶ **Serology that may obviate biopsy** — **anti-PLA2R antibody** positive with normal creatinine and no other cause supports primary MGN.
- ▶ **Kidney biopsy** — the diagnostic cornerstone in adults (light + immunofluorescence + electron microscopy). In children, MCD is assumed and **only steroid non-responders are biopsied**. Diabetic nephropathy with typical features and retinopathy usually needs **no biopsy**.

Principles of management

- ▶ **General / supportive (all causes):**
 - **Reduce proteinuria & preserve GFR** — inhibitors of the **renin–angiotensin system** (ACEi/ARB) plus **SGLT2 inhibitors**.
 - **Oedema** — dietary salt restriction and **diuretics**, avoiding intravascular volume depletion.

- **Dyslipidaemia** — **lipid-lowering (statin)** therapy, given the raised cardiovascular risk.
- **Thromboprophylaxis/anticoagulation** for venous thrombotic complications; prophylaxis considered in select patients with severe hypoalbuminaemia (esp. MGN).
- ▶ **Disease-specific immunosuppression:**
 - **MCD** — **prednisone** first-line; 90–95% of children and 80–90% of adults achieve complete remission (adults respond more slowly; not called steroid-resistant until 4 months). Cyclophosphamide, MMF, **calcineurin inhibitors (CNIs)** or **rituximab** for frequent relapsers/steroid-dependent/steroid-resistant disease.
 - **Primary FSGS** — steroids (remission in only 20–45% over 6–12 months), CNIs as steroid-sparing; *secondary/genetic FSGS* — treat the cause, **no role for immunosuppression**; recurs in ~30% of transplants (plasmapheresis for presumed circulating factor).
 - **Primary MGN** — immunosuppression for persistent proteinuria, risk-stratified by proteinuria/GFR/albumin: **steroids + cyclophosphamide, CNIs, or rituximab**.
 - **Diabetic nephropathy** — glycaemic and BP control, ACEi/ARB, SGLT2i, and the non-steroidal MRA **finerenone**.
 - **Amyloid/paraprotein** — treat the underlying plasma-cell dyscrasia/inflammatory disease.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Glomerular filtration barrier (normal vs MCD)** — label: *capillary lumen, fenestrated endothelium, glomerular basement membrane (GBM), podocyte with foot processes, slit diaphragm/slit-pore membrane*; show **foot-process effacement (fusion)** in MCD and **subepithelial deposits with “spikes”** in MGN (“Foot process fusion”, “Subepithelial deposits”, “MEMBRANOUS GLOMERULONEPHRITIS”).
- ▶ **FSGS schematic (Glomerular Schematic 5)** — label: *Detachment of cell from GBM, Collapsed capillary and scar, Proliferation of subepithelial cells, Afferent arteriole, Efferent arteriole, FOCAL SCLEROSING GLOMERULONEPHRITIS*.

Clinical / Diagnostic significance

- ▶ Distinguishing **nephrotic** (bland sediment, heavy proteinuria) from **nephritic** (haematuria, RBC casts, hypertension, azotaemia) syndrome directs the whole work-up.
- ▶ **Age stratifies the differential:** child → MCD; adult → MGN/FSGS/diabetes; older adult with paraproteinaemia → amyloid/LCDD/MGRS.
- ▶ **Secondary screen is mandatory** — diabetes, SLE, hepatitis B/C, HIV, malignancy and drugs are reversible/treatable causes.
- ▶ **Anti-PLA2R** has transformed MGN into a partly serology-based, biopsy-sparing diagnosis and a **biomarker of disease activity/response**.

- ▶ Remission of proteinuria is the key prognostic goal: it markedly improves outcome across MCD, FSGS and MGN.

High-yield exam pointers

- ▶ Nephrotic syndrome = proteinuria >3.0 g/24 h + hypoalbuminaemia + oedema + hyperlipidaemia + hypertension; sediment is **bland**.
- ▶ MCD = commonest cause in children (70–90%); EM shows **foot-process effacement**; exquisitely **steroid-responsive**.
- ▶ MGN = commonest *primary* cause in adults (~25%); **anti-PLA2R IgG4**; **subepithelial deposits** + silver “**spikes**”; highest risk of **renal vein thrombosis**.
- ▶ FSGS = leading cause of primary glomerular ESKD (US); **APOL1**; collapsing variant in HIVAN; biopsy from corticomedullary junction (else misdiagnosed as MCD).
- ▶ **Diabetic nephropathy** = most common cause of CKD overall; **Kimmelstiel-Wilson nodules**; usually no biopsy if retinopathy present.
- ▶ **Amyloid** = **Congo-red positive**, apple-green birefringence; LCDD is **Congo-red negative**.
- ▶ Universal therapy = **RAAS blockade** + **SGLT2i** + **statin** + **diuretic** ± **anticoagulation**; add disease-specific immunosuppression.
- ▶ Complications to write: **infection**, **thromboembolism** (renal vein thrombosis), **AKI**, **dyslipidaemia/CVD**, **protein malnutrition**.
- ▶ Urine clue: **oval fat bodies** / **Maltese-cross** lipiduria.

SOURCE & COVERAGE

Harrison 22e — Ch 326 “Glomerular Diseases” (Tables 326-1, 326-2, 326-4, 326-5; Glomerular Schematics 5 & 6). **Coverage note:** the chapter is organised by individual glomerulopathy rather than as a single “nephrotic syndrome” review — the unified definition, oedema/hyperlipidaemia mechanisms and the infection/thrombosis complication list above are assembled from scattered passages plus universally accepted standard internal medicine; points marked [*standard medicine*] (immunoglobulin-loss infection susceptibility, detailed lipid mechanism) are not given verbatim in this chapter but are standard and accurate.



Renal manifestations in Systemic Lupus Erythematosus (SLE)

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — **Lupus nephritis (LN)** is the immune-complex-mediated glomerular injury of SLE and is one of its most common and serious organ complications. Nephritis occurs in ~35% of patients with SLE; clinical kidney involvement is present in about 30% at diagnosis, and the majority

develop renal abnormalities during the disease course. It is more severe in non-White patients, who more often progress to **end-stage renal disease (ESRD)** despite therapy. Renal involvement carries major weight in classification (a biopsy showing class III/IV LN alone meets diagnostic criteria) and is the dominant driver of morbidity, mortality and treatment intensity in SLE.

Pathogenesis

- ▶ LN results from deposition of **circulating immune complexes** composed primarily of **DNA and anti-DNA**, which activate the **complement cascade** → complement-mediated damage, leukocyte infiltration, activation of procoagulant factors and cytokine release.
- ▶ **In-situ immune-complex formation** in the glomerulus also contributes to injury.
- ▶ The anatomical site of deposits determines the histological class and clinical picture — deposits may be **mesangial, subendothelial and/or subepithelial**.
 - *Subendothelial/mesangial deposits* (accessible to inflammatory cells) → proliferative, **nephritic** lesions (class III/IV).
 - *Subepithelial deposits* (separated from the circulation by the GBM) → **membranous**, largely non-inflammatory, **nephrotic** lesion (class V).
- ▶ **Anti-dsDNA antibodies that fix complement** correlate best with the presence of kidney disease; **hypocomplementemia** (low C3/C4) is present in **70–90%** of acute LN.
- ▶ **Antiphospholipid antibodies** can produce **glomerular microthrombi and thrombotic microangiopathy (antiphospholipid nephropathy)**, worsening renal prognosis despite anticoagulation.

Clinical spectrum of renal involvement

- ▶ Manifestations parallel the underlying pathology and range from clinically silent to rapidly progressive renal failure.
- ▶ **Proteinuria** is the most common sign — sub-nephrotic to **nephrotic-range**.
- ▶ **Glomerular (active) urinary sediment** — microscopic **haematuria**, dysmorphic red cells and **red-blood-cell casts**.
- ▶ **Hypertension** and varying degrees of reduced GFR / acute kidney injury.
- ▶ **Nephrotic syndrome** — characteristic of class V and severe class IV; class V predisposes to **renal vein thrombosis** and other thrombotic complications.
- ▶ **Rapidly progressive glomerulonephritis (RPGN)** — when crescents complicate class III/IV.
- ▶ Nephritis may occur **with or without extrarenal SLE activity** and is frequently **asymptomatic**, mandating active surveillance.

Histological classification (ISN/RPS, revised 2003–04)

First outlined by the WHO (1974) and revised by the International Society of Nephrology / Renal Pathology Society (ISN/RPS) Study Group in 2003–04 (with a 2018 revision recommendation). It guides therapy and prognosis.

Class	Designation	Key histology	Clinical correlate
I	Minimal mesangial	Normal light microscopy; mesangial deposits on IF/EM	Minimal manifestations; excellent prognosis
II	Mesangial proliferative	Mesangial hypercellularity + matrix expansion	Mild haematuria/proteinuria; nephrotic syndrome rare
III	Focal nephritis (<50% glomeruli)	Focal endocapillary ± extracapillary hypercellularity, focal subendothelial deposits ± fibrinoid necrosis	Haematuria, proteinuria, ± active sediment/nephrotic; variable course
IV	Diffuse nephritis (>50% glomeruli)	Diffuse endocapillary ± extracapillary hypercellularity, diffuse subendothelial deposits; segmental (IV-S) or global (IV-G); ± crescents ± fibrinoid necrosis	Most severe — high anti-dsDNA, low complement, RBC casts, ~50% nephrotic; worst untreated prognosis (IV-S worse than IV-G)
V	Membranous	Thickened GBM with diffuse subepithelial deposits; may coexist with III/IV (mixed membranous + proliferative)	Nephrotic syndrome (~60%); thrombotic risk; ~20% of LN with significant proteinuria
VI	Advanced sclerosing	Global sclerosis of >90% of glomeruli, interstitial fibrosis	ESKD; immunosuppression not useful

- ▶ Lesions are **dynamic** — patients can **transform** between classes, so **repeat biopsy** is often required (e.g., non-response or change in trajectory).
- ▶ Class III/IV are presented under **acute nephritic syndromes** because of their aggressive proliferative behaviour; class V behaves like a nephrotic/membranous lesion.

Investigations, serology and monitoring

- ▶ **Urinalysis** — proteinuria, haematuria, RBC/cellular casts (active sediment).
- ▶ **Quantitation** — random urine **protein-to-creatinine ratio (UPCr)** or 24-h urine protein; screen every 3 months.

- ▶ **Renal function** — serum creatinine, eGFR.
- ▶ **Serology** — **anti-dsDNA titre** (rising titre + falling C3/C4 herald a flare and impending active nephritis).
- ▶ **Renal biopsy** — the key investigation; generally prompted by **UPCr >0.5 and/or declining kidney function**. It establishes the **ISN/RPS class**, distinguishes active (treatable) from chronic (sclerotic) lesions, and guides therapy. Note: a biopsy showing class III/IV LN independently satisfies SLE classification criteria.

Management by class

- ▶ **General/adjunctive measures (all classes):** **hydroxychloroquine** (renoprotective, reduces flares); **ACE inhibitor or ARB** for class III/IV/V to reduce proteinuria and glomerular hypertension; an **SGLT2 inhibitor** if eGFR is reduced; blood-pressure, lipid and cardiovascular-risk control; **anticoagulation (vitamin K antagonist/heparin)** if antiphospholipid nephropathy is present on biopsy.
- ▶ **Class I / II:** little or no specific immunosuppression; excellent prognosis.
- ▶ **Class III / IV (± V) — proliferative LN (aggressive therapy):**
 - **Induction (2–6 months):** high-dose glucocorticoids — including **IV methylprednisolone 125–1000 mg/day for 1–3 days** for severe/crescentic disease — **plus either IV cyclophosphamide or mycophenolate mofetil (MMF)**.
 - **Cyclophosphamide regimens:** **low-dose 500 mg IV every 2 weeks for six doses** (the *Euro-Lupus* regimen — as effective as high dose with better tolerability) or **high-dose monthly pulses for 6 months**; a **GnRH agonist** can be given before each dose to protect against ovarian failure.
 - **MMF 2–3 g/day** is particularly favoured for induction in **Black/Hispanic** patients.
 - **Newer triple therapies (FDA-approved, steroid-sparing):** **belimumab** (anti-BAFF, 2020) added to MMF or low-dose cyclophosphamide; **voclosporin** (a calcineurin-inhibitor/cyclosporine analogue, 2021) added to MMF + glucocorticoids.
 - **Maintenance:** lower-dose glucocorticoids (taper prednisone to **≤5 mg/day**) plus **MMF or azathioprine**; total immunosuppression (induction + maintenance) generally **≥36 months** (KDIGO).
 - **Refractory disease:** **rituximab** (anti-CD20) may be considered.
- ▶ **Class V — membranous LN:** treat nephrotic syndrome; severe nephrosis, rising creatinine or progressive course warrant steroids + an additional immunosuppressant; RAS blockade reduces proteinuria.
- ▶ **Class VI:** advanced sclerosis — manage as CKD/ESKD with **dialysis or transplantation**; kidney transplant after **~6 months of inactive disease** gives allograft survival comparable to other indications.

- ▶ **Treatment targets:** $\geq 25\%$ reduction in UPCr by **3 months**, $\geq 50\%$ reduction to **< 3 g/day** by **6 months**, and **< 0.5 – 0.7 g/day** by **12–24 months**, each with eGFR within 10% of baseline.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Glomerular capillary loop — sites of immune deposits.** Labels: *Capillary lumen, Endothelial cell, Glomerular basement membrane (GBM), Visceral epithelial cell (podocyte), Mesangium, Mesangial deposits (Class I/II), Subendothelial deposits (Class III/IV), Subepithelial deposits (Class V), Crescent in Bowman's space (extracapillary proliferation), Fibrinoid necrosis, Bowman's capsule.*
- ▶ **LN management algorithm.** Labels: *Renal biopsy $\rightarrow$ ISN/RPS class $\rightarrow$ Class I/II (HCQ + RAS blockade, no specific immunosuppression); Class III/IV $\pm$ V (Induction: glucocorticoid + MMF or low-dose IV cyclophosphamide $\pm$ belimumab/voclosporin $\rightarrow$ Maintenance: low-dose steroid + MMF or azathioprine); Pure Class V (nephrotic management); Class VI (dialysis/transplant) — with the adjunct box HCQ, ACEi/ARB, SGLT2i, anticoagulation if APS nephropathy.*

Clinical / Diagnostic significance

- ▶ LN is a leading determinant of prognosis: **up to 20% reach ESKD** requiring dialysis/transplant, and in the USA **$\sim 20\%$ of class IV patients die or develop ESRD within 10 years**; LN markedly raises mortality versus the general population.
- ▶ Achieving **remission** (near-normal kidney function with proteinuria reduced to near-normal) dramatically improves renal outcome.
- ▶ A **renal biopsy showing class III or IV LN** is the only single item that, by itself, satisfies the SLE classification criteria — underscoring renal disease as a defining feature.
- ▶ Both LN and its corticosteroid treatment accelerate **atherosclerosis, hypertension, hyperglycaemia and hyperlipidaemia**, so cardiovascular risk reduction is integral to care.

High-yield exam pointers

- ▶ Nephritis in $\sim 35\%$ of SLE; $\sim 30\%$ have renal disease at diagnosis.
- ▶ ISN/RPS classes I–VI — *III = focal ($< 50\%$), IV = diffuse ($> 50\%$), V = membranous, VI = sclerotic; IV-S worse than IV-G.*
- ▶ Subendothelial/mesangial deposits $\rightarrow$ **proliferative/nephritic**; subepithelial $\rightarrow$ **membranous/nephrotic**.
- ▶ **Anti-dsDNA high + C3/C4 low** = best correlate of active LN; hypocomplementemia in **70–90%**.
- ▶ **Renal biopsy** is essential to assign class and guide therapy (prompted by UPCr > 0.5 / falling GFR); screen UPCr **every 3 months**.

- ▶ Proliferative LN (III/IV): induction = steroids + MMF or cyclophosphamide; maintenance = MMF or azathioprine.
- ▶ Newer agents: belimumab (2020) and voclosporin (2021) for steroid-sparing triple therapy.
- ▶ Class V → nephrotic syndrome + renal vein thrombosis risk; antiphospholipid antibodies → thrombotic microangiopathy with worse prognosis.
- ▶ HCQ, ACEi/ARB and (if low eGFR) SGLT2 inhibitor in all proliferative/membranous LN.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 326 "Glomerular Diseases" (lupus nephritis section, Table 326-3 ISN/RPS classification) and Ch 368 "Systemic Lupus Erythematosus" (Renal Manifestations; Fig. 368-5 treatment of lupus nephritis). *Coverage note:* the "Euro-Lupus" eponym for the low-dose cyclophosphamide regimen (500 mg q2-weekly × 6) is standard, universally accepted internal medicine added for completeness; Harrison describes the regimen and dose but does not use the eponym.



Renal Osteodystrophy

Asked in: Paper IV May 2022 — RGUHS MD General Medicine

Definition / Introduction — *Renal osteodystrophy* is the spectrum of bone histological abnormalities that complicates chronic kidney disease (CKD), arising from disordered calcium, phosphate, parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23) and vitamin D metabolism. It is the skeletal component of the wider systemic disorder of mineral metabolism in CKD (which also encompasses biochemical derangements and extraskeletal/vascular calcification). The principal complications of abnormal mineral metabolism in CKD occur in the **skeleton** and the **vascular bed**, with occasional soft-tissue involvement, and disorders of bone turnover and of vascular calcification are pathophysiologically linked.

Pathophysiology — the engine of secondary hyperparathyroidism

The high-turnover lesion is driven by a self-amplifying cascade that begins early (changes start as GFR falls below 60 mL/min, with phosphate retention and FGF-23 rise possibly antedating measurable GFR decline):

- ▶ Declining GFR → phosphate retention. Reduced excretion of phosphate is the initiating event.
- ▶ Retained phosphate stimulates increased synthesis of FGF-23 by osteocytes, increased PTH synthesis, and growth of parathyroid gland mass.

- ▶ **Decreased ionized calcium** results from reduced renal calcitriol [$1,25(\text{OH})_2\text{D}_3$] production — itself a consequence of phosphate retention and of elevated FGF-23, which both suppresses 1α -hydroxylation and *increases calcitriol degradation*.
- ▶ **Low calcitriol** drives hyperparathyroidism in two ways: by causing hypocalcaemia, and by a *direct effect on PTH gene transcription*.
- ▶ The normal inhibitory effect of FGF-23 on PTH secretion is **Klotho-dependent** and is *attenuated* in CKD, removing a brake on PTH.
- ▶ Net result: **secondary hyperparathyroidism**, sustained high bone turnover, and progressive parathyroid hyperplasia. PTH itself acts as a **uremic toxin** (muscle weakness, cardiac muscle fibrosis, constitutional symptoms, and ESA-resistant anaemia from marrow fibrosis).

Classification — histological types of renal bone disease

The major bone disorders are classified by **bone turnover** and **PTH level** (with mineralisation as a third axis); most patients show a *combination*.

Type	Bone turnover / PTH	Underlying mechanism	Hallmark
Osteitis fibrosa cystica	High turnover, high PTH	Secondary hyperparathyroidism	Abnormal osteoid, peritrabecular & marrow fibrosis; bone cysts with haemorrhage = *brown tumours*
Osteomalacia	Low/defective mineralisation	Reduced production & action of $1,25(\text{OH})_2\text{D}_3$	Accumulation of non-mineralised osteoid; fractures, bowing
Adynamic bone disease	Low turnover, low/normal PTH	Over-suppression of PTH (vitamin D, high-Ca binders/dialysate), chronic inflammation	Reduced bone volume & mineralisation; microfractures unrepaired
Mixed uremic osteodystrophy	Combined	Osteitis fibrosa + osteomalacia coexisting	Features of both

- ▶ **Osteitis fibrosa cystica** is the *classic lesion of secondary hyperparathyroidism*: bone pain, fragility, *brown tumours* with compression syndromes, and erythropoiesis-stimulating-agent (ESA) resistance from marrow fibrosis.
- ▶ **Adynamic bone disease** is *increasing in prevalence*, especially among **diabetics and older patients**. Complications include increased **fracture**, bone pain, and an association with **vascular and cardiac calcification**; calcium that cannot enter low-turnover bone may deposit in soft tissue as ***tumoral calcinosis**. *These patients often have the most severe musculoskeletal pain** owing to inability to repair normal microfractures.

Extraskkeletal manifestations

- ▶ **Vascular / valvular calcification:** strong association between **hyperphosphataemia** and cardiovascular mortality. CKD patients show calcification of the **media of coronary arteries** and **heart valves** far exceeding non-CKD patients; magnitude is proportional to age, hyperphosphataemia, and (paradoxically) **low PTH/low turnover**. Hyperphosphataemia induces an **osteoblast-like gene-expression** switch in vascular cells → calcification/ossification; low **fetuin** permits more rapid calcification.
- ▶ **Calciophylaxis** (calcific uraemic arteriolopathy): a devastating disorder almost exclusive to advanced CKD. Heralded by painful **livedo reticularis** and subcutaneous nodules that progress to **ischaemic necrosis/ulceration** (legs, thighs, abdomen, breasts), with vascular occlusion plus extensive vascular & soft-tissue calcification. **Warfarin** is a recognised risk factor (it decreases vitamin-K-dependent activation of **matrix GLA protein**, which normally inhibits vascular calcification).
- ▶ **Tumoral calcinosis:** large periarticular calcified concretions in severely, chronically hyperphosphataemic, non-adherent dialysis patients.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Vicious-cycle flow diagram of CKD secondary hyperparathyroidism.** Labels: ↓GFR → *Phosphate retention* → ↑FGF-23 (osteocytes) and ↑PTH / *parathyroid hyperplasia*; ↓Renal 1 α -hydroxylase → ↓Calcitriol; ↓Ionised calcium; *Klotho-dependent FGF-23 brake on PTH attenuated*; outputs → *High-turnover bone (osteitis fibrosa cystica)* and *Vascular calcification*.
- ▶ **Spectrum bar of renal bone disease.** Single horizontal axis labelled *Bone turnover / PTH*: left end *Low (Adynamic bone disease)* → middle *Normal* → right end *High (Osteitis fibrosa cystica)*; place *Osteomalacia* (mineralisation defect) and *Mixed uremic osteodystrophy* annotated on the bar.

Clinical / Diagnostic significance

- ▶ **Biochemistry (serial trends):** serum **phosphate** (hyperphosphataemia, defined in adults as >1.8 mmol/L [5.5 mg/dL]), **calcium**, **intact PTH**, **alkaline phosphatase** (turnover marker), **25-OH vitamin D**; FGF-23 is elevated early. High FGF-23 is an *independent risk factor for left ventricular hypertrophy* and increased mortality in CKD, dialysis and transplant patients.
- ▶ **Bone biopsy with double tetracycline labelling** (TMV system — turnover, mineralisation, volume) is the definitive method to distinguish high- from low-turnover disease and to confirm adynamic bone or osteomalacia (*standard nephrology practice; see Coverage note*).
- ▶ **Imaging:** radiographs may show subperiosteal resorption, brown tumours, vascular calcification; CT/electron-beam CT quantifies coronary and valvular calcification.

- **Management pearls:** prevention is paramount — *once parathyroid mass is very large the disease is hard to control*. KDOQI guidance targets **intact PTH 2–9 × the upper limit of normal**, because *very low PTH predisposes to adynamic bone disease, fracture and ectopic calcification*. Avoid over-suppression of PTH (excess vitamin D analogue, calcium-based binders, high-calcium dialysate). For anticoagulation in CKD, **avoid warfarin** where feasible to reduce calciphylaxis risk.

Management / Treatment

Strategy	Agents (per Harrison)	Rationale / caution
Lower serum phosphate	Low-phosphate diet; phosphate binders with meals — Ca acetate, Ca carbonate (Ca-based); sevelamer , lanthanum (non-Ca polymers); tenapanor (Na ⁺ /H ⁺ inhibitor reducing GI phosphate absorption)	Ca-based binders risk hypercalcaemia & worsen low-turnover/adynamic bone; non-Ca binders avoid this and may attenuate vascular calcification
Suppress PTH (vitamin D)	Calcitriol ; analogue paricalcitol	Direct PTH suppression + raises ionised Ca; calcitriol can cause hyperCa/hyperphosphataemia → paricalcitol suppresses PTH with less hypercalcaemia
Calcimimetics	Cinacalcet , etelcalcetide	Increase parathyroid sensitivity to extracellular calcium → dose-dependent fall in PTH and plasma calcium; help lower calciphylaxis risk
Refractory disease	Parathyroidectomy	For severe, autonomous (tertiary) hyperparathyroidism unresponsive to medical therapy (<i>standard; see Coverage note</i>)
Calciphylaxis	Sodium thiosulfate (IV) , hyperbaric oxygen , discontinue warfarin	Multimodal; correct mineral derangements; wound care

High-yield exam pointers

- Renal osteodystrophy = **bone-histology arm** of CKD mineral-bone disorder; turnover + PTH axis classifies it.
- **Phosphate retention** is the prime mover → ↑FGF-23 + ↑PTH + ↓calcitriol → **secondary hyperparathyroidism**; begins at GFR <60 mL/min.
- **Osteitis fibrosa cystica** (high PTH) ↔ ***brown tumours**; *adynamic bone disease** (low PTH) — rising in diabetics/elderly, over-suppression risk, fracture + calcification.
- **Osteomalacia** = defective mineralisation from low 1,25(OH)₂D₃ → excess **osteoid**.

- ▶ **FGF-23** is Klotho-dependent, raised early, an independent predictor of LVH and mortality.
- ▶ **Calciphylaxis**: painful livedo reticularis → ischaemic skin necrosis; **warfarin** (anti-matrix-GLA-protein) is a risk factor; treat with **IV sodium thiosulfate**.
- ▶ Drugs to recall: binders (Ca acetate/carbonate, **sevelamer**, **lanthanum**, **tenapanor**); vitamin D (**calcitriol**, **paricalcitol**); calcimimetics (**cinacalcet**, **etelcalcetide**).
- ▶ Target **intact PTH 2–9× ULN**; avoid both extremes — high PTH → osteitis fibrosa, over-suppressed PTH → adynamic bone.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 322 "Chronic Kidney Disease" (Disorders of Calcium and Phosphate Metabolism; bone manifestations, calciphylaxis, treatment) and Ch 421 "Bone and Mineral Metabolism in Health and Disease" (FGF-23, hyperphosphataemia, osteomalacia, secondary hyperparathyroidism of renal failure). *Coverage note*: The eponymous term "*renal osteodystrophy*" and the KDIGO "CKD-MBD" label are not used verbatim in Harrison 22e Ch 322 (which titles the section "Disorders of Calcium and Phosphate Metabolism"); the histological entities, mechanisms, drugs and doses above are all faithful to the provided text. The **TMV bone-biopsy/double-tetracycline-labelling** classification and **parathyroidectomy** for refractory disease are universally accepted standard nephrology not detailed in these two chapters, and are flagged accordingly.



Renal replacement therapy

Asked in: Paper IV 17 Apr 2026 · Paper IV Nov 2022 (2×) — RGUHS MD General Medicine

Definition / Introduction — **Renal replacement therapy (RRT)** denotes the techniques that substitute for the excretory (and partly the endocrine/metabolic) functions of the kidney when native function is inadequate, whether transiently in acute kidney injury (AKI) or permanently in end-stage kidney disease (ESKD). The three pillars are **haemodialysis (HD)**, **peritoneal dialysis (PD)** and **kidney transplantation**, supplemented in the critically ill by **continuous renal replacement therapy (CRRT)**. Dialysis exploits two physical principles — **diffusion** of solute down a concentration gradient across a semipermeable membrane, and **convection** (solvent drag with ultrafiltrated plasma water) — while transplantation alone restores all renal functions and is the treatment of choice for ESKD.

Indications for RRT

- ▶ **Chronic / ESKD (maintenance dialysis)**: uraemic symptoms; **hyperkalaemia** unresponsive to conservative measures; persistent **extracellular volume expansion** despite diuretics; **acidosis** refractory to medical therapy; uraemic **bleeding diathesis**; and an eGFR/creatinine clearance **<10 mL/min/1.73 m²**. There is *no absolute* level of creatinine, BUN, cystatin C or eGFR that

mandates dialysis, and no benefit to preemptive initiation at GFR 10–14 over symptom-guided start (IDEAL trial). CMDT: consider initiation as GFR nears 5–10 mL/min/1.73 m² with uraemic symptoms.

- ▶ **Acute (AKI) — mnemonic “AEIOU”:** Acid–base (refractory metabolic acidosis); Electrolyte (hyperkalaemia unresponsive to medical therapy); Intoxications (dialysable poisons); volume Overload unresponsive to diuretics; Uraemic complications — encephalopathy, asterixis, pericarditis/rub, seizures, uraemic bleeding. Randomised trials (STARRT-AKI) show **no survival benefit from earlier vs later** initiation; dialysis should not, however, await a life-threatening complication.
- ▶ **Nephrology referral** is advised when GFR <30 mL/min/1.73 m², rapid decline (>5 mL/min/1.73 m²/yr) or albuminuria >300 mg/day — to plan access and modality.

Modalities at a glance

Feature	Haemodialysis	Peritoneal dialysis	CRRT (AKI)	Transplantation
Membrane	Synthetic hollow-fibre dialyzer	Patient's own peritoneum	Extracorporeal haemofilter	— (whole organ)
Clearance	Diffusion + convection	Diffusion + osmotic UF	Convective ± diffusive	Physiological
Setting	In-centre (>80% US) or home	Home, self-care	ICU, haemodynamically unstable	Definitive
Tempo	3–4 h × 3/week	Continuous, daily	Continuous (24 h)	Permanent
Key limit	Intradialytic hypotension	Peritonitis	Needs ICU/anticoagulation	Donor shortage, immunosuppression

Haemodialysis

- ▶ **Three components:** the dialyzer (hollow-fibre, **biocompatible synthetic polysulfone** membrane — replaced older “bioincompatible” cellulose membranes that activated complement); the dialysate; and the **blood-delivery system**.
- ▶ **Dialysate composition:** potassium 0–4 mmol/L (very low-K baths increase sudden-death risk), calcium usually 1.25 mmol/L (2.5 mEq/L), sodium 135–140 mmol/L (*sodium modelling* may reduce intradialytic hypotension). Water is purified by softening, deionisation and **reverse osmosis** (~120 L exposure per session).
- ▶ **Prescription:** heparinised blood pumped at 250–450 mL/min with dialysate running **counter-current** at 500–800 mL/min; small molecules (urea, 60 Da) cleared far better than larger ones (creatinine, 113 Da).

- ▶ **Vascular access (in order of preference — “Fistula First”):** native arteriovenous fistula (*Brescia–Cimino*: cephalic vein at wrist anastomosed end-to-side to radial artery) — highest patency, lowest infection, matures in 6–8 weeks; **AV graft** (interposed PTFE, usable ~2 weeks, fails by intimal hyperplasia/thrombosis); **tunnelled cuffed catheter** (internal jugular preferred; highest infection/thrombosis — a “lifeline” only). Subclavian access is avoided (stenosis risk).
- ▶ **Adequacy: urea reduction ratio (URR) >65–70 %** and **Kt/V >1.2** (single-pool) or 1.05 (equilibrated); standard schedule 9–12 h/week in 3 sessions.
- ▶ **Acute complications: hypotension** (commonest — excess/rapid ultrafiltration; avoid removal >13 mL/kg/h), muscle cramps, and **dialyzer reactions** — *type A* (IgE-mediated anaphylaxis to ethylene-oxide, within minutes) and *type B* (complement/cytokine-mediated chest & back pain). **Dialysis disequilibrium syndrome** (cerebral oedema from rapid urea/osmolar shifts) may occur with aggressive early sessions — mitigated by short, low-efficiency initial runs.

Peritoneal dialysis

- ▶ **Principle:** 1.5–3 L of hypertonic **dextrose** solution dwells in the peritoneal cavity (2–4 h); solute is removed by diffusion and water by **osmotic ultrafiltration**. **Icodextrin**, a non-absorbable glucose polymer, gives sustained ultrafiltration in the long dwell of high transporters.
- ▶ **Forms:** CAPD (manual exchanges, 3–5/day with an overnight dwell) and CCPD/APD (automated cycler performs exchanges overnight). The **peritoneal equilibration test (PET)** classifies membranes as **low, low-average, high-average, high transporters** — high transporters need short, frequent (cycler) dwells.
- ▶ **Access:** soft silicone catheter with **two Dacron cuffs** that scar to anchor and seal against bacterial tracking.
- ▶ **Complications: peritonitis** (commonest serious complication) — cloudy effluent + abdominal pain, **dialysate leukocytes >100/mm³ with >50% neutrophils**; usually **gram-positive cocci** (*Staphylococcus*, skin origin), treated with intraperitoneal/oral antibiotics; *Pseudomonas* or fungal peritonitis mandates **catheter removal**. Also tunnel-exit infections, **protein loss/hypoalbuminaemia**, hyperglycaemia, weight gain, hypertriglyceridaemia and late **encapsulating peritoneal sclerosis**. Advantage: continuous potassium/phosphate removal allows a more liberal diet and suits haemodynamically labile patients.

Continuous & hybrid therapies (AKI)

- ▶ **CVVH** (purely convective — plasma water forced across the membrane, replaced by crystalloid), **CVVHD** (diffusive, low blood/dialysate flows), **CVVHDF** (combined). **SLED/EDD** (“hybrid”, ≤12 h) capture CRRT’s gentleness without 24-h staffing.
- ▶ Preferred for **haemodynamic instability, cerebral oedema or severe volume overload**; trials show no survival/recovery superiority over intermittent HD, and no benefit of higher dialysis dose.

Kidney transplantation — the definitive RRT

- ▶ **Treatment of choice for ESKD**, conferring longer survival and better quality of life than dialysis; first successful transplant Boston 1954 (identical twins). One-year graft survival ~98% (**living**) and 93% (**deceased**); mean graft survival ~19 vs 12 years. The graft is placed **extraperitoneally in the iliac fossa** — donor renal artery→external iliac artery, renal vein→external iliac vein, ureter→bladder.
- ▶ **Matching**: ABO compatibility plus **HLA** (chromosome 6; class I = A, B, C; class II = DR, DQ, DP) — more A/B/DR mismatches predict poorer survival. A **positive cytotoxic T-cell crossmatch** (preformed donor-specific anti-HLA class I antibody) predicts **hyperacute rejection** and is the *only absolute immunologic contraindication*.
- ▶ **Absolute contraindications**: predicted survival <2 years, active malignancy, active infection, non-adherence/psychosocial barriers, active substance abuse.
- ▶ **Rejection**: *hyperacute* (preformed antibody, minutes); *acute T-cell-mediated* (Banff-graded interstitial/tubular/vascular infiltrate → IV **methylprednisolone 500–1000 mg/day × 3**, then ATG); *antibody-mediated* (C4d in peritubular capillaries + circulating DSA → plasmapheresis, IVIG, rituximab, bortezomib); and chronic (fibrosis/vasculopathy).
- ▶ **Immunosuppression**: *Induction* — depleting **antithymocyte globulin (ATG)** or **alemtuzumab** (anti-CD52); non-depleting **basiliximab** (anti-IL-2Rα/CD25). *Maintenance* — a **calcineurin inhibitor** (tacrolimus [binds FKBP-12] or cyclosporine [binds cyclophilin] → blocks IL-2 transcription) + an **antimetabolite** (mycophenolate, or azathioprine — check TPMT) + **steroids**; alternatives **mTOR inhibitors** (sirolimus/everolimus) and **belatacept** (CTLA-4-Ig, blocks CD80/86–CD28 costimulation). CNI toxicity: nephrotoxicity, hypertension; cyclosporine causes hirsutism & gingival hyperplasia, tacrolimus causes post-transplant diabetes.
- ▶ **Post-transplant infection timeline**: <1 month — bacterial wound/UTI, HSV, candidiasis; 1–6 months — opportunistic CMV (D+/R– highest risk; valganciclovir), **Pneumocystis** (TMP-SMX prophylaxis 6 months), **BK polyomavirus nephropathy** (manage by reducing immunosuppression), Listeria, Nocardia; >6 months — Aspergillus, zoster, community pathogens. **Malignancy** (~100× general population): **skin/lip cancers** commonest; **EBV-driven PTLD**. Leading causes of recipient death: cardiovascular (~29%), infection (~18%), malignancy (~17%).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Haemodialysis circuit**: label *arterial line from AV fistula → blood pump → heparin infusion → hollow-fibre dialyzer (blood vs counter-current dialysate compartments) → air/leak detector → venous line back to patient*; on the dialysate side label *purified water (reverse osmosis) + acid/bicarbonate concentrate → dialysate inflow → drain*. Mark **diffusion** and **ultrafiltration/convection** across the membrane.

- ▶ **Transplant anatomy:** label *graft kidney in right iliac fossa, donor renal artery → external iliac artery, donor renal vein → external iliac vein, donor ureter → recipient bladder*, native kidneys left in situ.

Clinical / Diagnostic significance

- ▶ **Modality choice** balances comorbidity, vascular/peritoneal access, lifestyle and resources; outcomes of HD vs PD are broadly similar, so quality-of-life often decides. PD predominates in resource-limited settings (lower cost).
- ▶ **Pre-emptive transplantation** (before dialysis) gives the best outcomes; living-donor grafts outperform deceased-donor.
- ▶ **Cardiovascular disease** is the leading cause of death in both dialysis and transplant populations; aggressive BP, lipid and volume control are essential.
- ▶ Monitoring tools: **URR/Kt/V** for HD adequacy, **PET** for PD membrane typing, **donor-specific antibody + allograft biopsy (Banff)** for rejection.

High-yield exam pointers

- ▶ RRT = HD + PD + CRRT + **transplantation**; dialysis works by **diffusion + convection**.
- ▶ AEIOU = AKI dialysis indications; ESKD dialysis when GFR ~5–10 with uraemia.
- ▶ **Brescia–Cimino radiocephalic fistula** = preferred access (“Fistula First”); matures 6–8 weeks; highest patency, lowest infection.
- ▶ **HD adequacy:** URR >65–70 %, Kt/V >1.2; commonest acute complication = **hypotension**.
- ▶ **PD peritonitis:** cloudy effluent, >100 WBC/mm³ (>50% **neutrophils**), usually **gram-positive cocci**; *Pseudomonas*/fungal → remove catheter.
- ▶ **CRRT** preferred in haemodynamic instability/cerebral oedema; no survival edge over intermittent HD.
- ▶ **Positive cytotoxic crossmatch** = only absolute immunologic contraindication (hyperacute rejection).
- ▶ Transplant maintenance = **CNI + antimetabolite + steroid**; **C4d** in peritubular capillaries = antibody-mediated rejection.
- ▶ Commonest post-transplant malignancy = **skin cancer**; **CMV** and **BK virus** are key opportunists.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Dialysis in the Treatment of Kidney Failure”; “Kidney Transplantation”; “Acute Kidney Injury” (CRRT/SLED modalities); “Interventional Nephrology” (access).

- **Brenner & Rector's The Kidney** — “Hemodialysis” (Kt/V, adequacy, urea kinetics) and “Peritoneal Dialysis” (icodextrin, transporter status, automated PD).
- **CMDT 2026** — “Kidney Disease” (AEIOU indications, ESKD treatment thresholds, access maturation times, prognosis).

Coverage note: “Dialysis disequilibrium syndrome” and the AEIOU framing are universally accepted standard internal medicine, included for completeness; the Harrison/Brenner dialysis chapters describe the underlying osmolar-shift and indication concepts but do not use these exact labels.



Renal tubular Acidosis

Asked in: Paper IV May 2022 · Paper IV Nov 2021 (2×) — RGUHS MD General Medicine

Definition / Introduction — Renal tubular acidosis (RTA) is a group of disorders characterised by a **normal anion-gap (hyperchloraemic) metabolic acidosis** caused by impaired renal tubular acidification—either failure of the proximal tubule to reabsorb filtered bicarbonate or failure of the distal nephron to secrete H^+ / generate ammonium—**despite a relatively preserved glomerular filtration rate**. It is recognised biochemically by a hyperchloraemic acidosis with reciprocal fall in $[\text{HCO}_3^-]$ and a **positive urine anion gap** (signifying low urinary NH_4^+ of renal origin). The clinically important forms are **proximal (type 2)**, **classic distal (type 1)**, and **hyperkalaemic / generalised distal nephron dysfunction (type 4) RTA**.

Classification (Harrison Table 58-5)

Type	Defect	Serum K^+	Representative causes
Proximal (type 2)	Reduced proximal HCO_3^- reabsorptive threshold (T_m) → bicarbonaturia	Low	Acetazolamide, topiramate, ifosfamide; Fanconi syndrome; light-chain (myeloma) injury; inherited <i>SLC4A4</i> (basolateral NBCe1, with ocular abnormalities), <i>NHE3</i> (AD, short stature)
Distal / classic (type 1)	Impaired distal H^+ secretion / acidification	Low	Amphotericin B, ifosfamide; Sjögren's syndrome; SLE; inherited <i>ATP6V1B1</i> defect (distal tubule/collecting duct)

Type	Defect	Serum K ⁺	Representative causes
Generalised distal nephron dysfunction (type 4)	Aldosterone deficiency or resistance → impaired NH ₄ ⁺ generation + impaired K ⁺ /H ⁺ secretion	High	Hyporeninaemic hypoaldosteronism (diabetes, tubulointerstitial disease); mineralocorticoid resistance (PHA I); voltage defect (PHA I recessive, PHA II); drugs

- ▶ Within type 4, Harrison subdivides causes into (a) **selective aldosterone deficiency**, (b) **mineralocorticoid resistance** — pseudohypoaldosteronism (PHA) I, autosomal dominant, (c) **voltage defect** — PHA I autosomal recessive and PHA II, (d) **hyporeninaemic hypoaldosteronism**, and (e) **tubulointerstitial disease**.
- ▶ **Normokalaemic renal acidosis** of chronic progressive kidney disease (the “uraemic” non-AG acidosis of CKD stages 3–4) is a separate category requiring oral alkali.

Pathophysiology by type

- ▶ **Proximal RTA (type 2)**: generalised proximal tubular dysfunction reduces the bicarbonate reabsorptive threshold. At normal plasma [HCO₃⁻] there is **bicarbonaturia** with an inappropriately alkaline urine; once plasma [HCO₃⁻] falls **below the reduced threshold**, the distal nephron is intact, so the urine can be acidified to **pH <5.5**. It is frequently part of **Fanconi syndrome** — glycosuria, generalised aminoaciduria and phosphaturia. Alkali therapy enhances distal Na⁺/HCO₃⁻ delivery and **renal K⁺ secretion**, aggravating hypokalaemia.
- ▶ **Distal RTA (type 1)**: failure of distal H⁺ secretion produces an inability to lower urine pH appropriately. Classic features are **hypokalaemia**, **non-AG metabolic acidosis**, **low urinary NH₄⁺ excretion (positive urine anion gap)**, and an **inappropriately high urine pH (>5.5)** for the degree of systemic acidosis. **Hypocitraturia** and **hypercalciuria** are usual, so **nephrolithiasis**, **nephrocalcinosis** and **metabolic bone disease** are common.
- ▶ **Type 4 (hyperkalaemic) RTA**: aldosterone deficiency or tubular resistance impairs both potassium and acid secretion. **Hyperkalaemia** is **disproportionate to the reduction in GFR**, and hyperkalaemia itself **suppresses renal ammoniogenesis**, depressing urinary NH₄⁺ and net acid excretion. **Hyporeninaemic hypoaldosteronism** typically presents in **older adults with diabetes mellitus or tubulointerstitial disease and stage 3–4 CKD**, with K⁺ 5.2–6.0 mmol/L, **hypertension and congestive heart failure**, both acidosis and hyperkalaemia being out of proportion to the GFR. NSAIDs, trimethoprim, pentamidine, ACE inhibitors and ARBs increase the risk, especially in diabetic nephropathy.

Diagnostic approach

- ▶ **Confirm a normal anion-gap (hyperchloraemic) acidosis** — reciprocal rise in $[\text{Cl}^-]$ with the fall in $[\text{HCO}_3^-]$; calculate AG (correct for albumin) to exclude a high-AG process.
- ▶ **Urine anion gap (UAG)** = $([\text{Na}^+] + [\text{K}^+])_{\text{u}} - [\text{Cl}^-]_{\text{u}}$ to estimate urinary NH_4^+ :
 - **Negative UAG** → urinary NH_4^+ appropriately high → **extrarenal / gastrointestinal (diarrhoea)** cause.
 - **Positive UAG** → urinary NH_4^+ inappropriately low → **renal (RTA)** origin.
- ▶ **Urine pH**: inappropriately >5.5 in classic distal RTA and during the bicarbonaturic phase of proximal RTA; in proximal RTA the urine acidifies to <5.5 once plasma $[\text{HCO}_3^-]$ falls below threshold; in type 4 the dominant abnormality is **depressed urinary NH_4^+** .
- ▶ **Caveat (Harrison)**: the UAG correlates poorly with directly measured urine ammonium, so laboratories are encouraged to **measure urine NH_4^+ directly** (enzymatic assay on a 1:200 saline-diluted sample) rather than rely on the UAG.
- ▶ **Supportive findings**: proximal — glycosuria, aminoaciduria, phosphaturia (Fanconi); distal — hypokalaemia, hypercalciuria, hypocitraturia, nephrocalcinosis; type 4 — hyperkalaemia disproportionate to GFR, often diabetic/obstructive/tubulointerstitial kidney disease.

Treatment

- ▶ **Proximal RTA (type 2)**: the **most difficult RTA to fully correct**, because alkali increases urinary bicarbonate and potassium loss; **potassium supplementation is usually required**. An oral **sodium + potassium citrate** solution (citric acid 334 mg, sodium citrate 500 mg, potassium citrate 550 mg per 5 mL) is used; large alkali doses are often needed to restore serum $[\text{HCO}_3^-]$ (important for normal growth in children).
- ▶ **Distal RTA (type 1)**: **correct hypokalaemia first**, then give alkali — **sodium citrate (Shohl's solution)** or NaHCO_3 tablets (650-mg tablet = 7.8 meq) — to maintain serum $[\text{HCO}_3^-]$ at 24–26 meq/L. Patients respond readily; benefits include **fewer kidney stones, improved bone density, resumption of normal growth, and preservation of kidney function**.
- ▶ **Type 4 RTA**: **correct the metabolic acidosis** (alkali, as for type 1) and **correct the plasma $[\text{K}^+]$** ; restoring normokalaemia restores ammoniagenesis and net acid excretion. Hyperkalaemia is managed with the **calcium–potassium cation-exchange polymer patiromer** (8.4-g packets PO twice daily, titrated weekly to plasma K^+ , **max 25.2 g/day**) plus a **low-potassium diet** and withdrawal of potassium-retaining drugs; **documented isolated hypoaldosteronism is treated with fludrocortisone** (cautiously, with furosemide if there is oedema/hypertension).
- ▶ **CKD acidosis**: oral alkali to keep $[\text{HCO}_3^-] >22\text{--}24\text{ mmol/L}$ ($\approx 1.0\text{--}1.5\text{ mmol/kg/day}$ as NaHCO_3 or Shohl's solution); a diet rich in fruit and vegetables also raises plasma $[\text{HCO}_3^-]$ and slows CKD progression.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Nephron schematic of acidification** — label: *proximal tubule* (Na^+/H^+ exchanger NHE3, basolateral NBCe1, HCO_3^- reabsorption — site of **type 2**); *distal tubule / α -intercalated cell of collecting duct* (apical H^+ -ATPase, basolateral $\text{Cl}^-/\text{HCO}_3^-$ exchanger AE1 — site of **type 1**); *principal cell / aldosterone action* (ENaC, $\text{Na}^+/\text{K}^+/\text{H}^+$ secretion — site of **type 4**); annotate **urine pH** and **serum K^+** for each.
- ▶ **Diagnostic flow box** — label: *Hyperchloraemic non-AG acidosis* → *Urine anion gap*; *Negative UAG = GI/diarrhoea*; *Positive UAG = RTA* → *check serum K^+ (low = type 1/2; high = type 4) and urine pH (>5.5 distal)*.

Clinical / Diagnostic significance

- ▶ **Tubulointerstitial disease** is a major secondary cause: chronic TIN produces **type II RTA** from bicarbonaturia (Fanconi) or **type IV RTA** from impaired ammoniogenesis; Sjögren's syndrome classically causes **distal RTA** and **nephrogenic diabetes insipidus** (anti-Ro/SS-A, anti-La/SS-B positive); **lupus nephritis** may present with **type IV RTA**; **calcineurin inhibitors** cause hyperkalaemia via **tubular resistance to aldosterone**.
- ▶ **Proximal RTA** points to Fanconi syndrome — screen for **multiple myeloma / light-chain cast nephropathy**, drugs (ifosfamide, acetazolamide, topiramate) and heavy-metal (lead) tubulopathy.
- ▶ **Distal RTA** must be considered in any patient with **recurrent calcium nephrolithiasis**, **nephrocalcinosis**, **hypokalaemic paralysis**, or **unexplained osteomalacia/rickets**.
- ▶ **Type 4 RTA** is the commonest RTA in adult practice — suspect it in a **diabetic with mild CKD** and **hyperkalaemia disproportionate to GFR**, particularly on ACE inhibitors/ARBs, NSAIDs, trimethoprim, pentamidine or heparin.

High-yield exam pointers

- ▶ RTA = normal anion-gap (hyperchloraemic) metabolic acidosis with positive urine anion gap.
- ▶ Type 1 & 2 → hypokalaemia; Type 4 → hyperkalaemia.
- ▶ **Distal (type 1)**: urine pH >5.5, stones/nephrocalcinosis, hypercalciuria + hypocitraturia; causes — amphotericin B, Sjögren's, SLE, ATP6V1B1.
- ▶ **Proximal (type 2)**: Fanconi syndrome (glycosuria, aminoaciduria, phosphaturia); urine can still acidify <5.5 when plasma HCO_3^- is low; causes — acetazolamide, topiramate, ifosfamide, myeloma.
- ▶ **Type 4**: hyporeninaemic hypoaldosteronism in elderly diabetics; hyperkalaemia suppresses ammoniogenesis.
- ▶ **Positive UAG = renal cause**; **negative UAG = diarrhoea/GI** (but Harrison: measure urine NH_4^+ directly as UAG is unreliable).

- ▶ Treatment anchors: **Shohl's solution** / NaHCO_3 (650 mg = 7.8 meq); K^+ + alkali (citrate) for type 2; **patiomer + fludrocortisone** for type 4.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 58 "Acidosis and Alkalosis" (non-AG acidoses, Table 58-5 classification, UAG, treatment of types 1/2/4) and Ch 328 "Tubulointerstitial Diseases of the Kidney" (Fanconi/type II and type IV RTA in TIN, Sjögren's, SLE, CNI hyperkalaemia). **Coverage note:** the *SLC4A1* (*AE1/band-3*) gene for autosomal-dominant distal RTA, the formal "type 3 (mixed)" designation, and the ammonium chloride / bicarbonate-infusion (fractional excretion of HCO_3^- >10–15% in type 2) provocative tests are standard textbook additions used here for completeness but are not detailed in the two provided chapters; Harrison lists *ATP6V1B1* as the inherited distal-RTA gene.



Renovascular Hypertension

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — **Renovascular hypertension (RVH)** is a rise in systemic arterial pressure *definitely induced by reduced renal perfusion*, most often from occlusive disease of a main or branch renal artery. It is the prototypical **potentially curable** ("secondary") **cause of hypertension**, because restoration of renal perfusion can reverse the pressor pathways. *Renal artery stenosis (RAS)* denotes the anatomical lesion; RVH is the *functional* consequence — the two are not synonymous, since many incidentally found stenoses are haemodynamically trivial. Renovascular disease is found in up to 25% of autopsies, yet RVH accounts for only ~1–2% of all hypertension.

Aetiology & Classification

- ▶ **Two dominant causes** account for the vast majority:
 - **Atherosclerotic RAS (ARAS)** — ~90%; older patients with diffuse atherosclerotic risk factors.
 - **Fibromuscular dysplasia (FMD)** — ~10%; younger women (age 15–50).
- ▶ ARAS is *common*: ~6.8% of a community sample over age 65, rising to 18–23% with coronary artery disease and >30% with peripheral/aortic disease. Untreated, ARAS **progresses in ~50% over 5 years**, sometimes to total occlusion.
- ▶ Other causes (Brenner Box 47.1): renal artery aneurysm, arterial embolus/thrombosis, dissection, arteriovenous fistula, extrinsic compression (e.g. pheochromocytoma, tumour), aortic coarctation, systemic vasculitis (**Takayasu arteritis**, polyarteritis), atheroembolic disease, and iatrogenic occlusion by an **endovascular aortic stent-graft**.

Feature	Atherosclerotic RAS (ARAS)	Fibromuscular dysplasia (FMD)
Proportion	~90%	~10%
Typical patient	Older, M≈F, ASCVD risk factors, smoker, diabetic	Young/middle-aged women (15–50 y)
Lesion site	Ostial / proximal third of renal artery	Mid–distal artery, branches; often bilateral
Angiographic look	Discrete proximal stenosis, often aortic plaque extension	“String of beads” / sawtooth (medial fibroplasia) ± aneurysm
Natural history	Progressive; causes ischaemic nephropathy	Rarely threatens GFR; may occlude / form aneurysm
Response to angioplasty	Poor — medical therapy preferred	Often curative (PTR)

- **FMD subtypes** (Brenner Box 47.1): *medial fibroplasia* (commonest, classic string-of-beads), *perimedial fibroplasia*, *intimal fibroplasia*, and *medial hyperplasia*.

Pathophysiology — the Goldblatt paradigm

- **Goldblatt (1932–34)** showed that clipping a renal artery reliably produces hypertension — the foundation of RAAS discovery.
- A lesion becomes **haemodynamically “critical”** only when **luminal obstruction reaches ~70–80%**; a translesional aorto-renal pressure gradient of **10–20 mmHg** is needed before measurable renin release occurs.
- Two physiologically distinct models explain the syndrome:

	Two-kidney, one-clip (2K1C) — unilateral RAS, normal contralateral kidney	One-kidney, one-clip (1K1C) — bilateral RAS or stenosis to a solitary kidney
Driving mechanism	Renin → Angiotensin II–dependent	Volume-dependent (impaired Na ⁺ /water excretion)
Contralateral kidney	Intact → pressure natriuresis keeps it volume-deplete → <i>sustained</i> renin release from stenotic side	Absent escape → Na ⁺ /water retention, volume expansion
Plasma renin activity	Elevated	Normal or low
Lateralisation of tests	Present (renal-vein renin, captopril renography)	None

	Two-kidney, one-clip (2K1C) — unilateral RAS, normal contralateral kidney	One-kidney, one-clip (1K1C) — bilateral RAS or stenosis to a solitary kidney
Effect of RAAS blockade	Lowers BP; may drop GFR in stenotic kidney; sharpens test lateralisation	Lowers BP only after volume depletion; may sharply lower GFR

- ▶ **Downstream Angiotensin II effects:** efferent arteriolar vasoconstriction, aldosterone secretion ($\rightarrow$ Na^+ retention, hypokalaemia), sympathetic activation, plus chronic **vascular remodelling**, LV hypertrophy, endothelin release, oxidative stress and fibrosis.
- ▶ **Three temporal phases (experimental):** **Phase I** — high circulating renin, BP fully reversible by clip removal; **Phase II** — renin returns to normal, BP persists but still clip-reversible; **Phase III** — BP becomes *clip-independent* (structural remodelling, oxidative injury, contralateral microvascular damage) and is no longer cured by revascularisation. This explains why **late revascularisation often fails to normalise BP**.
- ▶ **Ischaemic nephropathy:** with advanced ARAS, falling cortical perfusion and tissue hypoxia $\rightarrow$ tubulointerstitial fibrosis and loss of GFR. ~85% of revascularisation candidates already have stage 3–5 CKD (eGFR <60).

Clinical features — when to suspect RVH

- ▶ **Demographic/temporal clues:** onset of hypertension **before age 20–30 or after 50–55 years**; abrupt-onset or rapidly worsening previously controlled hypertension.
- ▶ **Resistant hypertension** — uncontrolled despite ≥ 3 drugs (one a diuretic).
- ▶ **Abdominal / flank (epigastric) bruit**; evidence of atherosclerosis elsewhere (claudication, CAD) — 15–25% of symptomatic lower-limb PAD have RAS.
- ▶ **Abrupt rise in serum creatinine** (>25–30%) after starting an ACE inhibitor / ARB — a *functional, reversible* loss of GFR from removing efferent vasoconstriction; strongly suggests **bilateral RAS or stenosis to a solitary kidney**.
- ▶ **Recurrent “flash” pulmonary oedema** with surges of BP and preserved LV systolic function (*Pickering syndrome*).
- ▶ **Unprovoked hypokalaemia** (secondary hyperaldosteronism), proteinuria, and **asymmetric kidney size** (>1.5 cm difference) on ultrasound.
- ▶ *Note:* the Cooperative Study (Simon 1972) confirmed that although early age of onset, abdominal bruit, hypokalaemia and grade 3–4 fundi are commoner in RVH, **no single clinical feature reliably discriminates it from essential hypertension**.

Diagnostic evaluation

- **Principle:** screen non-invasively, confirm by angiography — and *only investigate aggressively if a corrective procedure would be undertaken on a positive result.*

Modality	Role / strength	Caveat
Duplex Doppler ultrasonography	Peak systolic velocity >200 cm/s predicts >60% stenosis; renal resistive index predicts viability; cheap, repeatable	Highly operator- and habitus-dependent
CT angiography (CTA)	Excellent vascular images; best for accessory vessels & distal disease; no stent artefact	Iodinated contrast toxicity
MR angiography (MRA)	Good images of artery + perirenal aorta	Gadolinium / nephrogenic systemic fibrosis risk — avoid if eGFR <30; cannot image stents
Captopril renography (^{99m}Tc -MAG3)	Strong negative predictive value — a normal study excludes RVH	Affected by drugs, Na^+ , bilateral disease
Intra-arterial (digital subtraction) angiography	Gold standard; usually combined with intended intervention	Invasive; atheroembolism, contrast, dissection

- **Plasma renin activity / renal-vein renin sampling** is transient and drug/sodium-sensitive — it does **not** reliably predict response and is now **rarely performed** (high false-positive and false-negative rates).

Management

- **Optimal medical therapy is the cornerstone** for most patients (especially ARAS):
 - **RAAS blockade (ACE inhibitor or ARB)** — most effective antihypertensives in RVH; **monitor creatinine and potassium** after initiation; not absolutely contraindicated in unilateral disease.
 - **Statin, antiplatelet (aspirin), smoking cessation, attainment of goal BP, glycaemic control.**
- **Revascularisation** — endovascular stenting (ARAS) or **percutaneous transluminal renal angioplasty (PTRA)**:
 - **FMD** → PTRA is **often curative** — the single most important reason to *identify* FMD.
 - **ARAS** → the randomised trials **ASTRAL (2009), STAR (2009) and CORAL (2014)** showed **no added benefit of stenting over optimal medical therapy** for BP or renal preservation in moderate stenosis.
 - **Reserve intervention** (Harrison Table 289-2; AHA 2022) for: refractory hypertension / medical failure; **rapidly declining or recurrent fall in GFR**, including a fall precipitated by ACEi/ARB; **flash pulmonary oedema** or recurrent unexplained heart failure; high-grade (>70%) stenosis to the whole functioning renal mass; transplant renal-artery stenosis.

- **Procedural risk** <5% with experienced operators: renal artery dissection, capsular perforation, haemorrhage, and **atheroembolic disease** (which can paradoxically accelerate hypertension and renal failure). Renal flow is usually restored, but function recovers in only ~25% of cases.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Goldblatt 2K1C vs 1K1C schematic** — Draw two kidneys. *Left (2K1C)*: stenosed renal artery → “↓perfusion → ↑Renin → Angiotensin II → Aldosterone → Angiotensin-II-dependent HTN; PRA HIGH; lateralises”; contralateral kidney labelled “pressure natriuresis (volume-deplete)”. *Right (1K1C)*: bilateral stenoses / solitary kidney → “↓perfusion → Na⁺ + water retention → Volume expansion → volume-dependent HTN; PRA normal/low; NO lateralisation”.
- ▶ **RAAS cascade box** — Labels: *Angiotensinogen* → (*Renin*) → *Angiotensin I* → (*ACE*) → *Angiotensin II* → branches to **Vasoconstriction**, **Aldosterone** → Na⁺ retention, **Sympathetic activation**, LV hypertrophy / vascular remodelling.

Clinical / Diagnostic significance

- ▶ RVH is a **treatable secondary hypertension** — but in the modern era the chief goal has shifted from *curing BP* to **preserving renal function and preventing cardiovascular events**.
- ▶ A >25–30% **creatinine rise after ACEi/ARB** is a clinical “stress test” that unmasks bilateral RAS/solitary-kidney stenosis — recognise it early, as it is reversible.
- ▶ ARAS is an independent marker of **cardiovascular morbidity and mortality** regardless of whether revascularisation is done.
- ▶ **Atheroembolic (cholesterol-crystal) renal disease** is a key differential/complication after angiography or vascular surgery: **livedo reticularis**, **blue toes**, **eosinophilia** (60–80%), **hypocomplementaemia** (15%), stuttering renal failure, biopsy showing biconvex cholesterol “clefts”; 1-year mortality >38%. Withdraw anticoagulation; no specific therapy.

High-yield exam pointers

- ▶ RVH = **functional consequence**; RAS = **anatomical lesion** — not interchangeable.
- ▶ ~90% ARAS (ostial, older men) vs ~10% FMD (string-of-beads, young women); FMD responds to PTCA, ARAS usually does not.
- ▶ **Critical stenosis** = 70–80% lumen loss; **gradient 10–20 mmHg** triggers renin release.
- ▶ 2K1C = **renin/angiotensin-dependent**, PRA high, lateralises; 1K1C = **volume-dependent**, PRA normal/low, no lateralisation.
- ▶ **Captopril renography**: a *normal* scan excludes RVH (high NPV); DSA = **gold standard**.
- ▶ **Suspect RVH**: age <30 or >50, resistant HTN, abdominal bruit, flash pulmonary oedema, **creatinine** ↑ >25% on ACEi/ARB, hypokalaemia, asymmetric kidneys.

- ▶ **ASTRAL / CORAL / STAR:** stenting **no better than medical therapy** in ARAS — reserve intervention for refractory HTN, flash pulmonary oedema, or rapidly falling GFR.
- ▶ Medical bundle = RAAS blockade + statin + antiplatelet + smoking cessation + BP control.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Renovascular Disease” (Textor) and “Hypertension” (secondary hypertension / renovascular section).
- ▶ **Brenner & Rector's The Kidney** — “Renovascular Hypertension and Ischemic Nephropathy” (Goldblatt 2K1C/1K1C models, phases of RVH, critical-stenosis thresholds, lesion classification Box 47.1, Cooperative Study clinical clues).
- ▶ **CMDT 2026** — “Systemic Hypertension” (renal vascular hypertension) and “Kidney Disease — Renal Artery Stenosis” (diagnostic criteria, ASTRAL/CORAL evidence, revascularisation indications, AHA 2022 statement).

Coverage note: The eponym “Pickering syndrome” for recurrent flash pulmonary oedema with bilateral RAS is universally accepted standard medicine but is not named in the cited corpus (which uses “flash pulmonary edema”); trial acronyms ASTRAL/CORAL/STAR appear in the corpus on the RVD historical timeline and CMDT's “two large randomized trials” statement.



Tubulointerstitial Diseases of the Kidney

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Tubulointerstitial diseases are a group of disorders that **primarily** target the renal tubules and the interstitium, with relative sparing of the glomeruli and renal vessels (distinguishing them from the *secondary* interstitial fibrosis that complicates almost every chronic glomerular or vascular disease). They are conveniently divided into **acute** (acute tubulointerstitial/interstitial nephritis, AIN/ATIN) and **chronic** (CIN/CTIN) forms. They account for roughly **10–20% of acute kidney injury (AKI)** and are an important, frequently unrecognised, cause of chronic kidney disease (CKD), with **interstitial fibrosis and tubular atrophy** as the final common pathway.

Classification (Causes)

Acute tubulointerstitial disorders	Chronic tubulointerstitial disorders
Drug-induced AIN — antibiotics (β -lactams, sulfonamides, quinolones, vancomycin, rifampin, ethambutol, acyclovir), NSAIDs/COX-2 inhibitors, PPIs/H ₂ -blockers, diuretics (thiazide, loop, triamterene), anticonvulsants (phenytoin, valproate,	Toxins/drugs — analgesics (phenacetin), lithium, heavy metals (lead, cadmium), aristolochic acid , calcineurin inhibitors (cyclosporine, tacrolimus)

Acute tubulointerstitial disorders	Chronic tubulointerstitial disorders
carbamazepine), allopurinol, mesalazine, immune checkpoint inhibitors , lenalidomide	
Infection-associated — <i>Streptococcus</i> , <i>Staphylococcus</i> , <i>Legionella</i> , <i>Leptospira</i> ; EBV, CMV, hantavirus, polyomavirus (BK), HIV	Reflux nephropathy (vesicoureteral reflux); sickle cell nephropathy
Autoimmune — TINU, Sjögren's, SLE, sarcoidosis (granulomatous), IgG4-related disease , anti-brush-border (anti-LRP2) disease	Metabolic — hypercalcaemia/nephrocalcinosis, hyperuricaemia (gouty), chronic hypokalaemia, hyperoxaluria
Acute obstructive (crystal) — light-chain cast nephropathy, acute urate nephropathy, acute phosphate nephropathy	Cystic/hereditary — ADPKD, nephronophthisis, ADTKD (medullary cystic kidney disease), medullary sponge kidney
	Other — chronic GN, obstruction, ischaemia, radiation; CINAC/CKDu (agricultural communities)

Pathogenesis / Mechanisms of injury

- ▶ **Acute** disease results from aggressive inflammatory infiltrates causing interstitial **oedema**, **tubular cell injury** and **compromised tubular flow**, or from frank **tubular obstruction** by casts, cellular debris or crystals; capsular distension may produce **flank pain**.
- ▶ **Drug-induced ATIN** is a **T-cell-mediated delayed (Type IV) hypersensitivity reaction** — drugs act as **haptens/pro-haptens**, bind tubular basement membrane (TBM) proteins or generate neoantigens (molecular mimicry). It is most often a **Type IVb** reaction (IL-5 driven, tissue/blood eosinophilia); NSAID-induced disease lacks eosinophils. The infiltrate is **>80% T lymphocytes** (CD4⁺ and CD8⁺) with macrophages and eosinophils, plus **tubulitis** (lymphocytes crossing the TBM).
- ▶ **Chronic** disease shows interstitial fibrosis, patchy mononuclear infiltrate, widespread **tubular atrophy**, luminal dilation and **TBM thickening**. Mechanisms of fibrosis include chronic **hypoxia** (peritubular capillary rarefaction), proteinuria-induced proximal tubular injury, persistent inflammation and epithelial–mesenchymal transition (TGF- β driven).
- ▶ Because the chronic histology is non-specific, **diagnosis relies on history, drug/toxin exposure and imaging** more than biopsy.

Acute Interstitial Nephritis — clinical features, diagnosis, treatment

- ▶ First described by **Councilman (1897)** in scarlet fever and diphtheria; today it is most often an **allergic drug reaction**, accounting for ~10–15% of intrinsic AKI. Drugs cause >70% of cases (top classes: antibiotics ~49%, PPIs ~14%, NSAIDs ~11%; commonest single drugs — omeprazole, amoxicillin, ciprofloxacin).

- ▶ **Classic triad** — fever, rash and (peripheral) eosinophilia with oliguric AKI ~7–10 days after a β -lactam — is the **exception (only ~5–15%)**, and is commonest with β -lactams/sulfonamides. Latency is long and “silent” with PPIs (~11 weeks) and NSAIDs (6–18 months, often with heavy/nephrotic proteinuria $\pm$ minimal-change or membranous lesion). Rifampin-induced AIN is dose-dependent, antibody-mediated and severe on re-exposure.
- ▶ **Urinalysis**: sterile pyuria, WBC casts, microscopic haematuria and low-grade tubular proteinuria (<1–2 g/day). Urinary eosinophils are **NEITHER sensitive nor specific and are no longer recommended**. Eosinophilia, raised ESR/CRP and IgE are supportive but inconsistent.
- ▶ **Kidney biopsy is the gold standard** (interstitial inflammation + tubulitis $\pm$ eosinophils $\pm$ granuloma). Ancillary: $^{67}\text{Gallium}$ / FDG-PET show enhanced renal uptake; ultrasound shows enlarged echogenic kidneys (non-specific).
- ▶ **Treatment** — **withdraw the offending agent** (often reversible) and give supportive care; **up to one-third require temporary dialysis**. Glucocorticoids are added if there is no recovery within ~5–7 days, severe AKI/impending dialysis, or diffuse infiltrate — efficacy falls if started >1–2 weeks after onset. Regimen: IV methylprednisolone 250–500 mg/day for 1–4 days or prednisone ~1 mg/kg (60 mg/day) for 4–6 weeks with taper. *Absolute* steroid indications: Sjögren’s, sarcoidosis, SLE interstitial nephritis, adult TINU, IgG4-related and granulomatous/idiopathic IN.
- ▶ **Immune-mediated subtypes**: TINU (<5% of AIN; female 3:1; median age 15 yr; painful bilateral anterior uveitis $\pm$ Fanconi, raised ESR); Sjögren’s (anti-Ro/La, distal RTA, nephrogenic DI); sarcoidosis (non-caseating granulomas, hypercalcaemia — *exclude TB first*); IgG4-related disease (IgG4⁺ plasma cells, storiform fibrosis; with autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis); checkpoint-inhibitor AIN (kidney affected in ~2% monotherapy, up to 5% dual therapy; onset usually 2–3 months).
- ▶ **Crystal/obstructive tubulopathies**: sulfadiazine (“sheaf-of-wheat” crystals), indinavir/atazanavir (needle crystals), acyclovir (red-green birefringent needles); **acute urate nephropathy** (tumour-lysis — treat with rasburicase/dialysis, prophylactic allopurinol); acute phosphate nephropathy (oral Phosphosoda). **Light-chain cast nephropathy** (“myeloma kidney”) — filtered monoclonal light chains (Bence-Jones) aggregate with Tamm-Horsfall protein in distal tubules forming obstructing casts with giant-cell reaction; clues are anaemia, bone pain, hypercalcaemia and a narrow anion gap.

Chronic Tubulointerstitial Nephritis — key entities

Entity	Key features
Analgesic nephropathy	Chronic compound analgesics (phenacetin — banned in US since 1983; ≥ 6 tablets/day for >3 yr); papillary necrosis; small scarred kidneys with

Entity	Key features
	papillary calcifications; F:M 5–7:1; risk of urothelial malignancy (8–10%)
Aristolochic acid nephropathy	<i>Chinese-herb</i> + <i>Balkan endemic</i> nephropathy; <i>Aristolochia</i> species; aristolactam-DNA adducts, A:T→T:A transversions; bland sediment, severe anaemia; high upper-tract urothelial cancer risk
Lithium nephropathy	Nephrogenic diabetes insipidus (enters principal cells via ENaC, inhibits GSK-3β, downregulates aquaporin-2); chronic TIN after >10–20 yr; distal-tubule microcysts; amiloride for NDI
Calcineurin inhibitor (cyclosporine/tacrolimus)	“Striped” interstitial fibrosis, arteriolar hyalinosis, hyperkalaemia (aldosterone resistance)
Heavy-metal (lead) nephropathy	Triad of “saturnine gout,” hypertension and renal impairment; chelation may slow decline
Reflux nephropathy	VUR in childhood (old “chronic pyelonephritis”); secondary FSGS; asymmetric small scarred kidneys; ACEI/ARB/SGLT2 inhibitor for proteinuria
ADTKD	Autosomal dominant; genes <i>UMOD</i> , <i>MUC1</i> , <i>REN</i> , <i>HNF1β</i> ; bland sediment, <i>UMOD</i> form → early gout/hyperuricaemia (median ESKD ~54 yr)
Metabolic	Hypercalcaemic (nephrocalcinosis, concentrating defect), gouty/uric-acid, hypokalaemic, hyperoxaluric nephropathy
CINAC / CKDu	Young male agricultural workers — Mesoamerican, Sri Lankan, Uddanam (S. India) nephropathy; heat/dehydration ± agrochemicals

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- Schematic of the nephron in tubulointerstitial disease — label: glomerulus (relatively spared), proximal tubule (Fanconi: glycosuria, phosphaturia, aminoaciduria, type II RTA), distal tubule/collecting duct (type IV RTA, distal RTA, nephrogenic DI), interstitial inflammatory infiltrate + oedema (acute) vs interstitial fibrosis + tubular atrophy + thickened TBM (chronic), and tubulitis (lymphocytes crossing TBM).
- Treatment algorithm for AIN — label: AKI with features of AIN → withdraw offending agent → supportive care/observe → improvement (continue) OR no improvement in 1 week / rapid progression → corticosteroids; renal biopsy → classic AIN / granulomatous IN → steroids ± immunosuppressives; fibrosis → conservative.

Clinical / Diagnostic significance

- ▶ Suspect TIN in otherwise unexplained AKI/CKD with a bland or mildly active sediment, low-grade tubular proteinuria, and tubular dysfunction — polyuria (nephrogenic DI), Fanconi syndrome, type II or type IV RTA, and a serum uric acid that is lower than expected for the GFR.
- ▶ Type IV (hyperkalaemic, hyperchloraemic) RTA out of proportion to renal failure is a classic pointer to tubulointerstitial injury.
- ▶ Papillary necrosis (mnemonic) — Analgesics, Sick cell, Diabetes with UTI, prolonged NSAIDs (and obstruction/pyelonephritis); presents with flank pain, haematuria and ureteric colic from a sloughed papilla.
- ▶ Aristolochic acid and analgesic nephropathy carry a high urothelial-cancer risk — warrant surveillance (urine cytology, CT, ureteroscopy).
- ▶ Prognosis of drug-induced AIN: full recovery ~64%, partial ~23%, and ~12% progress to CKD/dialysis — early drug withdrawal (<2 weeks) is the strongest determinant of recovery.

High-yield exam pointers

- ▶ TIN = primary tubular + interstitial disease, glomeruli/vessels spared; acute vs chronic; final common pathway = interstitial fibrosis + tubular atrophy.
- ▶ Drugs cause >70% of AIN; antibiotics > PPIs > NSAIDs; mechanism = Type IV (delayed) hypersensitivity.
- ▶ Classic triad (fever + rash + eosinophilia) seen in only 5–15% — its absence does NOT exclude AIN; NSAIDs/PPIs give “silent” AIN.
- ▶ Urinary eosinophils are obsolete; kidney biopsy is the gold standard (tubulitis).
- ▶ Treatment = stop drug + supportive care ± steroids (IV methylprednisolone 0.25–0.5 g/day × 1–4 days, or prednisone 60 mg/day × 4–6 weeks); start early.
- ▶ TINU — adolescent girls, anterior uveitis, raised ESR; Sjögren’s — distal RTA + anti-Ro/La; sarcoid — granulomatous + hypercalcaemia (rule out TB); IgG4 — storiform fibrosis.
- ▶ Chronic toxins — analgesic (phenacetin, papillary necrosis), aristolochic acid (urothelial cancer), lithium (NDI), CNI (striped fibrosis), lead (saturnine gout).
- ▶ ADTKD genes — UMOD, MUC1, REN, HNF1β; CINAC/CKDu in agricultural communities (Uddanam, Mesoamerican, Sri Lankan).

SOURCE & COVERAGE

- ▶ Harrison’s Principles of Internal Medicine, 22e — “Tubulointerstitial Diseases of the Kidney” (Beck & Salant), including Table 328-1 (classification), Table 328-2 (steroid indications) and Table 328-3 (papillary necrosis).

- ▶ **Brenner & Rector's The Kidney** — “Tubulointerstitial Diseases” (Perazella & Rosner): mechanisms, ADTKD (Table 35.2), ATIN diagnostics/biopsy, drug-specific data and steroid regimens, chronic entities (analgesic, aristolochic).
- ▶ **CMDT 2026** — “Kidney Disease: Interstitial Nephritis / Chronic Tubulointerstitial Diseases”: current diagnostic criteria, corticosteroid dosing, and CINAC management.



Rheumatology & immune system



ANCA-associated vasculitis

Asked in: Paper III Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — ANCA-associated vasculitis (AAV) is a group of necrotising, predominantly small-vessel vasculitides that share a paucity of vascular immunoglobulin deposition (*pauci-immune*) and an association with circulating **antineutrophil cytoplasmic antibodies (ANCA)**. Three clinicopathologically distinct entities are grouped under AAV: **granulomatosis with polyangiitis (GPA, formerly Wegener)**, **microscopic polyangiitis (MPA)** and **eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss)**. Although they share ANCA positivity and small-vessel injury, each has a unique phenotype and is treated as a separate disease.

Classification, nomenclature & ANCA serology

- ▶ The 1992/2012 Chapel Hill Consensus Conference nomenclature places GPA, MPA and EGPA among the **predominantly small-vessel vasculitides** (with frequent overlap into medium vessels); not all cases are ANCA-positive.
- ▶ ANCA are autoantibodies directed against proteins in the cytoplasmic granules of neutrophils and monocytes; two patterns are recognised on indirect immunofluorescence (IIF):
- ▶ **c-ANCA (cytoplasmic, granular pattern)** — major antigen is **proteinase-3 (PR3)**, a 29-kDa neutral serine proteinase of azurophilic granules. >90% of *active* GPA cases have anti-PR3.
- ▶ **p-ANCA (perinuclear pattern)** — major antigen is **myeloperoxidase (MPO)**; predominant in MPA and EGPA. Other targets (elastase, cathepsin G, lactoferrin, lysozyme) give a p-ANCA pattern but only anti-MPO is convincingly vasculitis-associated.
- ▶ Every positive IIF must be **confirmed by antigen-specific enzyme immunoassay** for PR3 or MPO.
- ▶ A non-MPO p-ANCA may occur in IBD, autoimmune disease, drugs, endocarditis and cystic-fibrosis airway infection (false positives).

Pathogenesis

- ▶ PR3 and MPO normally reside inside resting neutrophil/monocyte granules, inaccessible to serum antibody.
- ▶ **Priming by TNF- α or IL-1** (or alternative-complement activation) translocates PR3/MPO to the cell surface, where ANCA bind.
- ▶ ANCA engagement causes neutrophil **degranulation, reactive oxygen species production, adhesion to and killing of endothelial cells**, and release of IL-1 and IL-8 $\rightarrow$ necrotising vascular injury. Adoptive-transfer experiments in mice support a direct pathogenic role of ANCA.
- ▶ Caveats against ANCA being solely causal: disease can occur ANCA-negative, titre correlates poorly with activity, and high titres may persist in remission.
- ▶ In GPA, an **aberrant TH1 cytokine pattern** ($\uparrow$ IFN- γ , $\uparrow$ TNF- α , $\uparrow$ IL-12) and the airway-centred granulomatous reaction suggest a cell-mediated response to an inhaled/mucosal antigen; chronic nasal *Staphylococcus aureus* carriage is linked to higher relapse rates.

The three AAV entities compared

Feature	GPA (Wegener)	MPA	EGPA (Churg-Strauss)
Epidemiology	Prevalence ~3/100,000; incidence ~12/million/yr; mean age 40–60; M:F 1:1; rare in blacks	Incidence 3–5/100,000; mean age ~57; M slightly > F	Incidence 1–3/million; mean age 48; F:M 1.2:1
Histology	Necrotising granulomatous vasculitis of small arteries & veins	Necrotising vasculitis, no granuloma , few/no immune deposits	Necrotising vasculitis + extravascular eosinophilic granuloma , tissue/blood eosinophilia
Upper airway	Sinusitis, nasal ulcer/septal perforation, saddle-nose , subglottic stenosis (~16%)	Typically absent (if present, suspect GPA)	Allergic rhinitis, nasal polyposis, sinusitis
Lung	Nodular/cavitary infiltrates; alveolar haemorrhage	Pulmonary capillaritis , alveolar haemorrhage (12%)	Asthma , fleeting eosinophilic infiltrates
Kidney	Pauci-immune crescentic GN (~77%)	Crescentic GN very common ($\geq$ 79%)	Less common than GPA/MPA
Cardiac	~8%	Uncommon	Myocarditis ~14% — leading cause of death (39%)

Feature	GPA (Wegener)	MPA	EGPA (Churg-Strauss)
ANCA	~90% PR3 (c-ANCA); 10–25% MPO; up to 20% none	~75% MPO (p-ANCA)	<50% positive, usually MPO

Clinical features

- ▶ **GPA (organ frequency through course):** upper airway 95%, ENT 92%, lung 85–90%, kidney 77%, eye 52% (episcleritis, scleritis, granulomatous sclerouveitis, retro-orbital pseudotumour → proptosis), skin 46% (palpable purpura, nodules, ulcers), CNS/PNS 23% (cranial neuritis, **mononeuritis multiplex**), cardiac 8% (pericarditis). **Venous thromboembolism** is notably increased. Renal disease, once clinically apparent, tends to progress rapidly.
- ▶ **MPA: the most common cause of pulmonary-renal syndrome** (diffuse alveolar haemorrhage + rapidly progressive GN), several-fold commoner than anti-GBM disease; palpable purpura, mononeuritis multiplex; may show UIP-like interstitial fibrosis (poor prognosis). **Drug-induced MPA** (high-titre p-ANCA) — *propylthiouracil, hydralazine, allopurinol, penicillamine, minocycline, sulfasalazine*.
- ▶ **EGPA (three classic phases):** prodromal **asthma/allergic rhinitis** → blood and tissue **eosinophilia** (>1000/μL in >80%) → systemic **vasculitis**. Mononeuritis multiplex in up to 72%; purpura and subcutaneous nodules in ~51%; cardiac involvement is the chief cause of death — echocardiography in all new cases.

Investigations & Diagnosis

- ▶ **Bloods/urine:** raised ESR/CRP, normocytic anaemia, leukocytosis, thrombocytosis; eosinophilia in EGPA. Urinalysis for dysmorphic RBCs, **RBC casts**, proteinuria signals GN.
- ▶ **ANCA:** IIF screen (c-/p-ANCA) confirmed by PR3/MPO EIA. Predictive value of a positive ANCA is ~90% with **active glomerulonephritis**, but falls to 30–60% in sinus/lung-limited disease — so **tissue biopsy is usually required**, especially when ANCA-negative or features are atypical (to exclude infection/malignancy).
- ▶ **Biopsy:** lung gives the highest yield in GPA (necrotising granulomatous vasculitis); renal biopsy shows **pauci-immune segmental necrotising crescentic glomerulonephritis** (relative absence of IgG/IgM/IgA/complement) — the hallmark common to all AAV.
- ▶ **Imaging:** chest CT (more sensitive than CXR) — nodules, masses, cavities, ground-glass of haemorrhage; sinus imaging may show bony erosion.
- ▶ In EGPA, work up unexplained eosinophilia: ANCA, serum tryptase, flow cytometry/PDGFR for eosinophilic leukaemia, and helminth serology.

Treatment

- ▶ Management has two phases — **induction of remission** then **maintenance** — stratified by severity. **Severe = organ- or life-threatening** (e.g. RPGN, alveolar haemorrhage); **active glomerulonephritis is always classed as severe** even with normal creatinine.
- ▶ **Induction (severe GPA/MPA)**: glucocorticoid (historically **prednisone 1 mg/kg/day**; a *reduced-dose regimen is non-inferior with fewer infections*) **plus either**:
 - **Cyclophosphamide** 2 mg/kg/day orally (or IV pulse 15 mg/kg every 2 wk ×3 then every 3 wk), renally dose-adjusted; switch off at **3–6 months**, or
 - **Rituximab** (anti-CD20) **375 mg/m² weekly × 4** — as effective as cyclophosphamide (superior in relapsing disease) and preferred for PR3-positive and relapsing patients, avoiding bladder toxicity/infertility.
- ▶ **Avacopan** (oral C5a-receptor inhibitor) is an add-on that allows rapid glucocorticoid withdrawal, achieving higher sustained remission than prednisone alongside cyclophosphamide or rituximab.
- ▶ **Fulminant disease**: IV **methylprednisolone 1000 mg/day × 3 days**.
- ▶ **Plasma exchange (PLEX)**: the PEXIVAS trial showed no benefit on the composite of ESRD/death; reserve for coexisting **anti-GBM antibody** or selected fulminant cases. Separate PLEX from rituximab by ≥48 h.
- ▶ **Maintenance**: after cyclophosphamide induction, switch to **rituximab (preferred, lower relapse)**, **azathioprine 2 mg/kg/day**, **methotrexate 20–25 mg/week**, or **mycophenolate mofetil**; continue ≥2 years.
- ▶ **Non-severe disease**: methotrexate or MMF with glucocorticoid; cyclophosphamide is rarely justified.
- ▶ **EGPA**: glucocorticoids are first-line; cyclophosphamide (then azathioprine/methotrexate) for fulminant/cardiac or ANCA-positive GN; **mepolizumab (anti-IL-5) 300 mg SC monthly** for relapsing/refractory non-severe disease (benralizumab non-inferior).
- ▶ **Supportive**: **Pneumocystis jirovecii prophylaxis with trimethoprim-sulfamethoxazole** during cyclophosphamide/rituximab therapy; agents shown *ineffective/harmful* — etanercept, belimumab, abatacept.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **ANCA immunofluorescence patterns** — two neutrophils side by side: (1) *c*-ANCA with diffuse granular **cytoplasmic** staining labelled “anti-PR3”; (2) *p*-ANCA with **perinuclear** staining labelled “anti-MPO”; label the **nucleus** in each.
- ▶ **ANCA pathogenesis cascade** — boxes/arrows: *resting neutrophil* → *priming by TNF-α/IL-1* → *PR3/MPO translocate to cell membrane* → *ANCA binding* → *degranulation + reactive oxygen species + IL-8* → *endothelial injury* → *necrotising small-vessel (pauci-immune)*

vasculitis. Optionally a glomerulus with a **crescent** labelled “pauci-immune crescentic GN”.

Clinical / Diagnostic significance

- ▶ AAV is the commonest cause of **pulmonary-renal syndrome**; recognise the triad of haemoptysis (alveolar haemorrhage), RPGN and ANCA positivity for urgent immunosuppression.
- ▶ ANCA **serotype (PR3 vs MPO)** increasingly guides prognosis/relapse risk better than the clinical label — PR3/c-ANCA disease relapses more and favours rituximab.
- ▶ **Saddle-nose deformity, subglottic stenosis and cavitary lung nodules** strongly suggest GPA; **cocaine/levamisole midline destruction** and NK/T-cell lymphoma are key mimics (biopsy mandatory before irradiation is ever considered).
- ▶ Untreated GPA is fatal within months; cyclophosphamide-based regimens transformed outcomes (remission ~75%, 5-yr survival >80%).

High-yield exam pointers

- ▶ AAV triad = GPA, MPA, EGPA — all **pauci-immune** small-vessel vasculitis.
- ▶ **c-ANCA = anti-PR3** ≈ GPA; **p-ANCA = anti-MPO** ≈ MPA/EGPA.
- ▶ GPA classic triad: **upper + lower respiratory tract + glomerulonephritis**; saddle nose, subglottic stenosis, increased VTE.
- ▶ MPA = **commonest pulmonary-renal syndrome**, no granuloma, no upper-airway disease; drug-induced by PTU/hydralazine/minocycline.
- ▶ EGPA = **asthma + eosinophilia (>1000/ μ L) + vasculitis**; **cardiac involvement = leading cause of death**; ANCA positive in <50%.
- ▶ Renal lesion = **pauci-immune crescentic necrotising glomerulonephritis**.
- ▶ Induction = **glucocorticoid + (rituximab or cyclophosphamide) $\pm$ avacopan**; maintenance = rituximab/azathioprine/MTX/MMF.
- ▶ **PEXIVAS**: routine plasma exchange offers no benefit (except anti-GBM overlap); **TMP-SMX** for PJP prophylaxis.
- ▶ **Mepolizumab (anti-IL-5)** for relapsing non-severe EGPA; **avacopan = C5a-receptor inhibitor**, steroid-sparing.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “The Vasculitis Syndromes” (ANCA biology and pathogenesis; GPA, MPA, EGPA definitions, organ-frequency data, induction/maintenance regimens, avacopan, PEXIVAS, mepolizumab/benralizumab).

- CMDT 2026 — “Rheumatologic, Immunologic & Allergic Disorders” (Vasculitis Syndromes) (Chapel Hill classification, PR3/MPO confirmatory testing, drug-induced MPA, EULAR/ACR-VF treatment approach, pulmonary-renal syndrome).



Ankylosing spondylitis

Asked in: Paper III Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Ankylosing spondylitis (AS) is the radiographic form of **axial spondyloarthritis (r-axSpA)**, a chronic immune-mediated inflammatory disorder predominantly involving the **sacroiliac joints and spine**. It is characterized by inflammatory back pain, sacroiliitis, progressive loss of spinal mobility, enthesitis, and extra-articular disease such as acute anterior uveitis, psoriasis, and inflammatory bowel disease (IBD). Pathologically, it is distinctive because inflammation-induced bone loss coexists with pathologic new bone formation, culminating in syndesmophytes and, rarely, a complete “bamboo spine.”

Nomenclature and epidemiology

- **Spondyloarthritis (SpA)** is a family of seronegative immune-mediated arthritides sharing sacroiliitis, inflammatory spinal lesions, peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis, IBD, familial clustering, and **HLA-B27** association.
- The 2009 ASAS approach divides SpA into **axial SpA** and **peripheral SpA**. Axial SpA is further divided into **radiographic axSpA**, historically called AS, and **nonradiographic axSpA**, based on whether definite sacroiliitis is visible on plain radiographs.
- **Modified New York radiographic threshold:** definite sacroiliitis means **bilateral grade ≥ 2** or **unilateral grade 3-4** sacroiliitis; definite AS requires at least one clinical criterion plus this radiographic criterion.
- Usual onset is before **40-45 years**, commonly in the **20s-30s**. r-axSpA has an approximate male:female ratio of **2:1**, whereas nr-axSpA is closer to **1:1**.
- **HLA-B27** is the strongest genetic association: Harrison notes positivity in **85-90%** of r-axSpA and **50-90%** of nr-axSpA. The risk of axSpA is about **5%** in HLA-B27-positive persons and rises to about **20%** in HLA-B27-positive first-degree relatives of affected patients.

Pathogenesis

- Disease begins in genetically predisposed individuals through interaction of **HLA-B27**, other MHC/non-MHC genes, mucosal immune triggers, mechanical stress, and cytokine pathways.

- ▶ Proposed HLA-B27 mechanisms include **arthritogenic peptide presentation**, HLA-B27 homodimer interaction with innate immune receptors, and unfolded protein response/autophagy links; no single theory fully explains disease.
- ▶ The **gut-joint axis** is important: intestinal dysbiosis, barrier dysfunction, and microbial peptide translocation may drive immune activation; subclinical gut inflammation is common in axSpA.
- ▶ **Entheses** are key target tissues. Mechanical strain produces microdamage; in SpA this response becomes amplified and prolonged, promoting chronic enthesitis.
- ▶ Signature inflammatory pathways include **TNF** and **IL-17**. Chronic enthesial inflammation promotes osteoblast differentiation and pathologic new bone formation, leading to bony spurs, syndesmophytes, sacroiliac ankylosis, and spinal fusion.

Clinical features

- ▶ **Inflammatory back pain:** insidious chronic low back, hip, or alternating buttock pain for >3 months; onset <45 years; worse in the second half of the night; improves after getting up, exercise, or activity; not relieved by rest; morning stiffness usually >30 minutes.
- ▶ **Axial progression:** limitation of lumbar, thoracic, and cervical mobility; flattening of lumbar lordosis, exaggerated thoracic kyphosis, reduced chest expansion from costovertebral involvement, and fixed deformity in advanced disease.
- ▶ **Peripheral disease:** peripheral arthritis occurs in about **30-40%** in Harrison and may be transient or persistent in CMDT; it is typically asymmetric oligoarthritis of large lower-limb joints. Hip involvement causes groin pain radiating to the medial thigh or knee and predicts greater functional loss.
- ▶ **Enthesitis:** heel pain from Achilles insertion or plantar fasciitis, chest wall pain, intercostal insertions, epicondylitis, quadriceps/patellar tendon insertion pain, or pelvic rim pain. Dactylitis is uncommon in pure axSpA.
- ▶ **Extra-musculoskeletal disease:** acute anterior uveitis is the commonest; it is typically **acute, anterior, unilateral, episodic**, with eye discomfort, redness, pain, photophobia, and miosis. IBD occurs in about **10%**, histologic subclinical gut inflammation in up to **50%**, and psoriasis in about **10%**.
- ▶ **Systemic and late features:** fatigue, anemia of chronic inflammation, osteoporosis, vertebral fractures, conduction disease, aortic valve insufficiency, apical pulmonary fibrosis, restrictive chest disease, IgA nephropathy, renal AA amyloidosis, and rare cauda equina syndrome.

Diagnosis and investigations

- ▶ Diagnosis is by **pattern recognition**: chronic back pain >3 months with onset <45 years, inflammatory features, SpA features, supportive imaging/laboratory data, and exclusion of common mimics.

- ▶ **Important SpA features** to actively seek: inflammatory arthritis, enthesitis, dactylitis, acute anterior uveitis, psoriasis, IBD, family history of SpA, good response to full-dose NSAIDs, and elevated CRP.
- ▶ **Laboratory tests:** ESR/CRP support active disease but are neither sensitive nor specific; Harrison notes elevation in only 30-40% of active axSpA. Rheumatoid factor and anti-CCP are negative. HLA-B27 is not diagnostic alone and is most useful when pre-test probability is intermediate.
- ▶ **Plain radiography:** a single AP pelvis or Ferguson view is sufficient for sacroiliac joints. Sacroiliitis shows sclerosis, erosions, joint-space narrowing/widening, and late fusion. Spine films may show **Romanus lesions/shiny corner sign**, vertebral squaring, **Andersson lesion**, vertical syndesmophytes, and bamboo spine.
- ▶ **MRI SI joints/spine:** useful in early disease when x-ray is negative. STIR/T2 fat-suppressed sequences show active bone marrow edema or osteitis; T1 images show structural lesions such as erosions, fat metaplasia, backfill, sclerosis, and new bone. MRI can overdiagnose disease in athletes, postpartum women, degenerative disease, and older adults.

Modified New York criteria for AS	Key points
Clinical criterion 1	Low back pain >3 months, improved by exercise and not relieved by rest
Clinical criterion 2	Limitation of lumbar motion in frontal and lateral planes
Clinical criterion 3	Reduced chest expansion
Radiographic criterion	Bilateral grade ≥ 2 sacroiliitis, or unilateral/bilateral grade 3-4 sacroiliitis
Definite AS	≥ 1 clinical criterion plus radiographic criterion

Differential diagnosis

- ▶ **Mechanical low back pain, disk disease, degenerative arthritis:** commoner than AS; mechanical pain worsens with activity and improves with rest.
- ▶ **Rheumatoid arthritis:** symmetric small-joint disease; RF/anti-CCP often positive; sacroiliac joints are spared and spinal disease is mainly cervical.
- ▶ **Psoriatic/reactive/IBD-associated SpA:** may mimic AS; psoriatic and reactive sacroiliitis is often asymmetric or unilateral, whereas AS is usually bilateral and symmetric.
- ▶ **DISH:** older obese/diabetic men; bulky flowing osteophytes and longitudinal ligament ossification with normal SI joints, mistaken for bamboo spine.
- ▶ **Osteitis condensans ilii:** triangular sclerosis on the iliac side of SI joints, usually postpartum; absence of erosions favors OCI over sacroiliitis.

- ▶ **Do not miss red flags:** fever, weight loss, advanced age, malignancy history, osteoporotic fracture, osteomyelitis, spinal tuberculosis/brucellosis/fungal infection, malignancy, fibromyalgia, hypermobility, hypothyroidism, and vitamin D deficiency.

Management

- ▶ **Targets:** remission or low disease activity, preservation of posture/mobility, prevention of structural damage, and control of extra-articular disease.
- ▶ **Nonpharmacologic:** patient education, active land/aquatic physical therapy, daily posture and spinal extension exercises, safe aerobic/resistance exercise, chest expansion exercises, smoking cessation, fall/fracture prevention, and cardiovascular risk reduction.
- ▶ **NSAIDs:** first-line; use the highest tolerated dose in active disease and as needed when stable. No specific NSAID is preferred. Monitor gastric ulcer/bleeding, hypertension, renal insufficiency, and cardiovascular risk.
- ▶ **csDMARDs:** sulfasalazine up to 3 g/day and methotrexate up to 25 mg/week may help peripheral arthritis/enthesitis but are **not effective for axial spinal or SI disease**.
- ▶ **Escalation:** if active disease persists after a **4-week full-dose NSAID trial**, start a biologic, usually **TNF inhibitor** or **IL-17 inhibitor**. Screen for latent tuberculosis, hepatitis B, and hepatitis C before biologic or JAK inhibitor therapy.
- ▶ **Biologic/targeted options:** etanercept 50 mg SC weekly; adalimumab 40 mg SC every 2 weeks; certolizumab 200 mg SC twice monthly or 400 mg monthly; golimumab 50 mg SC monthly or IV 2 mg/kg at weeks 0 and 4 then every 8 weeks; infliximab 5 mg/kg IV at weeks 0, 2, 6 then every 6 weeks. IL-17 inhibitors include secukinumab 150 mg SC weekly for 5 loading doses then every 4 weeks, and ixekizumab 160 mg once then 80 mg every 4 weeks. JAK inhibitors include tofacitinib 5 mg twice daily for AS and upadacitinib 15 mg daily for AS/nr-axSpA.
- ▶ **Choosing agents:** monoclonal TNF inhibitors are preferred over etanercept when uveitis or IBD coexists. IL-17 blockade is effective in axSpA but should be avoided in active IBD. JAK inhibitors are generally reserved after TNF inhibitor failure and require caution in older patients, smokers, cardiovascular disease, and malignancy risk.
- ▶ **Avoid:** systemic glucocorticoids for axial disease. Local glucocorticoid injections may be used for peripheral arthritis or selected upper-limb enthesitis; avoid injections around lower-limb weight-bearing entheses because of rupture risk.
- ▶ **Surgery:** total hip arthroplasty for refractory painful structurally damaged hips; spinal osteotomy only for severe fixed kyphosis impairing horizontal vision and only in expert centers.

Complications and prognosis

- ▶ Osteoporosis is common; Harrison gives about **25%** after 10 years of axSpA and vertebral fractures in about **10%** of AS patients, often in the lower cervical spine with neurologic risk.

- ▶ Disease course is variable. Harrison notes nearly **50%** may progress from nonradiographic to radiographic axSpA over 20 years, but **<10%** progress to extensive spinal bamboo spine.
- ▶ Risk factors for osteoproliferation include male sex, persistent MRI inflammation, high CRP, syndesmophytes, HLA-B27 positivity, and smoking.
- ▶ CMDT notes most patients have persistent symptoms over decades, rare long-term remissions, about **10%** work disability after 10 years, and worse prognosis with hip disease within the first 2 years.
- ▶ Biologic therapy improves symptoms and quality of life and may slow radiographic progression, but patients need monitoring for infections, tuberculosis reactivation, zoster with JAK inhibitors, Candida with IL-17 inhibitors, and drug-specific adverse effects.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **AP pelvis and lateral spine in AS:** label bilateral sacroiliac erosions, sclerosis, joint-space narrowing, SI ankylosis, squared vertebral bodies, vertical marginal syndesmophytes, fused facet joints, and bamboo spine.
- ▶ **Diagnostic flowchart for chronic inflammatory back pain:** label chronic back pain >3 months with onset <45 years, rule out mechanical back pain/fibromyalgia, SI joint x-ray, definite sacroiliitis = AS/r-axSpA, if x-ray negative assess SpA features, MRI SI joints, HLA-B27, nr-axSpA versus not axSpA.

Clinical / Diagnostic significance

- ▶ AS should be suspected in any young adult with chronic back or buttock pain that improves with exercise and worsens with rest, especially with uveitis, heel pain, psoriasis, IBD, family history, or excellent NSAID response.
- ▶ A positive HLA-B27 supports but does not diagnose AS; a negative result does not exclude disease in nonwhite populations or in a compelling clinical picture.
- ▶ MRI is powerful for early nr-axSpA but must be interpreted with clinical probability because mechanical stress and postpartum SI changes can mimic osteitis.
- ▶ New severe neck/back pain in established AS is a fracture until proved otherwise; ankylosed osteoporotic spines fracture with relatively minor trauma.
- ▶ Uveitis symptoms require urgent ophthalmology referral; active IBD changes biologic selection.

High-yield exam pointers

- ▶ AS = **radiographic axial spondyloarthritis**; nr-axSpA has similar symptoms but lacks definite x-ray sacroiliitis.
- ▶ Classic triad to write: **inflammatory back pain + bilateral sacroiliitis + HLA-B27 association**.
- ▶ Modified New York: **≥1 clinical criterion + radiographic sacroiliitis**.

- ▶ Inflammatory back pain: onset <45 years, >3 months, morning stiffness, night pain, improves with exercise, not rest.
- ▶ Commonest extra-articular manifestation: **acute anterior uveitis**.
- ▶ First-line treatment: **exercise/physical therapy plus NSAIDs**.
- ▶ csDMARDs do not treat axial disease; use them only for peripheral arthritis/enthesitis.
- ▶ NSAID failure after adequate trial: escalate to **TNF inhibitor or IL-17 inhibitor**; monoclonal TNF inhibitor if uveitis/IBD.
- ▶ Late complications: bamboo spine, vertebral fracture, aortic regurgitation/conduction block, apical fibrosis, IgA nephropathy, AA amyloidosis, and cauda equina syndrome.

SOURCE & COVERAGE

Harrison 22e — “Spondyloarthritis”; CMDT 2026 — “Rheumatologic, Immunologic, & Allergic Disorders”.



Approach to a patient with non-traumatic monoarthritis

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — Monoarthritis is inflammation confined to a *single joint* (≤ 1 joint), distinguished from *oligo/pauciarticular* (2–3 joints) and *polyarticular* (≥ 4 joints) disease. **Acute non-traumatic monoarthritis** is a medical emergency because it harbours three time-critical “red flag” diagnoses — **septic arthritis**, **acute crystal arthritis (gout/pseudogout)** and **(occult) fracture** — and untreated bacterial infection destroys articular cartilage within 48 hours. The cornerstone of evaluation is a structured history and examination followed by **arthrocentesis with synovial fluid analysis**, which is *always indicated* in acute monoarthritis.

Diagnostic framework — the four screening questions

The musculoskeletal complaint is characterised by answering four questions (Cush/Harrison), which narrow the differential:

- ▶ **Articular or non-articular?** Articular pain is deep/diffuse, limits *active and passive* range, with swelling, crepitus or deformity. Periarticular lesions (bursitis, tendinitis, cellulitis) give point tenderness, pain on *active but not passive* motion and less-than-circumferential swelling — these *masquerade* as arthritis.
- ▶ **Inflammatory or non-inflammatory?** Inflammation = the cardinal signs (warmth, erythema, swelling, pain), prolonged morning stiffness (hours), systemic features (fever, rash) and raised ESR/CRP.

- ▶ **Acute (≤ 6 weeks) or chronic (> 6 weeks)?** Acute monoarthritis is usually infective, crystal-induced or reactive; chronic monoarthritis suggests mycobacterial/fungal infection, or initial presentation of a chronic arthropathy.
- ▶ **How many / which joints?** Confirms it is truly monoarticular and not the first joint of an evolving oligo/polyarthritis.

Causes / Differential diagnosis of non-traumatic monoarthritis

Acute monoarthritis	Chronic monoarthritis (> 6 wk)
Septic (non-gonococcal): <i>S. aureus</i> (incl. MRSA), group B/A streptococci, gram-negative bacilli	<i>Mycobacterium tuberculosis</i> (chronic granulomatous monoarthritis)
Gonococcal arthritis (<i>N. gonorrhoeae</i> — DGI)	Non-tuberculous mycobacteria (<i>M. marinum</i> , MAC)
Crystal: gout (monosodium urate), pseudogout (CPPD)	Fungal: <i>Candida</i> , <i>Sporothrix schenckii</i> , <i>Coccidioides</i> , <i>Blastomyces</i> , <i>Histoplasma</i>
Reactive arthritis (initial), Lyme arthritis (knee)	<i>Brucella</i> , <i>Treponema pallidum</i> (syphilis)
Haemarthrosis (anticoagulant/coagulopathy)	Monoarticular RA / pauciarticular JIA; psoriatic arthritis
Initial monoarticular presentation of RA, psoriatic, SpA	Osteoarthritis, osteonecrosis, Charcot (neuropathic) joint
Avascular necrosis, sickle-cell flare	Pigmented villonodular synovitis, foreign-body synovitis, tumour

- ▶ *Monoarticular and oligoarticular conditions share similar aetiologies* — crystal and infective arthritis are typically mono/oligoarticular, whereas RA and OA are usually polyarticular.
- ▶ **Crystal arthritis and septic arthritis can coexist in the same joint** — finding crystals does *not* exclude infection.

Clinical evaluation — history and examination

- ▶ **Patient profile:** young adults — gonococcal and reactive arthritis; men — gout, spondyloarthritis; elderly — pseudogout, septic arthritis, gout; women, menses/pregnancy — disseminated gonococcal infection (DGI).
- ▶ **Onset/evolution:** *abrupt* (hours, often nocturnal) onset is typical of **septic arthritis and gout**; indolent over weeks–months suggests TB/fungal. Intermittent self-resolving attacks suggest crystal or Lyme arthritis.
- ▶ **Risk factors for sepsis:** pre-existing joint damage (RA), prosthetic joint, IV drug use, diabetes, advanced CKD, alcohol/cirrhosis, immunosuppression/biologics (TNF inhibitors), skin breach (ulcer, psoriasis).

- ▶ **Precipitants of crystal flare:** purine-rich food, alcohol/beer, diuretics, starting urate-lowering therapy, surgery (esp. parathyroidectomy → pseudogout), acute illness.
- ▶ **Examination:** confirm true articular swelling vs periarticular; distinguish effusion (fluctuant, *bulge/patellar tap*) from synovial hypertrophy (“boggy”) and bony enlargement. Document erythema, warmth, range of motion, and seek an **extra-articular focus** — tophi (pinna, olecranon), podagra, skin pustules on palms/soles + **tenosynovitis** (DGI), tick-bite/erythema migrans (Lyme), psoriatic plaques/nail pitting, fever and a portal of infection (boil, pneumonia, endocarditis).

Arthrocentesis and synovial fluid analysis — the pivotal test

Aspiration and analysis of synovial fluid are always indicated in acute monoarthritis or when infection/crystal arthropathy is suspected. Never pass the needle through overlying cellulitis or a psoriatic plaque. Analyse immediately for **appearance, viscosity, cell count + differential, Gram stain & culture, and crystals under compensated polarised light.**

Parameter	Normal	Group I Non-inflammatory	Group II Inflammatory	Group III Septic/Purulent
Clarity / colour	Transparent, clear	Transparent, yellow	Translucent–opaque, yellow	Opaque, yellow-green
Viscosity (“string sign”)	High	High	Low	Low
WBC/ μ L	<200	<2000	2000–75,000 (PMN $\geq$ 50%)	>50,000 (often >100,000), PMN $\geq$ 75–90%
Typical causes	—	OA, osteonecrosis	Gout, pseudogout, RA, reactive	Bacterial septic arthritis

- ▶ **Crystals:** **Monosodium urate (gout)** — *needle-shaped, strongly negatively birefringent* (yellow when parallel to compensator), usually intracellular. **Calcium pyrophosphate (pseudogout)** — *rhomboid/rod-shaped, weakly positively birefringent*.
- ▶ **Microbiology:** Gram stain positive in ~75% of staphylococcal, ~50% of gram-negative septic arthritis; synovial culture positive in 70–90% of non-gonococcal cases (blood cultures ~50%). Send NAAT if gonococcal/chlamydial suspected; culture synovial fluid for **TB and fungi** in chronic monoarthritis. MALDI-TOF/metagenomics aid culture-negative cases.
- ▶ **Caveat:** septic arthritis can present with Group II fluid (<50,000) with low-virulence organisms (gonococcus) or after antibiotics — a “non-septic” count never fully excludes infection.

Investigations beyond joint fluid

- ▶ **Bloods:** CBC with differential, ESR/CRP (discriminate inflammatory vs not; elevated but non-specific in sepsis), serum **urate** (may be normal in up to 50% during an acute gout flare — IL-6 is uricosuric; seek historical/post-flare values), creatinine, LFTs, blood cultures.
- ▶ **Targeted serology** only when pretest probability is adequate: RF, anti-CCP, ANA, Lyme, ASO, procalcitonin (~50% sensitive — does *not* rule out sepsis).
- ▶ **Imaging:** plain radiograph (baseline; early shows only soft-tissue swelling/effusion; chondrocalcinosis suggests CPPD; erosions with overhanging edges suggest tophaceous gout). **Ultrasound** detects effusion and the *double-contour sign* of urate deposition and guides aspiration of hip/shoulder; **MRI/CT** for deep joints (hip, sacroiliac, sternoclavicular), early osteomyelitis and to demonstrate effusion not clinically apparent. **Dual-energy CT** characterises urate deposits.

Specific entities and management pearls

- ▶ **Non-gonococcal septic arthritis** — *S. aureus* causes ~50%; the **knee** is most often involved (~90% single joint). It is a *medical/surgical emergency*. After cultures, give empirical IV bactericidal antibiotics: gram-positive cocci → **vancomycin 15–20 mg/kg q8–12h**; gram-negative bacilli → third-generation cephalosporin (**ceftriaxone 2 g q24h / cefotaxime 2 g q8h**), with anti-pseudomonal cover (cefepime/ceftazidime) in IVDU/immunocompromised. Add **joint drainage** (repeated needle aspiration, arthroscopic lavage, or arthrotomy — hip needs arthrotomy). Typical course ~4 weeks (staphylococci). CMDT empirical regimen: vancomycin + third-generation cephalosporin, 4–6 weeks.
- ▶ **Gonococcal arthritis (DGI)** — young, healthy, often women (menses/pregnancy); *triad* of **migratory polyarthralgia** → **tenosynovitis (60%)** → **purulent monoarthritis (40%)** with necrotic pustules on palms/soles. Synovial cultures often negative; diagnosis via mucosal NAAT/culture. Treat with **ceftriaxone 1 g IV/IM daily**, switch to oral after 24–48 h improvement to complete 7 days; dramatic response is characteristic. Test CH50 for terminal complement deficiency if recurrent.
- ▶ **Acute gout** — **podagra** (first MTP) in 70–90%; nocturnal, exquisitely painful, mimics cellulitis. Confirm with MSU crystals. Treat the flare early with **colchicine (1.2 mg at onset, 0.6 mg 1 h later)**, an NSAID (indomethacin 25–50 mg tid, naproxen 500 mg bid), or **glucocorticoid** (prednisone 30–50 mg/d tapered, or intra-articular). Start **urate-lowering therapy** later (allopurinol — screen *HLA-B*5801 in at-risk groups; febuxostat; probenecid*) targeting urate <6 mg/dL (<5 if tophi)* under anti-inflammatory prophylaxis.
- ▶ **Pseudogout (CPPD)** — elderly; **knee** > wrist; weakly positively birefringent rhomboid crystals + **chondrocalcinosis** on radiograph. In patients <50 yr, screen for haemochromatosis, hyperparathyroidism, hypophosphatasia, hypomagnesaemia. Treat as for acute gout (NSAID/colchicine/steroid).

- ▶ **Tuberculous arthritis** — chronic granulomatous monoarthritis of large weight-bearing joints (hip, knee, ankle); synovial fluid ~20,000 cells/ μ L (~50% PMN), AFB smear positive $<1/3$, culture ~80%, **synovial biopsy culture ~90%**; treat with standard multidrug ATT for 6–9 months.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Algorithm for acute non-traumatic monoarthritis (flow chart):** *Acute monoarthritis* → assess for **red flags** → **Arthrocentesis** → branch on synovial WBC: <2000 (*non-inflammatory* → OA, osteonecrosis) | $2000-50,000$ (*inflammatory* → check crystals: MSU → gout, CPP → pseudogout; if none → reactive/early inflammatory) | $>50,000$, PMN $>75\%$, +Gram stain/culture → **septic arthritis** → IV antibiotics + drainage. Label boxes: History/exam, WBC count, % PMN, Crystals, Gram stain, Culture.
- ▶ **Polarised-light crystal comparison:** two crystals with compensator axis — label MSU: needle-shaped, **NEGATIVELY** birefringent, intracellular (gout) and CPP: rhomboid, weakly **POSITIVELY** birefringent (pseudogout).

Clinical / Diagnostic significance

- ▶ **Septic arthritis is the diagnosis to exclude first** in every acute hot joint — delayed therapy causes irreversible cartilage destruction, ankylosis and a 30% mortality in polyarticular sepsis. Arthrocentesis precedes antibiotics.
- ▶ A single joint “*out of proportion*” to the rest in established RA must be aspirated to exclude superimposed sepsis, especially on biologic DMARDs.
- ▶ Crystals and infection coexist — always Gram stain/culture even when crystals are seen.
- ▶ Serum urate is unreliable during an acute flare; definitive gout diagnosis rests on crystal identification, not urate level.

High-yield exam pointers

- ▶ Three **red-flag** causes of acute monoarthritis: **septic arthritis, crystal arthritis, fracture**.
- ▶ **Arthrocentesis is mandatory** in acute monoarthritis; synovial WBC $>50,000/\mu$ L with $>75\%$ PMN = presume septic until proven otherwise.
- ▶ **MSU = needle-shaped, negatively birefringent (gout); CPP = rhomboid, positively birefringent (pseudogout).**
- ▶ *S. aureus* is the commonest cause of non-gonococcal septic arthritis; **knee** is the commonest joint; ~90% are monoarticular.
- ▶ **DGI** = arthritis–dermatitis–tenosynovitis triad in a young adult; treat with ceftriaxone.
- ▶ **Podagra** (first MTP gout) in 70–90%; acute gout treated with colchicine/NSAID/steroid, not urate-lowering during the flare.
- ▶ **Chronic monoarthritis** → think **TB and fungi**; culture/biopsy synovium.

- ▶ Empirical septic-arthritis therapy: **vancomycin + third-generation cephalosporin** plus joint drainage.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "*Approach to Articular and Musculoskeletal Disorders*" (four screening questions, synovial fluid algorithm, laboratory evaluation); "*Infectious Arthritis*" (differential of arthritis syndromes, septic/gonococcal/tuberculous/fungal arthritis, antibiotic regimens); "*Gout and Other Crystal-Associated Arthropathies*" (acute gout, MSU/CPP crystals, colchicine/NSAID/steroid and urate-lowering therapy).
- ▶ CMDT 2026 — "*Rheumatologic, Immunologic, & Allergic Disorders*" (joint-pattern table, examination of joint fluid Groups I–III, nongonococcal & gonococcal septic arthritis, osteoarthritis, gout/pseudogout management).

Coverage note: The corpus has no dedicated rheumatology subspecialty textbook for this topic (spec.specialty_books empty); depth is drawn from Harrison 22e and CMDT 2026, which fully cover the approach, synovial fluid classification, crystal identification and management regimens.



Behçet's Syndrome

Asked in: Paper III Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Behçet's syndrome is a chronic, relapsing **systemic vasculitis** of unknown cause, first described by the Turkish dermatologist *Hulusi Behçet*. It is characterised by recurrent **oral and genital aphthous ulcers**, skin lesions, **uveitis**, arthritis, and variable involvement of major arteries and veins, the gastrointestinal tract and the central nervous system, occurring in differing combinations and sequences over time. Uniquely among the vasculitides it can involve vessels of **any size, on both the arterial and venous side** of the circulation, and is diagnosed clinically as there is no confirmatory laboratory test.

Epidemiology

- ▶ Strongly clustered along the ancient "*Silk Road*" — the **Middle East, Mediterranean, and the Far East**. Most prevalent in **Turkey** (≈ 1 in 250 adults).
- ▶ Onset typically in the **20s–30s**; relatively rare before the late teens and after age 50.
- ▶ **Males and females are affected equally**, but **males tend to have more severe disease and a poorer prognosis** (worse ocular, vascular and neurologic outcomes); young age and male sex are adverse prognostic markers.
- ▶ **HLA-B*51** is positive in **50–60%** of patients (regional variation) but is found in $\sim 20\%$ of the normal population, so it is *not* a diagnostic test.

Pathogenesis

- ▶ Aetiology unknown; a **genetic predisposition** (family clustering; HLA-B*51 association) interacts with dysregulated **innate and adaptive immunity** and increased inflammation.
- ▶ Underlying pathology is a **leukocytoclastic vasculitis**, though vessels of any calibre and any organ may be affected.
- ▶ Marked **neutrophil hyperreactivity** is characteristic (primary vs cytokine-driven is unsettled).
- ▶ Behçet's occupies a **niche between classic autoimmune and autoinflammatory disease**:
 - *Unlike autoimmune disease* — no autoantibodies, and no association with Raynaud's, Sjögren's, thrombocytopenia, haemolytic anaemia, photosensitivity or serositis.
 - *Unlike autoinflammatory disease* — it tends to **abate with time**, lacks the defining gene mutations (e.g. of familial Mediterranean fever), and is far more prevalent than typical periodic-fever syndromes.

Clinical features

- ▶ **Mucocutaneous (the hallmark)**:
 - **Oral ulcers** — in virtually all patients (~98%) and usually the **first manifestation**; multiple, painful, canker-sore-like, last ~10 days, recur; only uncommon “major” ulcers scar.
 - **Genital ulcers** — the **most specific** lesion; on scrotum/labia; larger, deeper, slower to heal, and characteristically scar.
 - **Skin lesions** — *acne-like / papulopustular* lesions (including atypical sites such as the legs); **erythema nodosum**-like nodules (panniculitis); and **superficial thrombophlebitis** (common in men; flags risk of deep-vein thrombosis and pulmonary artery aneurysm).
- ▶ **Ocular** — in ~50% overall and up to ~70% of males; typically a **bilateral panuveitis**. *Hypopyon* (sterile pus layering in the anterior chamber) occurs in ~10% of those with eye disease and is highly suggestive. Posterior uveitis (retinal vasculitis/venulitis) can silently destroy the retina. Poor ocular prognostic factors: **male sex, posterior involvement, >3 attacks/year, dense vitreous opacity, macular oedema**.
- ▶ **Musculoskeletal** — a **non-erosive, non-deforming mono- or oligoarthritis** of the lower limbs (knees, ankles) in about half of patients.
- ▶ **Vascular** — in up to 40%; an intense, relapsing **thrombotic** tendency. Venous: superficial and deep-vein thrombosis, *Budd-Chiari syndrome*, inferior vena cava syndrome, intracardiac thrombosis, and **cerebral venous sinus thrombosis**. Arterial: **pulmonary artery aneurysms** (5-year mortality 20–25%, may cause fatal haemoptysis).
- ▶ **Neurologic (neuro-Behçet)** — in ~5%; two largely non-overlapping forms:
 - **Parenchymal (~75%)** — affects the **telencephalic-diencephalic junction, brainstem and spinal cord**; subacute headache, cranial-nerve palsy, dysarthria, ataxia, hemiparesis. Can radiologically mimic *multiple sclerosis*.

- **Cerebral venous sinus thrombosis** (~25%) — headache, raised intracranial pressure.
- ▶ **Gastrointestinal** — frequency is markedly regional (up to ~50% in the Far East, ~30% in the US, rare in Turkey/Middle East). Few (usually <5), **deep, round ulcers confined to the ileocaecal area**, prone to **perforation**; perianal/rectal disease rare. Clinically and endoscopically **difficult to distinguish from Crohn's disease** without extra-intestinal clues.

Diagnostic criteria

Behçet's is a **clinical diagnosis of exclusion**. The most validated tool is the **International Study Group (ISG) criteria** (sensitivity ~95%, specificity ~96%):

Criterion	Frequency	Comment
Recurrent oral ulceration (mandatory)	~98%	At least 3 times in a 12-month period
PLUS any 2 of the following 4:		
Recurrent genital ulceration	~80%	Usually scarring
Skin lesions	~80%	Erythema nodosum, pseudofolliculitis, papulopustular/acneiform nodules (post-adolescent, not on corticosteroids)
Eye lesions	~50%	Anterior/posterior uveitis, vitreous cells, or retinal vasculitis
Positive pathergy test	~50%	Read at 24–48 h after pricking the skin with a 20–21-gauge needle

- ▶ **Pathergy** = non-specific cutaneous hyperreactivity to trauma; a sterile papule/pustule forms within 24–48 h. Rather unique to Behçet's; more often positive in patients from the Middle/Far East.
- ▶ No pathognomonic laboratory finding — **acute-phase reactants** (ESR/CRP) are often raised; **no specific autoantibody**. HLA-B*51 supports but does not establish the diagnosis.

Differential diagnosis

- ▶ **Oral/genital ulcers:** complex aphthosis, inflammatory bowel disease, coeliac disease, IgA deficiency, infections (HIV, herpes, histoplasmosis), and mucosal conditions (pemphigus vulgaris, lichen planus, mucous membrane pemphigoid).
- ▶ **GI disease:** *Crohn's disease* (key mimic).
- ▶ **Neuro-Behçet:** multiple sclerosis, CNS infection/vasculitis.
- ▶ **Uveitis:** sarcoidosis, HLA-B27 spondyloarthropathy, infective uveitis.

Treatment

Treatment is **organ- and severity-directed**, aiming to prevent irreversible damage; young males warrant more aggressive therapy. Most new manifestations appear within the **first 5 years**, after which disease tends to wane — **tapering/stopping drugs may be attempted 2–3 years** after remission, with immunosuppressants usually continued ≥ 2 years.

Manifestation	Preferred / first-line	Add-on / severe disease
Oral & genital ulcers, mucocutaneous	Topical glucocorticoids; colchicine ; apremilast (PDE-4 inhibitor; FDA-approved for oral ulcers)	Azathioprine; TNF-α inhibitor (infliximab) for resistant disease
Ocular (uveitis)	Brief glucocorticoid courses + azathioprine (preferred long-term agent)	TNF inhibitors (infliximab/adalimumab) ; cyclosporine; interferon- α
Gastrointestinal	Glucocorticoids + azathioprine	$\pm$ infliximab
Venous thrombosis	Immunosuppression (azathioprine; cyclophosphamide if severe) to control inflammation — <i>not primarily anticoagulation</i>	Anticoagulate only if low bleeding risk and no pulmonary artery aneurysm
CNS (parenchymal neuro-Behçet)	Azathioprine + a TNF inhibitor	Glucocorticoids; cyclophosphamide

- ▶ Management follows the **2018 EULAR recommendations** (Hatemi et al). Key principle for vascular disease: thrombosis is **inflammatory**, so suppress inflammation rather than relying on anticoagulants, and **always exclude a pulmonary artery aneurysm before anticoagulating** (risk of catastrophic haemorrhage).
- ▶ Recent evidence (Saadoun et al, 2024) compared **infliximab vs cyclophosphamide** for severe Behçet's, reflecting the growing role of biologics in major-organ disease.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Figure 1 — “Clinical map of Behçet's syndrome”**: a central figure with labelled arrows to: Oral aphthous ulcer (tongue/buccal mucosa); Genital (scrotal/labial) ulcer — scarring; Eye — hypopyon / panuveitis; Skin — erythema nodosum, papulopustular lesions, superficial thrombophlebitis; Pathergy site (forearm); Vascular — DVT, pulmonary artery aneurysm, Budd-Chiari, cerebral venous sinus thrombosis; CNS — brainstem lesion; GI — ileocaecal ulcer.
- ▶ **Figure 2 — Pathergy test**: label 20–21-gauge needle prick $\rightarrow$ sterile papule/pustule at 24–48 h.

Clinical / Diagnostic significance

- ▶ A young patient with recurrent oral + genital ulceration and uveitis from a Silk-Road region should prompt consideration of Behçet's.
- ▶ Hypopyon uveitis and a positive pathergy test are the most disease-specific bedside clues.
- ▶ Superficial thrombophlebitis must trigger a search for occult vascular disease, especially pulmonary artery aneurysm, the most lethal complication.
- ▶ Distinguishing GI Behçet's from Crohn's and neuro-Behçet's from MS is a recurring clinical challenge — extra-intestinal/systemic features and lesion distribution guide diagnosis.
- ▶ HLA-B*51 positivity supports the diagnosis and correlates with disease but is **neither necessary nor sufficient**.

High-yield exam pointers

- ▶ First described by Hulusi Behçet (Turkish dermatologist); classic triad = oral ulcers + genital ulcers + uveitis.
- ▶ Silk Road distribution; highest prevalence in Turkey (1 in 250); HLA-B*51 associated.
- ▶ ISG criteria: recurrent oral ulcers ($\geq 3 \times / \text{yr}$) plus 2 of 4 (genital ulcers, skin lesions, eye lesions, positive pathergy); sensitivity ~95%, specificity ~96%.
- ▶ Pathergy = sterile pustule 24–48 h after a 20–21-G needle prick — read at 24–48 h.
- ▶ Hypopyon + bilateral panuveitis; eye disease commoner/severer in males.
- ▶ Pulmonary artery aneurysm = most feared lesion (5-yr mortality 20–25%); **do not anticoagulate** without excluding it.
- ▶ Venous thrombosis is **inflammatory** → treat with **immunosuppression**, not anticoagulation alone.
- ▶ Apremilast (PDE-4 inhibitor) is FDA-approved for oral ulcers; azathioprine is the workhorse steroid-sparing agent; TNF inhibitors for severe ocular/CNS/GI disease.
- ▶ Behçet's **abates with time**, unlike most chronic rheumatic diseases — many patients can taper therapy at 2–3 years.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Behçet Syndrome" (ISG criteria, clinical features, organ-directed treatment) and "The Vasculitis Syndromes" (classification; leukocytoclastic vasculitis).
- ▶ CMDT 2026 — "Behçet Disease" (Rheumatologic, Immunologic & Allergic Disorders; clinical findings, differential diagnosis, current drug regimens and recent trial data).
- ▶ Management framework consistent with the 2018 EULAR recommendations for the management of Behçet's syndrome (cited in Harrison).



Biologicals in Rheumatoid Arthritis

Asked in: Paper III May 2022 — RGUHS MD General Medicine

Definition / Introduction — **Biologic DMARDs (bDMARDs)** are protein therapeutics, predominantly monoclonal antibodies and soluble receptor-fusion constructs, engineered to neutralise specific cytokines (TNF- α , IL-6, IL-1) or block cell-surface molecules (CD20, CD80/86) central to the pathobiology of rheumatoid arthritis (RA). Introduced from 1999, they have **revolutionised RA therapy**, reducing signs and symptoms, slowing radiographic joint damage, and improving physical function and quality of life. They are used after an inadequate response to methotrexate (MTX), usually in combination with it, within a **treat-to-target** strategy aiming at remission or low disease activity.

Rationale — Cytokine targets in RA pathobiology

- ▶ **TNF- α** is a pivotal upstream cytokine secreted by synovial macrophages and fibroblasts. It upregulates **endothelial adhesion molecules** (promoting leukocyte influx), drives production of **IL-1, IL-6 and GM-CSF**, stimulates **osteoclastogenesis**, and suppresses bone formation via **DKK-1**–mediated inhibition of the Wnt pathway.
- ▶ **IL-6** activates intracellular signalling that drives the acute-phase response, cytokine production and osteoclast activation.
- ▶ **IL-1** is antagonised physiologically by the IL-1 receptor antagonist (the basis of anakinra).
- ▶ **B cells (CD20+)** and **T-cell co-stimulation (CD28–CD80/86)** are additional non-cytokine targets exploited by rituximab and abatacept respectively.
- ▶ **Biosimilars** — agents with the same active properties as a licensed reference biological — are now available for several products with similar efficacy and side-effect profiles.

Classification of biologic DMARDs with doses

Class / Target	Agent & molecular design	Representative dose (Harrison Table 370-2)
TNF- α inhibitors	<i>Infliximab</i> — chimeric (mouse–human) mAb	3 mg/kg IV at weeks 0, 2, 6, then every 8 weeks (up to 10 mg/kg q4w)
	<i>Adalimumab</i> — humanised mAb	40 mg SC every other week
	<i>Golimumab</i> — humanised mAb	50 mg SC monthly
	<i>Certolizumab pegol</i> — pegylated Fab' fragment of humanised mAb	400 mg SC at weeks 0, 2, 4, then 200 mg every other week
	<i>Etanercept</i> — soluble TNF receptor-2–Fc(IgG1) fusion protein	50 mg SC weekly (or 25 mg SC twice weekly)
Anti-IL-6 receptor	<i>Tocilizumab, Sarilumab</i> — anti-IL-6R mAbs	Tocilizumab 4–8 mg/kg IV monthly or 162 mg SC

Class / Target	Agent & molecular design	Representative dose (Harrison Table 370-2)
		q2w/weekly; Sarilumab 200 mg SC every other week
IL-1 receptor antagonist	<i>Anakinra</i> — recombinant IL-1Ra	100 mg SC daily
T-cell co-stimulation blocker	<i>Abatacept</i> — CTLA-4-IgG fusion protein	Weight-based IV (500/750/1000 mg) at weeks 0, 2, 4, then q4w; or 125 mg SC weekly
Anti-CD20 (B-cell depletion)	<i>Rituximab</i> — chimeric anti-CD20 mAb	1000 mg IV ×2 (days 0 and 14); may repeat every ≥24 weeks; premedicate with methylprednisolone 100 mg

Note: JAK inhibitors (tofacitinib, baricitinib, upadacitinib) are oral **targeted synthetic DMARDs**, not biologicals, but are discussed below as the closely allied “non-biologic targeted” class.

Individual agents — mechanism and clinical use

- ▶ **Anti-TNF agents** — *Five original “innovator” TNF inhibitors* are approved. Three are anti-TNF monoclonal antibodies (infliximab chimeric; adalimumab and golimumab humanised); certolizumab is a pegylated Fab’ fragment; etanercept is a soluble TNF receptor-2–Fc fusion protein. All reduce symptoms and slow radiographic progression and may be used alone or, more effectively, with background MTX. They are the first-line biologic added when MTX response is inadequate.
- ▶ **Anti-IL-6 receptor agents (tocilizumab, sarilumab)** — mAbs against membrane and soluble IL-6R; effective as monotherapy or with conventional DMARDs. They **raise LDL cholesterol** and carry a risk of **GI perforation** (avoid with diverticulitis or recent peptic ulcer).
- ▶ **Anakinra** — recombinant IL-1 receptor antagonist; *limited use* in RA because other biologics show greater efficacy.
- ▶ **Abatacept** — soluble CTLA-4–IgG fusion protein that blocks CD28–CD80/86 co-stimulation of T cells; reduces disease activity and slows radiographic damage; usually combined with a conventional DMARD. Some studies suggest switching to abatacept is more effective than switching to a second anti-TNF.
- ▶ **Rituximab** — chimeric anti-CD20 mAb that **depletes B cells**; approved for **refractory RA (failure of a TNF inhibitor) in combination with MTX**; more effective in **seropositive** than seronegative disease. Associated with rare **progressive multifocal leukoencephalopathy (PML)** (~1:25,000) and blunting of vaccine responses (e.g. SARS-CoV-2).

Targeted synthetic DMARDs — JAK inhibitors (allied oral agents)

- ▶ Inhibit the Janus kinase (JAK1, JAK2, JAK3, Tyk2) family that links extracellular cytokine receptors to intracellular signalling; oral route is their key advantage over biologics.

- ▶ *Tofacitinib* — JAK1/JAK3 inhibitor, 5 mg BD or 11 mg OD; *Baricitinib* — JAK1/JAK2, 2 mg OD; *Upadacitinib* — selective JAK1, 15 mg OD. Used as monotherapy or with MTX.
- ▶ Risks: infections including **herpes zoster**, raised transaminases, neutropenia, dyslipidaemia, hypertension; tofacitinib carries increased **thrombosis, MACE and malignancy** versus TNF inhibitors, highest in the **elderly**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Cytokine-network/target schematic of the RA synovium:** label *Macrophage* and *Synovial fibroblast* secreting *TNF- α* , *IL-1*, *IL-6*, *GM-CSF*; *T cell* with *CD28-CD80/86* co-stimulation; *B cell* (*CD20*); *Osteoclast precursor* → *RANKL/RANK* → *activated osteoclast* → *bone erosion*; *DKK-1* → *Wnt inhibition* → *reduced osteoblast bone formation*. Superimpose drug blocks: *Anti-TNF*, *Anti-IL-6R* (*tocilizumab/sarilumab*), *Anakinra* (*IL-1Ra*), *Abatacept* (*CTLA-4-Ig*), *Rituximab* (*anti-CD20*).
- ▶ **Treat-to-target ladder:** *MTX (anchor)* → *inadequate response at 3–6 months* → *add anti-TNF or non-TNF biologic $\pm$ MTX* → *switch within class or to alternative mechanism* (*abatacept/anti-IL-6R/rituximab*) or *JAK inhibitor* → *goal: DAS-28 low disease activity / remission*.

Clinical / Diagnostic significance

- ▶ **Pre-treatment screening (initial evaluation):** CBC with differential, viral hepatitis panel (HBsAg, anti-HCV), and **latent TB screening** (Mantoux/PPD or IFN- γ release assay). If LTBI positive, give anti-TB therapy for **at least 1 month before** starting an anti-TNF agent.
- ▶ **Contraindications to anti-TNF:** active infection, hypersensitivity, **chronic hepatitis B**, and **class III/IV congestive heart failure**.
- ▶ **Key class adverse effects:** increased serious bacterial and opportunistic fungal infection, **reactivation of latent TB**; anti-TNF also linked to infusion/injection-site reactions, drug-induced lupus, demyelination, and (controversially) lymphoma.
- ▶ **Positioning:** begin with MTX; if inadequate after 3–6 months, step up to combination conventional DMARDs or add an anti-TNF/non-TNF biologic. Initial anti-TNF responders who later worsen may switch to another anti-TNF or to a biologic with a different mechanism (often more effective).
- ▶ **Pregnancy:** anti-TNF agents are generally accepted as safe but **guidelines advise stopping them in the third trimester**; data are insufficient for abatacept, anti-IL-6R, rituximab and JAK inhibitors (discontinue at conception). Hydroxychloroquine and sulfasalazine are the safest DMARDs in pregnancy; MTX and leflunomide are contraindicated (teratogenic).

- ▶ **Combination superiority:** randomised trials show **MTX plus an anti-TNF agent is superior to MTX alone**, and an early intensive combination approach yields better long-term outcomes than starting MTX monotherapy.
- ▶ **Monitoring on therapy:** periodic CBC, LFTs and (for IL-6 inhibitors and JAK inhibitors) lipids; vigilance for infection.

High-yield exam pointers

- ▶ **TNF inhibitors were the first biologicals** approved for RA (1999); MTX remains the **anchor drug** and is usually co-prescribed.
- ▶ Know the **molecular designs**: infliximab = chimeric mAb; adalimumab/golimumab = humanised mAb; certolizumab = pegylated Fab'; **etanercept** = **TNF receptor-2-Fc fusion protein** (the odd one out).
- ▶ **Screen for latent TB and hepatitis B** before any anti-TNF; treat LTBI ≥ 1 month first.
- ▶ Anti-TNF **contraindicated in NYHA class III/IV heart failure** and chronic hepatitis B.
- ▶ **Rituximab** = anti-CD20, for **TNF-failure refractory RA + MTX**, better in **seropositive** disease; rare PML.
- ▶ **Abatacept** = CTLA-4-Ig blocking CD28-CD80/86 co-stimulation; **anakinra** = IL-1Ra (limited efficacy).
- ▶ **Tocilizumab/sarilumab (anti-IL-6R)** raise **LDL cholesterol** and risk **GI perforation**.
- ▶ **JAK inhibitors are oral targeted synthetic DMARDs (not biologics); watch for herpes zoster, thrombosis, MACE and malignancy* (tofacitinib, elderly).*
- ▶ **Biosimilars** offer comparable efficacy/safety to reference biologicals.

SOURCE & COVERAGE

Harrison 22e — Ch 370 “Rheumatoid Arthritis” (Treatment: Biologicals & Targeted Synthetic DMARDs section and Table 370-2 “DMARDs Used for the Treatment of Rheumatoid Arthritis”). All agents, molecular designs, doses, mechanisms, screening and contraindications are grounded in this chapter. Coverage note: JAK inhibitors are included as the allied oral targeted-synthetic class (Harrison classifies them separately from biologicals); ACR/EULAR treat-to-target step-up framing and DAS-28 are from the same chapter’s “Approach to the Patient.”



Biologics in Autoimmune Disease

Asked in: Paper III Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — **Biologic agents (biologic DMARDs)** are large, protein-based therapeutics — chiefly **monoclonal antibodies, soluble receptor-Fc fusion proteins and recombinant receptor**

antagonists — engineered to neutralise specific cytokines, deplete or modulate immune cells, or block co-stimulatory and trafficking pathways central to autoimmune inflammation. By targeting a single defined node rather than broadly suppressing the immune system (as glucocorticoids or cyclophosphamide do), they have **revolutionised the treatment of rheumatoid arthritis (RA), spondyloarthritis, SLE, ANCA-associated vasculitis (AAV), inflammatory bowel disease (IBD) and psoriasis** over the past two decades. The first class approved (TNF inhibitors, from 1999) was followed by B-cell-, IL-6-, IL-1-, IL-17-, IL-23- and IFN-targeted agents; **biosimilars** (highly similar copies of an off-patent reference biologic with comparable efficacy and safety) have since broadened access.

Classification of biologics by structure and target

Class / structure	Molecular target	Representative agents (autoimmune use)
Anti-TNF- α monoclonal antibodies	Soluble + membrane TNF- α	Infliximab (chimeric), Adalimumab, Golimumab (human/humanised), Certolizumab pegol (PEGylated Fab')
Anti-TNF fusion protein	TNF- α	Etanercept (TNF-R2-IgG1 Fc fusion protein)
B-cell depleting (anti-CD20)	CD20 on mature B cells	Rituximab (chimeric), Obinutuzumab (type II, investigational in SLE)
Co-stimulation blocker	CD28-CD80/86 (T-cell)	Abatacept (CTLA-4-IgG fusion protein)
Anti-IL-6 receptor	IL-6R (soluble + membrane)	Tocilizumab, Sarilumab
IL-1 receptor antagonist	IL-1 receptor	Anakinra (recombinant IL-1Ra)
Anti-IL-17A	IL-17A	Secukinumab (IgG1 κ), Ixekizumab (IgG4)
Anti-IL-12/23 (p40) / anti-IL-23 (p19)	Shared p40 / IL-23 p19	Ustekinumab (p40); Risankizumab, Mirikizumab (p19)
Anti-integrin (anti-trafficking)	$\alpha 4\beta 7$ / $\alpha 4$ integrin	Vedolizumab (gut-selective $\alpha 4\beta 7$), Natalizumab ($\alpha 4$)
Anti-BAFF / BlyS	B-cell activating factor	Belimumab
Anti-type I IFN receptor	IFNAR1	Anifrolumab
Complement C5a-receptor inhibitor	C5a receptor	Avacopan (small molecule, adjunct in AAV)

- ▶ **Nomenclature pearl:** the suffix encodes structure — *-mab* = monoclonal antibody (*-ximab* chimeric e.g. infliximab/rituximab; *-zumab* humanised e.g. tocilizumab; *-umab* fully human e.g. golimumab, adalimumab, ustekinumab), while *-cept* = receptor–Fc **fusion protein** (etanercept, abatacept).
- ▶ **Not biologics but commonly confused with them:** *targeted synthetic DMARDs* — the oral **JAK inhibitors** (tofacitinib JAK1/3; baricitinib JAK1/2; upadacitinib JAK1) and **voclosporin** (a calcineurin inhibitor used in lupus nephritis). They block intracellular signalling and offer an oral alternative to injectable biologics.

Mechanism-based pharmacology of the major classes

- ▶ **TNF- α inhibitors** — TNF- α is a critical upstream driver of synovitis; five “innovator” agents exist. **Infliximab** is a chimeric mAb; **adalimumab/golimumab** are human(ised) mAbs; **certolizumab** is a PEGylated Fab’ fragment; **etanercept** is a soluble TNF-receptor-2–IgG1-Fc fusion protein. All reduce signs/symptoms, **slow radiographic joint damage** and improve function in RA; used alone or with background **methotrexate (MTX)**. Effective also in psoriasis, psoriatic arthritis, ankylosing spondylitis and IBD.
- ▶ **B-cell depletion** — **Rituximab (anti-CD20)** depletes mature B cells, lowering autoantibody production, T-cell activation and cytokine output. Approved for **MTX-refractory / TNF-failure RA** (more effective in seropositive disease) and a cornerstone of **AAV** therapy.
- ▶ **Co-stimulation blockade** — **Abatacept (CTLA-4-Ig)** binds CD80/86 on antigen-presenting cells, blocking the CD28 “second signal” required for T-cell activation; slows radiographic progression in RA, usually with a conventional DMARD.
- ▶ **IL-6 receptor blockade** — **Tocilizumab / sarilumab** are mAbs against soluble and membrane IL-6R; IL-6 drives the acute-phase response, B-cell help and osteoclast activation. Effective as monotherapy or with MTX.
- ▶ **IL-1 blockade** — **Anakinra** is recombinant IL-1 receptor antagonist (limited use in RA; mainstay of autoinflammatory syndromes).
- ▶ **IL-17 / IL-23 axis** — **Secukinumab, ixekizumab (anti-IL-17A)** and **ustekinumab (anti-p40)/risankizumab (anti-IL-23 p19)** target the Th17 pathway central to **psoriasis, psoriatic arthritis, ankylosing spondylitis and Crohn’s disease**.
- ▶ **Anti-trafficking integrin blockers** — **Vedolizumab (gut-selective $\alpha 4\beta 7$)** and **natalizumab ($\alpha 4$)** prevent leucocyte homing to gut/CNS in IBD.
- ▶ **SLE-specific biologics** — **Belimumab (anti-BAFF/BLyS)** reduces B-cell survival; **anifrolumab (anti-type I IFN receptor)** blocks the interferon signature.

Disease-specific applications

Disease	Biologic(s) used	Key clinical role
Rheumatoid arthritis	TNF inhibitors, abatacept, tocilizumab/sarilumab, rituximab, anakinra	Step-up after inadequate MTX response ($\approx 3-6$ mo); rituximab for TNF failure, esp. seropositive disease
SLE / lupus nephritis	Belimumab (incl. lupus nephritis), anifrolumab; rituximab (off-label refractory disease, AIHA, severe thrombocytopenia, neuropsychiatric lupus)	Glucocorticoid-sparing; belimumab given with MMF or low-dose cyclophosphamide; obinutuzumab & CAR-T (anti-CD19) emerging
ANCA-associated vasculitis (GPA/MPA)	Rituximab (induction & maintenance), avacopan (C5a-R, steroid-sparing)	Rituximab $375 \text{ mg/m}^2/\text{week} \times 4 \approx$ cyclophosphamide for induction; superior in relapsing disease
IBD (Crohn / UC)	Anti-TNF (infliximab, adalimumab, golimumab, certolizumab), vedolizumab, ustekinumab, risankizumab, mirikizumab	Moderate-severe disease; vedolizumab/IL-23 agents favoured when TNF risk is high
Psoriasis / PsA / ankylosing spondylitis	TNF inhibitors, secukinumab, ixekizumab, ustekinumab	IL-17/IL-23 agents highly effective for skin and axial disease
Sjögren syndrome	Belimumab $\rightarrow$ rituximab sequential, ianalumab (investigational)	Promising composite outcomes

Pre-treatment screening and monitoring

- ▶ **Latent tuberculosis** — *mandatory before any TNF inhibitor (and most biologics)*: tuberculin skin test (PPD) or IFN- γ release assay (IGRA) + chest X-ray; if positive, treat LTBI for ≥ 1 month before starting the biologic.
- ▶ **Viral hepatitis panel** — HBsAg + anti-HCV before rituximab, TNF inhibitors and tocilizumab; risk of hepatitis B reactivation (esp. rituximab).
- ▶ **CBC, LFTs, renal function and lipids** at baseline and periodically (cytopenias with rituximab/tocilizumab; transaminitis and dyslipidaemia — raised LDL — with tocilizumab).
- ▶ **Vaccination** before initiation — *live vaccines are contraindicated* during therapy; rituximab markedly blunts vaccine responses (e.g. SARS-CoV-2).
- ▶ **Therapeutic drug monitoring** in IBD — target trough levels: infliximab $>7 \mu\text{g/mL}$, adalimumab $>7-10 \mu\text{g/mL}$, golimumab $>1 \mu\text{g/mL}$; scheduled maintenance or co-immunomodulator use reduces anti-drug antibody formation to $<10\%$.

Adverse effects and contraindications

- ▶ **Infection** (the dominant risk) — serious bacterial, opportunistic fungal and viral infections; **reactivation of latent TB** (TNF inhibitors), **HBV reactivation** (rituximab), and **Pneumocystis jirovecii** pneumonia with rituximab/cyclophosphamide in AAV (give TMP-SMX prophylaxis).
- ▶ **TNF inhibitors specifically contraindicated in:** active infection, hypersensitivity, **chronic hepatitis B**, and **NYHA class III/IV heart failure**; can precipitate **demyelinating/neurologic events** (avoid in multiple sclerosis), **drug-induced lupus** (anti-histone antibodies) and rarely lymphoma (controversial).
- ▶ **Rituximab** — infusion reactions (premedicate with methylprednisolone), cytopenias, hypogammaglobulinaemia with prolonged use, and rare **progressive multifocal leukoencephalopathy (PML)** ($\approx 1:25,000$ in RA).
- ▶ **Tocilizumab/sarilumab** — neutropenia, thrombocytopenia, raised LDL, raised LFTs, and **gastrointestinal perforation** (avoid with diverticulitis/recent peptic ulcer).
- ▶ **Natalizumab** — PML from JC virus; largely abandoned in Crohn's for this reason (vedolizumab's gut selectivity confers lower PML risk).
- ▶ **Abatacept** and rituximab blunt vaccine responses.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ “Cytokine and cell targets of biologics in the rheumatoid synovium” — central panel showing macrophage, T cell, B cell, synovial fibroblast and osteoclast. Label arrows for: TNF- α $\rightarrow$ infliximab/etanercept/adalimumab/golimumab/certolizumab; IL-6/IL-6R $\rightarrow$ tocilizumab/sarilumab; IL-1 $\rightarrow$ anakinra; CD20 (B cell) $\rightarrow$ rituximab; CD28-CD80/86 co-stimulation $\rightarrow$ abatacept (CTLA-4-Ig); JAK/STAT (intracellular) $\rightarrow$ tofacitinib (tsDMARD).
- ▶ “Site of action ladder by disease” — vertical bars labelled: *Skin/joints* $\rightarrow$ IL-17 (secukinumab), IL-23 (risankizumab); *Gut* $\rightarrow$ $\alpha 4\beta 7$ (vedolizumab); *SLE* $\rightarrow$ BAFF (belimumab), IFNAR (anifrolumab); *Vasculitis* $\rightarrow$ CD20 (rituximab) + C5aR (avacopan).

Clinical / Diagnostic significance

- ▶ **Treat-to-target / step-up strategy:** in RA, begin with MTX; if inadequate response after 3–6 months, **add a TNF or non-TNF biologic** — combination DMARD therapy is superior to MTX alone.
- ▶ **Choice is individualised:** seropositive RA and refractory disease favour rituximab; concomitant psoriatic arthritis favours ustekinumab/IL-17 agents; lupus nephritis favours belimumab/voclosporin-based combinations; relapsing AAV favours rituximab.
- ▶ **Steroid-sparing** is a key modern goal — belimumab/anifrolumab in SLE and avacopan in AAV all allow rapid glucocorticoid tapering.

- ▶ **Biosimilars** lower cost and improve access without loss of efficacy — important in the Indian/RGUHS context.

High-yield exam pointers

- ▶ **First biologic class = TNF inhibitors (1999)**; etanercept is a **fusion protein**, the rest are **monoclonal antibodies**; certolizumab is a **PEGylated Fab'**.
- ▶ **Always screen for latent TB and HBV** before TNF inhibitors; treat LTBI ≥ 1 month before starting.
- ▶ **Rituximab = anti-CD20**, key in **TNF-refractory seropositive RA** and **AAV induction** ($375 \text{ mg/m}^2 \times 4$); watch for **PML** and **HBV reactivation**.
- ▶ **Abatacept = CTLA-4-Ig** (co-stimulation blocker); **tocilizumab = anti-IL-6R** (raises LDL, risk of GI perforation); **anakinra = IL-1Ra**.
- ▶ **SLE biologics: belimumab (anti-BAFF)** and **anifrolumab (anti-IFNAR)**; belimumab also approved for **lupus nephritis** with MMF/cyclophosphamide.
- ▶ **IBD: anti-TNF**, **vedolizumab ($\alpha 4\beta 7$, gut-selective)**, **ustekinumab (IL-12/23 p40)**, **risankizumab (IL-23 p19)**.
- ▶ **Psoriasis/spondyloarthritis: IL-17 (secukinumab, ixekizumab)** and **IL-12/23 agents**.
- ▶ **TNF inhibitors contraindicated** in class III/IV CHF, chronic hepatitis B and demyelinating disease.
- ▶ **JAK inhibitors are oral targeted-synthetic DMARDs**, **NOT biologics** — carry boxed warnings for thrombosis, MACE and malignancy.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Rheumatoid Arthritis” (biologic DMARD classes, Table 370-2 doses/toxicities, TNF/IL-6/B-cell/co-stimulation mechanisms), “Autoimmunity and Autoimmune Diseases” (cytokine and B-cell targets in autoimmunity), “Systemic Lupus Erythematosus” (belimumab, anifrolumab, rituximab, voclosporin, obinutuzumab, CAR-T), “The Vasculitis Syndromes / Granulomatosis with Polyangiitis” (rituximab induction/maintenance, avacopan, failure of etanercept/abatacept/belimumab in AAV), “Inflammatory Bowel Disease” (anti-TNF, natalizumab/vedolizumab integrin blockers, ustekinumab/risankizumab, trough levels), and the psoriasis/spondyloarthritis chapters (IL-17 and IL-23 agents).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic, & Allergic Disorders” (abatacept, rituximab, tocilizumab/sarilumab, Sjögren and vasculitis biologics, drug-induced lupus) and “Gastrointestinal Disorders” (IBD anti-TNF and anti-IL agents, therapeutic drug monitoring).

- *Coverage note:* This corpus has **no single dedicated “biologics” chapter** (as the spec flags); the answer is synthesised from the disease-specific therapy sections across Harrison and CMDT. The *-mab/-cept* nomenclature framework is standard, universally accepted pharmacology added for exam completeness.



Calcium Pyrophosphate Deposition Disease

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — Calcium pyrophosphate deposition disease (CPPD) is a crystal-induced arthropathy caused by the deposition of **calcium pyrophosphate (CPP) crystals** in articular hyaline cartilage and fibrocartilage, producing the radiographic hallmark of **chondrocalcinosis**. The acute inflammatory presentation was originally termed *pseudogout* by McCarty and colleagues because it mimics acute gout. CPPD is overwhelmingly a disease of the elderly, with prevalence in articular tissues roughly **doubling with each decade after 60 years** (reaching nearly 50% in those >85 years). It encompasses a spectrum from asymptomatic chondrocalcinosis through acute crystal arthritis to several chronic arthropathies.

Pathogenesis

- The central abnormality is an **increased concentration of inorganic pyrophosphate (PPi) in the cartilage matrix** — pathogenically analogous to hyperuricaemia in gout. PPi combines with calcium to form CPP crystals within **cartilage matrix vesicles** or on collagen fibres.
- Most matrix PPi derives from breakdown of **extracellular ATP**. ATP efflux (and hence PPi levels) is tightly regulated by a multipass membrane transport protein, **ANKH**; mutations in the *ANKH* gene (described in both familial and sporadic disease) increase elaboration and extracellular transport of pyrophosphate.
- PPi production is also augmented by enhanced activity of **ATP pyrophosphohydrolase** and **5'-nucleotidase** (which generate adenosine and pyrophosphate from ATP). **Decreased cartilage glycosaminoglycans** and **increased transglutaminase** activity further favour CPP crystal nucleation.
- Once shed into the joint space, CPP crystals are phagocytosed by **monocyte-macrophages and neutrophils**, which release chemotactic/inflammatory mediators and activate the **NLRP3 inflammasome**, driving **IL-1 β** -mediated acute synovitis (shared final pathway with gout).
- Biochemical changes of **ageing or diseased cartilage** are thought to favour crystal nucleation in the common sporadic (“idiopathic”) form, where the underlying aetiology remains uncertain.

Associated conditions (“the four H’s and beyond”)

- ▶ A minority of patients have an underlying metabolic or hereditary cause. **CPPD presenting in a patient aged <50 years** must prompt a search for a secondary cause and inherited disease.
- ▶ Endocrine-metabolic and other associations (Harrison Table 384-2):

Category	Associations
Degenerative / mechanical	Ageing, osteoarthritis, post-menisectomy or joint trauma
Hereditary	Familial-genetic CPPD (<i>ANKH</i> mutations)
Endocrine-metabolic	Primary hyperparathyroidism, Hemochromatosis, Hypophosphatasia, Hypomagnesemia
Renal-tubular / electrolyte	Gitelman's syndrome, X-linked hypophosphatemic rickets, familial hypocalciuric hypercalcemia, malabsorption
Drug-associated	Thiazide and loop diuretics; potentially proton-pump inhibitors
Other crystal	Coexistent gout

- ▶ *Useful screening mnemonic:* the classic remediable causes are **Hyperparathyroidism, Haemochromatosis, Hypophosphatasia and Hypomagnesaemia**.
- ▶ **Work-up of the young patient** should include serum **calcium, phosphorus, alkaline phosphatase, magnesium, iron and transferrin**, plus enquiry for familial aggregation.

Clinical manifestations

- ▶ **Acute CPP crystal arthritis (pseudogout)** — an acute, self-limiting mono- or oligoarthritis closely mimicking gout. Distinguishing clinical clues:
 - The **knee is the most commonly affected joint**, followed by the **wrist**; the first metatarsophalangeal joint (*podagra*) is **rarely** involved (in contrast to gout). Shoulder, ankle, elbow and hands may also be affected.
 - **Initial attacks tend to last longer than gout** — often weeks to months.
 - Frequently provoked by **trauma, severe medical illness, or surgery** — especially **parathyroidectomy**, which causes rapid fall in serum calcium and magnesium, leading to crystal dissolution and shedding. Pseudogout characteristically develops **24–48 h after major surgery**.
 - Systemic features (fever, chills, raised acute-phase reactants) occur; in up to **50%** there is low-grade fever, occasionally as high as **40°C (104°F)** — synovial fluid culture is then essential to exclude coexistent sepsis.
- ▶ **Chronic CPPD arthropathies** (several patterns):

- **Pseudo-osteoarthritis** — the *most common* chronic form; a degenerative arthropathy with unusually severe damage in joints atypical for primary OA (**metacarpophalangeal, wrist, elbow, shoulder, glenohumeral, ankle, patellofemoral**).
- **Pseudo-rheumatoid arthritis** — chronic symmetric synovitis affecting MCP joints and wrists, clinically resembling RA.
- **Pseudo-neuropathic (pseudo-Charcot)** — severe destructive disease that radiographically mimics neuropathic arthropathy.
- **Spinal disease** — intervertebral disk and ligament calcification with restricted spinal mobility; **spinal stenosis** (elderly); and the **crowned dens syndrome** — CPP deposition at the atlanto-axial junction with “crown-like” calcification around the odontoid, presenting with severe neck pain, rigidity and high fever that can mimic **meningitis or giant cell arteritis**.
- Rarely, **tumoral CPP deposits** in soft tissue.

Diagnosis

- ▶ **Synovial fluid crystal analysis is definitive.** Under compensated polarized light microscopy CPP crystals are **rhomboid or rod-shaped** and **weakly positively birefringent (or non-birefringent)** — contrasting with the needle-shaped, strongly **negatively birefringent** MSU crystals of gout. Crystals may be seen within neutrophils, tissue fragments and fibrin clots; they may coexist with MSU or apatite.
- ▶ **Synovial fluid is inflammatory** — leukocyte counts range from several thousand to **100,000 cells/ μ L** (mean $\sim$ 24,000/ μ L), predominantly **neutrophils**. Always **Gram stain and culture** to exclude septic arthritis (which can coexist).
- ▶ **Imaging — chondrocalcinosis:** plain radiographs or ultrasound show **punctate and/or linear radiodense deposits** within fibrocartilage (knee menisci, triangular fibrocartilage of the wrist, symphysis pubis) and hyaline articular cartilage. In the absence of a tappable effusion, **chondrocalcinosis is presumptive of CPPD** — a key exception being chondrocalcinosis from **calcium oxalate** in chronic renal failure. Radiographs in pseudo-OA also show asymmetric joint-space narrowing and osteophytes in atypical joints.
- ▶ The **2023 ACR/EULAR classification criteria for CPPD** provide a formal weighted scheme (incorporating crystal identification, imaging chondrocalcinosis and clinical features) for research/diagnostic standardisation.

Differential diagnosis

- ▶ **Gout** — distinguished by joint distribution (podagra), negatively birefringent needle-shaped MSU crystals, usually elevated serum urate, and erosions with overhanging edges rather than chondrocalcinosis.
- ▶ **Septic arthritis** — must always be excluded by synovial fluid Gram stain and culture, particularly when fever is present.

- ▶ **Rheumatoid arthritis** (vs pseudo-RA), **osteoarthritis** (vs pseudo-OA), **neuropathic joint** (vs pseudo-neuropathic), **apatite / basic calcium phosphate disease** (e.g. Milwaukee shoulder), and **calcium oxalate arthropathy** in dialysis patients.

Treatment

- ▶ **Acute pseudogout** (management largely adapted from acute gout):
 - **Joint aspiration plus intra-articular glucocorticoid** — e.g. *triamcinolone 10–40 mg* depending on joint size; effective and well tolerated for one or a few joints.
 - **NSAIDs** in full anti-inflammatory dose (with gastroprotection where required).
 - **Colchicine** — up to *1.8 mg orally in the first 24 h*, then *0.6 mg once or twice daily* until resolution.
 - **Systemic glucocorticoids** — *oral prednisone 30–50 mg/day tapered over 7–10 days*, useful in polyarticular attacks or where NSAIDs/colchicine are contraindicated.
 - **IL-1 β antagonists (anakinra, canakinumab)** for severe polyarticular attacks or when conventional therapy fails/is contraindicated.
 - Adjuncts: ice-pack application and rest of the involved joint.
- ▶ **Recurrent attacks (≥ 3 per year)** — prophylactic **low-dose colchicine 0.6 mg once or twice daily** reduces flare frequency.
- ▶ **Chronic CPPD arthritis** — there is **no agent that dissolves or removes CPP crystals** from cartilage (a crucial contrast with urate-lowering therapy in gout). Symptomatic options for chronic synovitis include NSAIDs, colchicine, low-dose glucocorticoids, **hydroxychloroquine** or **methotrexate**. **Treat any underlying metabolic cause** (e.g. iron depletion in haemochromatosis, magnesium repletion). Progressive destructive large-joint arthropathy may require **joint replacement**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Compensated polarized-light comparison of CPP vs MSU crystals**: draw two adjacent panels. *Panel A (CPPD)* — short rhomboid/rod-shaped crystals, one lying intracellularly within a neutrophil; label “**weakly POSITIVELY birefringent — blue when parallel to compensator axis**”. *Panel B (gout)* — long needle-shaped crystals; label “**strongly NEGATIVELY birefringent — yellow when parallel**”. Add common axis label “slow axis of red compensator”.
- ▶ **Knee radiograph showing chondrocalcinosis**: outline the knee joint with **linear/punctate calcific deposits in the meniscal fibrocartilage** and a thin line of **hyaline articular cartilage calcification**. Labels: *menisci (fibrocartilage), hyaline articular cartilage, chondrocalcinosis, joint-space narrowing/osteophyte (pseudo-OA)*.

Clinical / Diagnostic significance

- ▶ CPPD is a leading cause of **acute monoarthritis in the elderly** and a key mimic of **gout and septic arthritis** — every acute hot joint warrants aspiration for crystals, Gram stain and culture.
- ▶ **Chondrocalcinosis on imaging in a patient <50 years** is a red flag mandating screening for **haemochromatosis, hyperparathyroidism, hypophosphatasia and hypomagnesaemia** — diagnosing these may avert systemic complications.
- ▶ The **crowned dens syndrome** is an important reversible cause of acute neck pain with fever and raised inflammatory markers that can be misdiagnosed as meningitis or giant cell arteritis.
- ▶ Recognising **pseudo-OA / pseudo-RA / pseudo-neuropathic** patterns prevents misdiagnosis and inappropriate therapy.

High-yield exam pointers

- ▶ CPP crystals = **rhomboid, weakly POSITIVELY birefringent**; MSU = **needle-shaped, strongly NEGATIVELY birefringent** (the single most-tested discriminator).
- ▶ **Knee** is the commonest joint in pseudogout; **podagra** is **characteristically rare** (unlike gout).
- ▶ **Chondrocalcinosis** = linear/punctate cartilage calcification; **presumptive of CPPD** when no effusion is obtainable.
- ▶ Secondary causes — **4 H's: Hyperparathyroidism, Haemochromatosis, Hypophosphatasia, Hypomagnesaemia** ($\pm$ thiazide/loop diuretics).
- ▶ **Parathyroidectomy** and **major surgery (24–48 h post-op)** are classic precipitants via abrupt falls in $\text{Ca}^{2+}/\text{Mg}^{2+}$.
- ▶ Central pathogenesis = **excess inorganic pyrophosphate** from ATP breakdown; **ANKH** gene mutation in familial/sporadic disease.
- ▶ Acute attacks: **aspiration + intra-articular steroid, NSAIDs, colchicine, prednisone**; refractory $\rightarrow$ **anakinra/canakinumab**.
- ▶ **No crystal-dissolving (urate-lowering equivalent) therapy** exists for CPPD — management is anti-inflammatory plus treatment of any underlying metabolic cause.
- ▶ Up to 50% have **fever** during attacks (up to 40°C) $\rightarrow$ always exclude **septic arthritis** by culture.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22nd edition** — “Gout and Other Crystal-Associated Arthropathies” (pathogenesis, **ANKH**/pyrophosphate mechanism, Table of associated conditions, clinical patterns, crystal morphology and treatment).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic, & Allergic Disorders” — Calcium Pyrophosphate Deposition section (current drug doses — triamcinolone 10–40 mg, colchicine 1.8 mg/24 h, prednisone 30–50 mg, anakinra/canakinumab, prophylaxis; crowned dens syndrome; 2023 ACR/EULAR classification criteria reference, Abhishek A et al, *Arthritis Rheumatol* 2023;75:1703, PMID 37494275).



Classify the biological agents used in the treatment of rheumatoid arthritis. What are the adverse effects and contraindications to their use

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Rheumatoid arthritis (RA) is a chronic, symmetric, erosive inflammatory polyarthritis driven by dysregulated cytokine and cellular immunity. **Biologic disease-modifying antirheumatic drugs (biologic DMARDs / bDMARDs)** are protein therapeutics engineered to target specific cytokines or cell-surface molecules in this inflammatory cascade. Introduced in 1999, they have revolutionised RA management by reducing signs and symptoms, retarding radiographic joint damage, and improving function. They are typically added when conventional synthetic DMARDs (especially methotrexate) fail to achieve low disease activity, and are usually given **in combination with background methotrexate** within a “treat-to-target” strategy.

Classification of biologic agents used in RA

Biologics are best classified by their molecular target and mechanism of action:

Class (target)	Agents	Molecular nature / mechanism
TNF- α inhibitors (5 innovators)	Infliximab; Adalimumab; Golimumab; Certolizumab pegol; Etanercept	Infliximab = chimeric (mouse-human) anti-TNF mAb; adalimumab & golimumab = human(ized) anti-TNF mAbs; certolizumab = PEGylated Fab' fragment of a humanized mAb; etanercept = soluble TNF-receptor-2-IgG1 Fc fusion protein . All neutralise TNF- α , a pivotal upstream cytokine of synovitis
T-cell co-stimulation blocker	Abatacept	Soluble fusion protein of extracellular CTLA-4 + modified human IgG Fc; blocks the CD28-CD80/86 second signal, inhibiting T-cell activation
B-cell depletion (anti-CD20)	Rituximab	Chimeric mAb against CD20 on mature B lymphocytes $\rightarrow$ B-cell depletion; approved for RA refractory to a TNF inhibitor; more effective in seropositive (RF/ACPA+) disease

Class (target)	Agents	Molecular nature / mechanism
IL-6 receptor inhibitors	Tocilizumab; Sarilumab	mAbs against membrane-bound and soluble IL-6 receptor; block acute-phase response, osteoclast activation
IL-1 receptor antagonist	Anakinra	Recombinant human IL-1 receptor antagonist; limited RA use owing to weaker efficacy than other bDMARDs

Biosimilars — agents with the same active properties as a licensed reference biologic (e.g. of infliximab, etanercept, adalimumab); demonstrate comparable efficacy and safety.

Related but distinct — **targeted synthetic DMARDs (tsDMARDs)**: The oral JAK inhibitors *tofacitinib* (JAK1/3), *baricitinib* (JAK1/2) and *upadacitinib* (selective JAK1) target intracellular signalling. They are **not biologics** (they are small molecules), but are often examined alongside them as the modern “targeted” therapy; their adverse-effect profile is summarised below for completeness.

Mechanism and standard adult dosing

Agent	Route & dose (Harrison Table 370-2)
Infliximab	3 mg/kg IV at weeks 0, 2, 6, then every 8 weeks (may ↑ to 10 mg/kg q4 weeks)
Etanercept	50 mg SC weekly (or 25 mg SC twice weekly)
Adalimumab	40 mg SC every other week
Golimumab	50 mg SC monthly
Certolizumab pegol	400 mg SC at weeks 0, 2, 4, then 200 mg every other week
Abatacept	Weight-based IV (<60 kg: 500 mg; 60–100 kg: 750 mg; >100 kg: 1000 mg) at weeks 0, 2, 4, then q4 weeks; OR 125 mg SC weekly
Rituximab	1000 mg IV × 2 (days 0 and 14); repeat course every ≥24 weeks; premedicate with methylprednisolone 100 mg
Tocilizumab	4–8 mg/kg IV monthly; OR 162 mg SC every other week (<100 kg) / weekly (≥100 kg)
Sarilumab	200 mg SC every other week
Anakinra	100 mg SC daily

Adverse effects

Common to all biologics — **increased infection risk** is the dominant class effect: serious bacterial infections, opportunistic fungal infection, and **reactivation of latent tuberculosis** (most marked with TNF inhibitors, which characteristically cause granulomatous/TB reactivation). Live-vaccine responses are blunted.

- ▶ **TNF- α inhibitors:** $\uparrow$ bacterial and fungal infections; **reactivation of latent TB**; infusion reactions (IV infliximab; rarely anaphylaxis) and injection-site reactions (SC agents); raised LFTs; **drug-induced lupus** (induction of anti-dsDNA antibodies); **demyelinating/neurologic deficits** resembling multiple sclerosis (rare); possible $\uparrow$ lymphoma risk (controversial — most observational data show no excess malignancy); worsening of moderate–severe heart failure.
- ▶ **Abatacept:** $\uparrow$ risk of bacterial and viral infection; can **blunt vaccine responses**.
- ▶ **Rituximab:** mild–moderate infusion reactions; $\uparrow$ infection; **hepatitis B reactivation**; cytopenias; rare **progressive multifocal leukoencephalopathy (PML)** ($\approx 1:25,000$, mostly with prior immunosuppression); markedly inhibits vaccine response (e.g. to SARS-CoV-2 vaccine).
- ▶ **IL-6 receptor inhibitors (tocilizumab, sarilumab):** $\uparrow$ infection; **neutropenia and thrombocytopenia** (reversible on stopping); **LFT elevation**; **dyslipidaemia** ($\uparrow$ LDL cholesterol); $\uparrow$ rate of **gastrointestinal perforation**.
- ▶ **Anakinra:** injection-site reactions; $\uparrow$ bacterial/viral infection; neutropenia.
- ▶ **JAK inhibitors (tsDMARDs):** $\uparrow$ infection including **herpes zoster**; raised transaminases; dyslipidaemia; neutropenia; **thrombosis/VTE**; **major adverse cardiovascular events (MACE)** and malignancy — these carry an **FDA black-box warning** (highest risk in the elderly, from the tofacitinib-vs-TNFi safety trial); $\uparrow$ creatinine and hypertension.

Contraindications & pre-treatment screening

- ▶ **Active infection** of any kind — a contraindication to starting (and reason to suspend) any biologic.
- ▶ **Untreated latent TB** — *all* candidates must be screened with a **tuberculin skin test** (Mantoux/PPD) or **interferon- γ release assay (IGRA)** before therapy; if positive, treat LTBI for at least 1 month before starting.
- ▶ **TNF- α inhibitors specifically:** contraindicated in **chronic/active hepatitis B**, **NYHA class III/IV congestive heart failure**, and prior **hypersensitivity**; use cautiously in demyelinating disease (relative).
- ▶ **Rituximab:** active hepatitis B (risk of reactivation) — **viral hepatitis screening** (HBsAg, anti-HBc, HCV antibody) **mandatory** before use.
- ▶ **IL-6 receptor inhibitors:** avoid where possible in **diverticulitis** or recent **gastric/duodenal ulcer** (GI perforation risk); pre-existing significant neutropenia/thrombocytopenia or transaminitis.
- ▶ **Pregnancy:** anti-TNF agents are generally regarded as acceptable but are **discontinued in the third trimester**; data are insufficient for abatacept, anti-IL-6, rituximab and JAK inhibitors, so

these are **stopped at conception**. (The teratogenic conventional DMARDs **methotrexate** and **leflunomide** are absolutely contraindicated in pregnancy, but are not biologics.)

- **General:** live vaccines should not be given during biologic therapy; combining two biologics is not recommended (no added efficacy, additive toxicity).

Baseline work-up before any biologic: TB screen (PPD/IGRA), viral hepatitis panel (especially for TNF inhibitors and rituximab), CBC and LFTs; with periodic monitoring of CBC, LFTs and lipids thereafter.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — “Cytokine/cell targets of biologic DMARDs in the rheumatoid synovium”:**
Draw an antigen-presenting cell (APC) presenting via MHC-II/peptide-TCR to a CD4⁺ T cell, with the CD80/86-CD28 co-stimulation pair, a B cell/plasma cell producing RF/ACPA, and a macrophage/fibroblast secreting TNF- α , IL-1, IL-6, driving an osteoclast (RANKL). Label each biologic at its target: TNF inhibitors $\rightarrow$ TNF- α ; Abatacept $\rightarrow$ CD80/86-CD28; Rituximab $\rightarrow$ CD20 (B cell); Tocilizumab/Sarilumab $\rightarrow$ IL-6 receptor; Anakinra $\rightarrow$ IL-1 receptor; JAK inhibitors $\rightarrow$ intracellular JAK-STAT (label as tsDMARD).
- **Diagram 2 — “Treat-to-target ladder”:** NSAIDs/short glucocorticoid $\rightarrow$ Methotrexate (anchor) $\rightarrow$ +conventional combination (oral triple therapy) $\rightarrow$ add anti-TNF or non-TNF biologic $\pm$ MTX $\rightarrow$ switch biologic class / JAK inhibitor. Label the goal box: low disease activity / remission.

Clinical / Diagnostic significance

- **Sequencing:** methotrexate remains the **anchor/first-choice DMARD**; a biologic (usually anti-TNF) is added on inadequate response after 3–6 months. Combination of methotrexate + anti-TNF is superior to methotrexate alone for both symptoms and radiographic progression.
- **Switching:** patients failing one anti-TNF may respond to a **second anti-TNF** or to a **different mechanism** (abatacept, rituximab, IL-6 inhibitor); some evidence favours switching class (e.g. to abatacept) over a second anti-TNF.
- **Serostatus guides choice:** rituximab is more effective in RF/ACPA-positive disease.
- **Monitoring:** vigilance for infection (suspend during febrile illness), serial CBC/LFTs/lipids; IL-6 inhibitors mask CRP/ESR, so acute-phase reactants are unreliable for detecting infection.
- **Comorbidity steering:** avoid TNF inhibitors in advanced heart failure and hepatitis B; avoid IL-6 inhibitors in diverticular disease; reserve JAK inhibitors cautiously in the elderly and those with cardiovascular/thrombotic/malignancy risk.
- **Extra-articular disease:** rituximab is useful for RA-associated interstitial lung disease (with corticosteroids $\pm$ azathioprine/MMF).

High-yield exam pointers

- ▶ Five TNF inhibitors: **infliximab** (chimeric mAb), **adalimumab**, **golimumab** (human mAbs), **certolizumab pegol** (PEGylated Fab'), **etanercept** (TNFR2–Fc fusion protein).
- ▶ **Abatacept** = CTLA-4-Ig (co-stimulation block); **rituximab** = anti-CD20 (B-cell depletion); **tocilizumab/sarilumab** = anti-IL-6R; **anakinra** = IL-1Ra.
- ▶ **JAK inhibitors (tofacitinib, baricitinib, upadacitinib) are targeted synthetic DMARDs, NOT biologics — oral, JAK-STAT pathway, carry an FDA black-box warning* (MACE, malignancy, thrombosis, death).*
- ▶ Class hazard = **infection + latent TB reactivation** → screen with PPD/IGRA in all; treat LTBI before starting.
- ▶ TNF inhibitors are contraindicated in **chronic hepatitis B**, **NYHA III/IV heart failure**; can cause **drug-induced lupus** and **demyelination**.
- ▶ **Rituximab**: hepatitis B reactivation, rare PML; check viral hepatitis panel first.
- ▶ **IL-6 inhibitors**: dyslipidaemia, cytopenias, **GI perforation** (avoid in diverticulitis).
- ▶ **Live vaccines contraindicated**; do **not** combine two biologics; anti-TNF stopped in third trimester.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e — "Rheumatoid Arthritis"** (classification, molecular design, dosing Table 370-2, adverse effects and contraindications, treat-to-target approach).
- ▶ **CMDT 2026 — "Rheumatologic, Immunologic & Allergic Disorders" (Rheumatoid Arthritis)** (current management framing, TNF-inhibitor/JAK-inhibitor safety, mandatory hepatitis and TB screening, EULAR 2022 update).



Classify vasculitis based on the pathology. Give the ACR classification criteria for any one type of vasculitis

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — Vasculitis is a clinicopathologic process characterised by **inflammation of and damage to blood vessel walls**, with luminal compromise leading to ischaemia of the tissues supplied. Because *any* type, size and location of vessel may be involved, the result is a broad, heterogeneous and overlapping group of syndromes that may be primary or secondary, single-organ or multisystem. Classification is anchored on the **dominant calibre of vessel involved** (the basis of the *Chapel Hill Consensus Conference, CHCC 2012* nomenclature), refined by the **immunopathological**

mechanism (immune-complex deposition, ANCA, or T-cell/granuloma formation) and by features such as granuloma, ANCA status and artery-vs-vein involvement.

Basis of pathological classification

- ▶ **Size of predominant vessel** — large, medium or small (the first and most important discriminator).
- ▶ **Type of vessel** — artery only, vein, or both.
- ▶ **Presence/absence of granulomatous inflammation** on biopsy.
- ▶ **Immune mechanism** — immune-complex (with vessel-wall immunoglobulin/complement deposition) versus *pauci-immune* (ANCA-associated, scant immunoglobulin) versus cell-mediated/granulomatous.
- ▶ **Demography & associations** — age, sex, ethnicity, smoking, and any underlying trigger (infection, drug, connective-tissue disease, malignancy).

Classification by vessel size (Chapel Hill Consensus Conference 2012)

Predominant vessel	Syndromes	Characteristic pathology
Large vessel (aorta + major branches)	Takayasu arteritis; Giant cell (temporal) arteritis	Granulomatous panarteritis, mononuclear infiltrate, giant cells, fragmentation of internal elastic lamina
Medium vessel (main visceral/muscular arteries)	Polyarteritis nodosa (PAN); Kawasaki disease	Necrotising arteritis, fibrinoid necrosis, micro-aneurysms; <i>no</i> glomerulonephritis or granuloma in PAN
Small vessel — ANCA-associated (pauci-immune)	Granulomatosis with polyangiitis (GPA); Microscopic polyangiitis (MPA); Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss)	Necrotising vasculitis of capillaries/venules/arterioles with <i>few or no</i> immune deposits; granuloma in GPA & EGPA; eosinophilia in EGPA
Small vessel — immune-complex	IgA vasculitis (Henoch-Schönlein); Cryoglobulinaemic vasculitis; Hypocomplementaemic urticarial (anti-C1q) vasculitis; Anti-GBM disease	Vessel-wall immune-complex/immunoglobulin deposition (e.g. IgA, cryoglobulins)
Variable vessel	Behçet disease; Cogan syndrome	May affect small, medium and large vessels; arteries <i>and</i> veins
Single-organ	Cutaneous leukocytoclastic angiitis; cutaneous arteritis; primary CNS vasculitis; isolated aortitis	Confined to one organ without systemic spread

Predominant vessel	Syndromes	Characteristic pathology
Associated with systemic disease	Lupus, rheumatoid, sarcoid vasculitis	Secondary to a defined connective-tissue/systemic illness
Associated with probable aetiology	HBV-associated (PAN-like); HCV-associated cryoglobulinaemic; drug-induced; cancer-associated	Identifiable antigenic trigger

Classification by immunopathogenic mechanism (pathology of vessel injury)

Dominant mechanism	Representative syndromes
Pathogenic immune-complex formation / deposition	IgA vasculitis (HSP); lupus vasculitis; serum-sickness & cutaneous vasculitis; HCV cryoglobulinaemic; HBV-associated
ANCA production (pauci-immune)	GPA (PR3/cANCA), MPA (MPO/pANCA), EGPA (MPO)
Pathogenic T-lymphocyte response & granuloma formation	Giant cell arteritis; Takayasu arteritis; GPA; EGPA

- ▶ ANCA serology further subdivides small-vessel disease: *cANCA/anti-proteinase-3* in >90% of active GPA; *pANCA/anti-myeloperoxidase* in ~75% of MPA and ~48% of EGPA. Up to 20% of GPA may be ANCA-negative.
- ▶ Renal lesion of GPA/MPA is a **pauci-immune crescentic glomerulonephritis** (no immune-complex deposition), distinguishing it from immune-complex small-vessel disease.

ACR classification criteria — Giant Cell (Temporal) Arteritis (1990 ACR criteria — featured example)

Classification criteria are designed to define a homogeneous patient population for study (and to distinguish one vasculitis from another once vasculitis is established) — they are not strict diagnostic criteria.

#	Criterion	Definition
1	Age at onset ≥ 50 years	Development of symptoms/findings beginning at age 50 or older
2	New headache	New onset of, or new type of, localised pain in the head
3	Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries

#	Criterion	Definition
4	Elevated ESR	Erythrocyte sedimentation rate ≥ 50 mm/h (Westergren method)
5	Abnormal artery biopsy	Vasculitis with a predominance of mononuclear-cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

- **Classification** is satisfied when ≥ 3 of 5 criteria are present $\rightarrow$ sensitivity **93.5%**, specificity **91.2%**.
- *Alternative example — GPA (1990 ACR):* (1) nasal/oral inflammation (oral ulcers or purulent/bloody nasal discharge); (2) abnormal chest radiograph (nodules, fixed infiltrates or cavities); (3) abnormal urinary sediment (microhaematuria >5 RBC/hpf or red-cell casts); (4) granulomatous inflammation on biopsy. ≥ 2 of 4 $\rightarrow$ sensitivity $\sim 88\%$, specificity $\sim 92\%$.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Vessel-size “tree” of vasculitis** — three concentric/parallel columns labelled **Large, Medium, Small**; place under each: Large $\rightarrow$ *Takayasu, Giant cell arteritis*; Medium $\rightarrow$ *PAN, Kawasaki*; Small $\rightarrow$ split into *ANCA-associated (GPA, MPA, EGPA)* and *Immune-complex (IgA vasculitis, cryoglobulinaemic, anti-GBM, urticarial)*; side boxes for *Variable vessel (Behçet, Cogan)* and *Single-organ*. Label overlapping zone “small + medium overlap (ANCA disease, PAN).”
- **Cross-section of an inflamed artery** — label: *lumen, thrombus, fibrinoid necrosis of media, transmural mononuclear/neutrophil infiltrate, fragmented internal elastic lamina, multinucleated giant cell, granuloma, adventitia/vasa vasorum.*

Clinical / Diagnostic significance

- **Vessel size predicts the clinical picture:** large-vessel $\rightarrow$ limb claudication, asymmetric BP/absent pulses, bruits, aortic dilatation; medium-vessel $\rightarrow$ cutaneous nodules, livedo reticularis, digital gangrene, mononeuritis multiplex, micro-aneurysms; small-vessel $\rightarrow$ palpable purpura, glomerulonephritis/haematuria, alveolar haemorrhage, splinter haemorrhages, scleritis.
- **Workup sequence:** consider vasculitis in any unexplained multisystem illness (palpable purpura, pulmonary infiltrates + haematuria, chronic sinusitis, mononeuritis multiplex, glomerulonephritis); **first exclude mimics** (endocarditis, atrial myxoma, cholesterol emboli, antiphospholipid syndrome, drug toxicity e.g. cocaine/levamisole). Confirm by **biopsy of involved tissue**; use **catheter angiography** when PAN, Takayasu or primary CNS vasculitis is suspected (micro-aneurysms / stenoses).
- **Serology directs categorisation:** PR3-ANCA, MPO-ANCA, cryoglobulins, complement, hepatitis B & C serology, eosinophil count.

- ▶ **Treatment is category-driven:** GPA/MPA — induction with **cyclophosphamide 2 mg/kg/day** *or* **rituximab 375 mg/m²/week ×4** + glucocorticoids ± **avacopan** (C5a-receptor inhibitor), then azathioprine/methotrexate/rituximab maintenance; GCA — **prednisone 40–60 mg/day** (urgent, to prevent blindness) ± **tocilizumab** (IL-6R); EGPA — glucocorticoids ± **mepolizumab** (anti-IL-5). Always weigh relapse risk and immunosuppression toxicity.

High-yield exam pointers

- ▶ First step in classifying vasculitis = **size of the dominant vessel** (large / medium / small) — CHCC 2012.
- ▶ **Pauci-immune** = ANCA-associated (GPA, MPA, EGPA); **immune-complex** = IgA vasculitis, cryoglobulinaemic, anti-GBM, urticarial.
- ▶ **GPA** = upper + lower airway granulomatous vasculitis + glomerulonephritis; PR3-cANCA >90%; saddle-nose, subglottic stenosis.
- ▶ **PAN** = medium-vessel necrotising arteritis, **sparing the lungs**, no glomerulonephritis/granuloma, HBV-associated, renal micro-aneurysms; ANCA usually negative; consider **DADA2** in early-onset disease.
- ▶ **GCA** = age >50, new headache, jaw claudication, ESR ≥50, temporal artery biopsy giant cells; dreaded complication = **anterior ischaemic optic neuropathy / blindness** — treat *before* biopsy.
- ▶ **Takayasu** = “pulseless disease” of young women, aortic arch and branches.
- ▶ **ACR classification** criteria define study populations (homogeneity) — they are **not** diagnostic criteria; e.g. GCA 3 of 5, GPA 2 of 4.
- ▶ EGPA triad = **asthma + eosinophilia (>1000/μL) + vasculitis**; MPO-ANCA in ~48%.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “The Vasculitis Syndromes” (classification tables, pathogenic mechanisms — immune-complex / ANCA / T-cell granuloma; syndrome-by-syndrome pathology and treatment).
- ▶ **CMDT 2026** — “Vasculitis Syndromes / Rheumatologic, Immunologic & Allergic Disorders” (classification scheme by size of predominant vessel — Table 23–11; clinical manifestations by vessel size — Table 23–12; revised International Chapel Hill Consensus Conference nomenclature, Jennette et al. 2012; current management).
- ▶ **Coverage note:** The provided corpus (Harrison 22e, CMDT 2026) tabulates the **vessel-size/CHCC classification** and pathogenic mechanisms fully, and references the **2022 ACR/EULAR** classification criteria for GCA, Takayasu and GPA, but does **not** reproduce the older **1990 ACR item-level classification criteria** as a list. The 1990 ACR criteria for giant cell arteritis (and GPA) given above are **universally accepted standard internal medicine** (Hunder et al., *Arthritis Rheum* 1990) and are supplied to satisfy the “give the

ACR criteria” stem; the cut-offs and sensitivity/specificity quoted are the published ACR figures.



Behçet Syndrome — Clinical Features, Evaluation, and Treatment

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Behçet syndrome is a chronic, relapsing **systemic vasculitis** of unknown cause, first described by the Turkish dermatologist *Hulusi Behçet*. It is unique among the vasculitides in being able to involve **vessels of all sizes (small, medium and large)** on **both the venous and arterial side** of the circulation. It is characterised clinically by **recurrent oral and genital aphthous ulcers**, skin lesions, **uveitis**, **arthritis**, **vascular thrombosis**, and **gastrointestinal and neurological involvement**, occurring in varying combinations and sequence over time. The diagnosis is purely **clinical** — there is no pathognomonic laboratory, imaging or histological test.

Epidemiology and Pathogenesis

- ▶ **Geographic distribution** — clusters along the ancient “*Silk Road*”: highest in the **Middle East, Mediterranean region and Far East**. Most prevalent in **Turkey** (≈ 1 in 250 adults).
- ▶ **Age/sex** — relatively rare before the late teens and after age 50. Males and females are affected equally, but **males generally have more severe disease and poorer outcomes**.
- ▶ **Regional variation in phenotype** — gastrointestinal involvement is rare in Turkey but common in Japan and is seen in $\sim 30\%$ of US patients.
- ▶ **Pathogenesis (unknown)** — a probable **genetic predisposition** with activation of both **innate and adaptive immunity**; **neutrophil hyperreactivity** is characteristic. **HLA-B*51** is positive in ~ 50 – 60% of patients (but in $\sim 20\%$ of the normal population, so it is *not* diagnostic).
- ▶ **Not a classic autoimmune disease** — typically **no autoantibodies**, and not associated with Raynaud’s phenomenon, Sjögren’s, thrombocytopenia, haemolytic anaemia, photosensitivity or serositis. It also differs from autoinflammatory disorders (e.g. familial Mediterranean fever) by its tendency to **abate with time** and absence of the relevant gene mutations.

Clinical Features (organ-system approach)

- ▶ **Mucocutaneous (the hallmark and usually the first manifestation)**
 - **Oral aphthous ulcers** — seen in *virtually all* patients ($\sim 98\%$); usually multiple, resemble canker sores, last ~ 10 days and recur; only the uncommon **major ulcers scar**.
 - **Genital ulcers** — the **most specific lesion** ($\sim 80\%$); on **scrotum or labia**, larger, deeper, slower to heal and **tend to scar**.

- **Skin lesions** — **papulopustular/acne-like** lesions (indistinguishable from acne vulgaris), **erythema nodosum**-like nodules (panniculitis), and **superficial thrombophlebitis**. Superficial thrombophlebitis occurs in men and flags a need to screen for deeper vascular involvement (including pulmonary artery aneurysms).
- ▶ **Ocular** — in ~half of patients (**up to ~70% of males**); typically a **bilateral panuveitis**. Hypopyon (layered pus in the anterior chamber) occurs in ~10% of those with eye disease and is **quite specific**. Posterior uveitis/retinal venulitis can silently destroy the retina. **Poor prognostic factors:** *male sex, posterior involvement, >3 attacks/year, dense vitreous opacity, macular oedema*.
- ▶ **Articular** — arthralgia/arthritis in about half (CMDT: up to two-thirds); usually a **non-erosive, non-deforming mono- or oligoarthritis** of the lower limbs (knees, ankles).
- ▶ **Vascular** — in up to 40%; intense, **relapsing thrombosis**. Venous lesions cluster: **superficial and deep-vein thrombosis, Budd-Chiari syndrome, inferior vena cava syndrome, intracardiac thrombosis, cerebral venous sinus thrombosis, and pulmonary artery aneurysms**. Pulmonary artery aneurysms carry a 5-year mortality of 20–25% and can cause fatal haemorrhage.
- ▶ **Neurological** (“neuro-Behçet”, ~5%) — two largely **mutually exclusive** forms:
 - **Parenchymal** (~three-quarters) — affects the **telencephalic–diencephalic junction, brainstem and spinal cord**; subacute severe headache, cranial-nerve palsy, dysarthria, ataxia, hemiparesis. May radiologically **mimic multiple sclerosis**.
 - **Non-parenchymal** — **cerebral venous sinus thrombosis** (headache, raised intracranial pressure). Sterile meningitis with lymphocytic pleocytosis may occur.
- ▶ **Gastrointestinal** — frequency varies widely (up to ~50% in the Far East, rare in the Middle East). Ulcers are usually **single or <5, confined to the ileocaecal region, deep, round and prone to perforation**; perianal/rectal disease is rare. **Difficult to distinguish from Crohn’s disease** unless extra-intestinal features are present.

Evaluation and Diagnosis

- ▶ **Diagnosis is clinical** — based on the constellation of features after *excluding mimics*. Some patients take months to years to evolve the full picture.
- ▶ **International Study Group (ISG) criteria** — most widely used; sensitivity ~95%, specificity ~96%:

Criterion	Frequency	Comments
Recurrent oral ulcers (<i>mandatory</i>)	~98%	At least 3 times in a 12-month period
<i>Plus two of the following four:</i>		
Recurrent genital ulcers	~80%	Usually scarring

Criterion	Frequency	Comments
Skin lesions	~80%	Erythema nodosum, pseudofolliculitis, papulopustular/acneiform nodules (post-adolescent, not on corticosteroids)
Eye lesions	~50%	Anterior or posterior uveitis, cells in vitreous, or retinal vasculitis
Positive pathergy test	~50%	Read at 24–48 h after dermal prick with a 20–21-gauge needle

- ▶ **Pathergy test** — non-specific cutaneous hyper-reactivity to trauma: a **papule/pustule develops at 24–48 h** after a needle prick. Rather unique to Behçet and part of the ISG criteria (positivity is higher in Mediterranean/Far-Eastern populations).
- ▶ **Laboratory** — *no pathognomonic test* and **no specific autoantibody**; acute-phase reactants (ESR/CRP) are often raised. **HLA-B51** supports but does not confirm the diagnosis.
- ▶ **Targeted work-up by organ involvement** — slit-lamp/ophthalmological assessment and fluorescein angiography for uveitis; **MRI brain/MR venography** for neuro-Behçet (and CSF showing lymphocytic pleocytosis); **CT/MR angiography or Doppler** for venous thrombosis and pulmonary artery aneurysms; **ileocolonoscopy** for GI ulcers (to differentiate from Crohn's).

Treatment

General principles: therapy is tailored to the **type and severity of organ involvement**, aiming to **prevent irreversible damage**. Most new manifestations appear within the **first 5 years**, and the natural course is one of diminishing activity toward potential remission; **glucocorticoids are tapered** once disease is controlled, while **immunosuppressants are continued ≥ 2 years** and tapering/stopping is attempted at 2–3 years. **Young male patients** warrant more aggressive treatment owing to worse prognosis.

Manifestation	Preferred management
Oral/genital ulcers & mucocutaneous	Topical glucocorticoids for mild/as-needed; colchicine (0.6 mg 1–3×/day) for nodular/genital lesions; if resistant — oral glucocorticoids, apremilast (PDE-4 inhibitor, <i>FDA-approved for oral ulcers</i>), azathioprine , or a TNF-α inhibitor (infliximab)
Ocular (uveitis)	Early, aggressive therapy — brief glucocorticoid courses + long-term immunosuppression; azathioprine is the usual first choice; infliximab or adalimumab (first-line monotherapy or with steroid + azathioprine); cyclosporine or interferon-α are alternatives

Manifestation	Preferred management
Gastrointestinal	Glucocorticoids plus an immunosuppressant (azathioprine alone or with infliximab)
Venous thrombosis	Treat the inflammation with immunosuppressants (azathioprine; cyclophosphamide for severe disease) rather than relying on anticoagulation. Standard anticoagulation may be added only if bleeding risk is low and there are no coexistent pulmonary artery aneurysms
CNS (neuro-Behçet)	Combination of azathioprine + a TNF inhibitor is usually first choice (glucocorticoids for acute attacks)
Severe/refractory systemic disease	Higher-dose glucocorticoids (prednisone ~1 mg/kg/day) plus cyclophosphamide or TNF inhibitor ; <i>Saadoun 2024 (NEJM Evid)</i> trial compared infliximab vs cyclophosphamide for severe disease

- **Key caveat:** anticoagulation is **contraindicated/avoided** when **pulmonary artery aneurysms** coexist because of the risk of fatal haemorrhage — immunosuppression is the cornerstone of vascular Behçet.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- “Clinical map of Behçet syndrome” — a central figure with labelled arrows to: *Oral aphthous ulcer (~98%), Genital ulcer (scrotum/labia — most specific), Skin: erythema nodosum / papulopustular / superficial thrombophlebitis, Eye: bilateral panuveitis with hypopyon, Joint: non-erosive lower-limb oligoarthritis, Vessel: DVT / Budd-Chiari / pulmonary artery aneurysm, CNS: brainstem parenchymal lesion / cerebral venous sinus thrombosis, Gut: ileocaecal deep round ulcers.*
- “ISG diagnostic criteria pyramid” — base = **mandatory recurrent oral ulcers (≥3×/12 months)**; second tier = **need 2 of 4: genital ulcers · skin lesions · eye lesions · positive pathergy**; with a side-box labelled *Pathergy: 20–21G needle prick → read papule/pustule at 24–48 h.*

Clinical / Diagnostic significance

- A **clinical diagnosis of exclusion** — investigations chiefly **rule out mimics** (ANCA-associated vasculitis, IBD/Crohn’s, celiac disease, HIV/histoplasmosis, complex aphthosis, pemphigus, lichen planus).
- **Hypopyon uveitis** and **positive pathergy** are the most specific bedside clues; HLA-B51 supports but never confirms.

- ▶ **Pulmonary artery aneurysm + thrombosis** is a feared, high-mortality combination — recognise that anticoagulation can be lethal here.
- ▶ **Neuro-Behçet** can masquerade as multiple sclerosis on MRI — differentiate by mucocutaneous/systemic features and CSF pattern.
- ▶ GI Behçet vs Crohn's is a recurring exam discriminator — **few (<5), deep, round, ileocaecal, perforation-prone** ulcers favour Behçet.

High-yield exam pointers

- ▶ Systemic vasculitis affecting ALL vessel sizes, both arterial and venous — the distinguishing one-liner.
- ▶ **ISG criteria:** recurrent oral ulcers ($\geq 3 \times / \text{yr}$) + 2 of 4 (genital ulcers, skin lesions, eye lesions, pathergy); sens ~95%, spec ~96%.
- ▶ **Genital ulcer = most specific lesion; hypopyon = highly specific eye sign; pathergy = read at 24–48 h.**
- ▶ HLA-B51 positive in ~50–60% of patients (not diagnostic).
- ▶ **Pulmonary artery aneurysm** → 5-year mortality 20–25%.
- ▶ Vascular/venous disease is treated with immunosuppression, not primarily anticoagulation; avoid anticoagulants if PA aneurysms coexist.
- ▶ **Apremilast** (PDE-4 inhibitor) is FDA-approved for oral ulcers; **azathioprine** is the workhorse immunosuppressant; **TNF inhibitors (infliximab/adalimumab)** for severe ocular, GI and CNS disease.
- ▶ Worse prognosis in **young males**; most manifestations appear in the **first 5 years** then tend to abate.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Behçet Syndrome” (epidemiology, pathogenesis, ISG criteria, organ-specific clinical features, and the treatment section continuing into the adjacent chapter file).
- ▶ **CMDT 2026** — “Behçet Disease” (Rheumatologic, Immunologic & Allergic Disorders) — current clinical findings, differential diagnosis, and drug regimens (colchicine, apremilast, prednisone 1 mg/kg/day, azathioprine 2 mg/kg/day, TNF inhibitors, cyclophosphamide; infliximab-vs-cyclophosphamide evidence).



Criteria for Systemic Lupus Erythematosus (SLE) diagnosis

Asked in: Paper III May 2022 — RGUHS MD General Medicine

Definition / Introduction — Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterised by loss of immune tolerance, production of autoantibodies to nuclear antigens (especially nucleic acids and nuclear proteins), and immune-complex-mediated inflammation and tissue damage. There is **no single confirmatory test**; the diagnosis is clinical, integrating a compatible multi-organ presentation with serology and *exclusion of mimics*. Standardised **classification criteria** (2019 EULAR/ACR and 2012 SLICC) were devised to enrol homogeneous patients into clinical trials — they are widely used as a structured diagnostic framework but are **not** a substitute for individualised clinical judgement.

Classification vs diagnosis — the cardinal exam point

- ▶ Harrison stresses that classification criteria were **developed for enrolment into clinical trials, not for diagnosis**. For an individual patient, diagnosis is made on the totality of clinical and laboratory features after **excluding other disease entities**, and ultimately rests on **clinical judgement**.
- ▶ Two criteria sets are currently in use for trial enrolment: the **2019 EULAR/ACR** classification criteria and the **2012 SLICC** (Systemic Lupus International Collaborating Clinics) criteria.
- ▶ Important limitation: because EULAR/ACR criteria mandate ANA positivity, they **exclude the ~5% of SLE patients who are ANA-negative**, as well as patients with *incomplete lupus* — both groups still require clinical recognition and management.

Entry criterion — ANA is the gateway

- ▶ The **2019 EULAR/ACR** criteria use a positive **antinuclear antibody (ANA) titre of $\geq 1:80$** (on HEp-2 cells or equivalent) as a **mandatory entry criterion**. If ANA is negative (and was never positive), the patient cannot be classified as SLE by these criteria.
- ▶ ANA is present in **~95%** of SLE patients; a titre of **$\geq 1:80$ is considered positive** — highly **sensitive but not specific**. *Repeatedly negative ANA by immunofluorescence makes SLE unlikely*, though rare ANA-negative cases occur.
- ▶ Only after the entry criterion is satisfied are the **additive weighted clinical and immunological criteria** applied; a **patient requires ≥ 10 points** across the domains to be classified as SLE.

2019 EULAR/ACR additive weighted criteria

Criteria are grouped into **7 clinical** and **3 immunological** domains, each item carrying a weight. Scoring rules: a criterion is counted only if there is **no more likely explanation**; it need occur on **only one occasion**; **at least one clinical criterion** is required; and within each domain **only the single highest-weighted item** is counted. **Total ≥ 10 points (with ANA $\geq 1:80$) = classify as SLE.**

Domain	Representative criteria (highest weight in domain)	Weight
Constitutional	Fever	2
Hematologic	Leukopenia (3); Thrombocytopenia (4); Autoimmune haemolysis (4)	up to 4
Neuropsychiatric	Delirium (2); Psychosis (3); Seizure (5)	up to 5
Mucocutaneous	Non-scarring alopecia / oral ulcers (2); Subacute cutaneous or discoid lupus (4); Acute cutaneous lupus / malar rash (6)	up to 6
Serosal	Pleural/pericardial effusion (5); Acute pericarditis (6)	up to 6
Musculoskeletal	Joint involvement (≥ 2 joints synovitis / tenderness + stiffness)	6
Renal	Proteinuria >0.5 g/24 h (4); biopsy Class II/V LN (8); biopsy Class III/IV LN (10)	up to 10
Antiphospholipid antibodies	Anticardiolipin OR anti- $\beta 2$ - glycoprotein-1 OR lupus anticoagulant	2
Complement proteins	Low C3 OR low C4 (3); low C3 AND C4 (4)	up to 4
SLE-specific antibodies	Anti-dsDNA OR anti-Sm	6

- ▶ Harrison highlights the practically important rule: **no single value reaches 10 points except a renal biopsy showing Class III or IV lupus nephritis** — biopsy-proven proliferative nephritis (with a positive ANA) alone satisfies classification.
- ▶ **Anti-dsDNA and anti-Sm are the only ANA subtypes included** in the EULAR/ACR criteria, reflecting their high specificity.

Other criteria sets — SLICC 2012 and ACR 1997

- ▶ **SLICC 2012:** classify as SLE if ≥ 4 of 17 criteria (11 clinical + 6 immunological) are met, with at least one clinical AND one immunological criterion; OR biopsy-proven lupus nephritis in the presence of ANA or anti-dsDNA. SLICC improved sensitivity over the older ACR set and formally recognised biopsy-proven nephritis as a stand-alone pathway.
- ▶ **ACR 1997 (revised) criteria:** historically, ≥ 4 of 11 criteria (present serially or simultaneously) classify SLE. The 11 items (mnemonic SOAP BRAIN MD): Serositis, Oral ulcers, Arthritis,

Photosensitivity, Blood disorder (cytopenias), Renal disorder, ANA, Immunologic (anti-dsDNA/anti-Sm/antiphospholipid), Neurologic, Malar rash, Discoid rash.

Autoantibody profile supporting the diagnosis

The immunologic, renal and haematologic domains form the laboratory backbone. After a positive ANA, test anti-dsDNA and anti-Sm; if ANA-negative but the picture is highly suggestive, anti-Ro (SS-A) confers a high likelihood of SLE.

Antibody	Prevalence	Diagnostic value / association
ANA	~95%	Best screening test; sensitive, not specific; $\geq 1:80$ positive
Anti-dsDNA	~70%	Higher titres specific for SLE; correlate with activity and nephritis
Anti-Sm	~30%	Most specific autoantibody for SLE
Anti-RNP / U1-RNP	~25% / ~13%	Overlap syndromes; pulmonary hypertension; high IFN signature
Anti-Ro (SS-A)	~30%	Often positive in ANA-negative SLE; sicca, neonatal lupus, congenital heart block, SCLE
Anti-La (SS-B)	~20%	Associated with anti-Ro
Antiribosomal P	~15%	CNS lupus; specific but not sensitive
Antihistone	~70%	Drug-induced lupus
Antiphospholipid (aCL, anti- $\beta 2$ GP-1, lupus anticoagulant)	~50%	Arterial/venous thrombosis, pregnancy loss, thrombocytopenia, Libman-Sacks endocarditis

- ▶ **Low C3/C4** falls during high disease activity; **anti-dsDNA + low complement** indicates a propensity to lupus nephritis and is used to track activity.
- ▶ Baseline work-up: CBC (leukopenia, lymphopenia, thrombocytopenia, anaemia of chronic inflammation/haemolytic anaemia), eGFR, serum creatinine, and **urine protein-to-creatinine ratio (UPCr)**; **renal biopsy when UPCR exceeds 0.5** to exclude active nephritis. Lupus nephritis is graded by the **ISN/RPS classification** (Class I–VI; Class III focal proliferative, IV diffuse proliferative, V membranous).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Flow algorithm** — “EULAR/ACR 2019 classification”: box 1 **Entry criterion**: ANA $\geq 1:80$ → if negative → not classified; if positive → box 2 **Apply additive weighted criteria** (label the 7 clinical domains: Constitutional, Hematologic, Neuropsychiatric, Mucocutaneous, Serosal, Musculoskeletal, Renal; and 3 immunology domains: Antiphospholipid, Complement, SLE-specific antibodies) → box 3 **Score (count only highest item per domain; ≥ 1 clinical required)** → decision diamond **Total ≥ 10 points?** → Classify as SLE.
- ▶ **Labelled face/hand sketch**: malar (“butterfly”) rash with **nasolabial sparing**; discoid plaques; Jaccoud arthropathy of the hand — label *malar rash, nasolabial sparing, discoid lesion, photosensitive distribution, Jaccoud deformity*.

Clinical / Diagnostic significance

- ▶ Criteria provide a **structured checklist** that improves diagnostic consistency, but a patient may be unequivocally diagnosed clinically **without** meeting classification points (e.g., early or ANA-negative disease) — never withhold treatment because a patient is “one point short.”
- ▶ **Biopsy-proven Class III/IV lupus nephritis** is diagnostically decisive (10 points) and dictates aggressive immunosuppression; renal involvement (~35% of patients) drives prognosis.
- ▶ **Drug-induced lupus (DIL)** is a key differential: ~6–12% of lupus cases; classic triggers **procainamide** (highest risk, up to 30%) and **hydralazine** (first described, 1954), plus isoniazid, minocycline, anti-TNF agents, etc.; **antihistone antibodies** typical, dsDNA usually absent; rarely affects kidney/brain; resolves on stopping the drug.
- ▶ Differentiate from RA (overlap = *rhupus*), mixed connective tissue disease (anti-U1-RNP), Sjögren’s (anti-Ro/La), and primary antiphospholipid syndrome.

High-yield exam pointers

- ▶ Classification criteria = **for trials, not diagnosis**; diagnosis = clinical + lab + exclusion + judgement.
- ▶ **EULAR/ACR 2019**: mandatory entry ANA $\geq 1:80$, then **additive weights, ≥ 10 points** to classify.
- ▶ **No single item = 10 points except renal biopsy Class III/IV LN.**
- ▶ **Anti-dsDNA and anti-Sm are the only ANA subtypes in EULAR/ACR criteria**; anti-Sm = most specific; anti-dsDNA tracks activity/nephritis.
- ▶ **SLICC 2012**: ≥ 4 of 17 (≥ 1 clinical + ≥ 1 immunologic) **OR** biopsy-proven LN with ANA/anti-dsDNA.
- ▶ **ACR 1997**: ≥ 4 of 11 — mnemonic *SOAP BRAIN MD*.
- ▶ ~5% of SLE is **ANA-negative** (anti-Ro often positive) and is excluded by EULAR/ACR.
- ▶ **Low C3/C4 + rising anti-dsDNA** = flag for active disease/nephritis.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 368 "Systemic Lupus Erythematosus." Coverage note: the chapter explicitly supports the entry criterion (ANA $\geq 1:80$), the ≥ 10 -point threshold, the renal-biopsy Class III/IV = 10 points rule, the use of EULAR/ACR 2019 and SLICC 2012, autoantibody prevalences/associations (Table 368-2), and that anti-dsDNA/anti-Sm are the only included ANA subtypes. The detailed per-item point weights of the EULAR/ACR table, the full SLICC $\geq 4/17$ rule, and the ACR 1997 11-criteria list (SOAP BRAIN MD) are not enumerated in the provided chapter; they are added here as universally accepted, accurate standard rheumatology to satisfy the exam ask.



Diagnostic Criteria and Extra-Articular Manifestations of Rheumatoid Arthritis

Asked in: Paper III Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Rheumatoid arthritis (RA) is a chronic, systemic, immune-mediated inflammatory disease characterised by a **symmetric, erosive polyarthritis** of the small joints of the hands and feet, driven by synovial proliferation (pannus) that destroys cartilage and bone. Although joints dominate the picture, RA is a *systemic* disease: up to **40%** of patients develop extra-articular manifestations, sometimes preceding the arthritis. Anti-citrullinated protein antibodies (ACPA / anti-CCP) and rheumatoid factor (RF) are key diagnostic and prognostic biomarkers. Early, aggressive disease-modifying therapy before irreversible damage ensues is the modern standard of care.

Articular features that anchor the diagnosis

- ▶ **Inflammatory pattern:** early-morning stiffness lasting **>1 hour** easing with activity; insidious, symmetric, additive small-joint synovitis.
- ▶ **Joints involved:** wrists, **metacarpophalangeal (MCP)** and **proximal interphalangeal (PIP)** joints, and metatarsophalangeal (MTP) joints. DIP-sparing is typical (DIP disease usually = coexisting osteoarthritis). RA affects the **cervical spine** (atlantoaxial C1–C2) but spares the thoraco-lumbar spine and sacroiliac joints.
- ▶ **Deformities of established disease:** ulnar deviation (MCP subluxation), **swan-neck** (PIP hyperextension + DIP flexion), **boutonnière** (PIP flexion + DIP hyperextension), **Z-line thumb deformity**, *piano-key* sign of the distal ulna, and pes planovalgus.
- ▶ **Tenosynovitis:** flexor tendon involvement → trigger finger, reduced grip; rupture of the flexor pollicis longus.

Diagnostic criteria — 2010 ACR/EULAR classification

The 2010 American College of Rheumatology / European League Against Rheumatism (ACR/EULAR) criteria replaced the 1987 set to enable *earlier* diagnosis. They apply to a patient with ≥ 1 joint with definite clinical synovitis not better explained by another disease. Points are summed across four domains; a score of ≥ 6 of 10 = definite RA.

Domain	Item	Score
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF <i>and</i> negative ACPA	0
	Low-positive RF <i>or</i> low-positive anti-CCP ($\leq 3 \times$ ULN)	2
	High-positive RF <i>or</i> high-positive anti-CCP ($> 3 \times$ ULN)	3
Acute-phase reactants	Normal CRP <i>and</i> normal ESR	0
	Abnormal CRP <i>or</i> abnormal ESR	1
Duration of symptoms	<6 weeks	0
	≥ 6 weeks	1

- **Key changes from 1987:** symptom duration > 6 weeks is no longer mandatory; ACPA (specificity $\approx 95\%$) is incorporated for the first time; nodules and radiographic erosions were dropped as they are rare in *early* RA.
- **Important caveat:** these are **classification** (not diagnostic) criteria — designed to identify early patients likely to progress to persistent, erosive disease for trials and early therapy. In established disease, radiographic erosions or subcutaneous nodules can also clinch the clinical diagnosis.
- (Historical 1987 ACR criteria — universally taught: ≥ 4 of 7 — morning stiffness ≥ 1 h, arthritis of ≥ 3 joint areas, arthritis of hand joints, symmetric arthritis, rheumatoid nodules, serum RF, radiographic changes; criteria 1–4 present for ≥ 6 weeks.)

Laboratory and imaging support for diagnosis

- **Rheumatoid factor (RF):** IgM RF positive in $\sim 75\%$; sensitive but *not* specific — also seen in Sjögren's, SLE, type II cryoglobulinaemia, SBE, hepatitis B/C, and 1–5% of healthy people; sensitivity only $\sim 50\%$ in *early* disease.

- ▶ **Anti-CCP / ACPA:** similar sensitivity to RF but **specificity ≈95%**; best predictor of erosive disease and worse outcome; testing **both** RF and anti-CCP adds incremental value. About three-fourths of RA is seropositive; one-fourth seronegative.
- ▶ **Other antibodies:** ANA positive in ~30%; p-ANCA may be present, but **anti-MPO / anti-PR3 are negative** (distinguishes from ANCA-associated vasculitis).
- ▶ **Acute-phase reactants:** ESR and CRP elevated in proportion to disease activity; normochromic-normocytic anaemia of chronic disease.
- ▶ **Synovial fluid:** inflammatory, WBC 5000–50,000/μL (neutrophil-predominant); analysis chiefly excludes septic and crystal arthritis.
- ▶ **Imaging:** plain x-ray shows **periarticular osteopenia** (earliest), symmetric joint-space narrowing, juxta-articular/marginal **erosions** (fifth MTP and ulnar styloid first). **MRI and power-Doppler ultrasound** are more sensitive, detecting synovitis, tenosynovitis, effusions, and **bone-marrow oedema** (predicts future erosions).

Extra-articular manifestations (systemic RA)

Extra-articular disease clusters in patients who are RF/ACPA-positive, smokers, shared-epitope carriers, and have high disease activity.

System	Manifestations
Constitutional	Fatigue, weight loss, low-grade fever, malaise, depression, cachexia (fever >38.3 °C suggests vasculitis/infection)
Skin / subcutaneous	Rheumatoid nodules (firm, non-tender, over pressure points — forearm, Achilles, sacrum), purpura, pyoderma gangrenosum , digital infarcts
Ocular	Keratoconjunctivitis sicca, episcleritis , scleritis , scleromalacia perforans, peripheral ulcerative keratitis
Oral / glandular	Secondary Sjögren's syndrome (~10%): xerostomia, xerophthalmia; periodontitis
Pulmonary	Pleuritis/exudative pleural effusion (commonest); interstitial lung disease (UIP & NSIP patterns; prevalence up to ~12%); pulmonary nodules; Caplan's syndrome (nodulosis + pneumoconiosis after silica exposure); bronchiectasis
Cardiac	Pericarditis (commonest; symptomatic in <10%, subclinical in ~half), myocarditis, cardiomyopathy, accelerated ischaemic heart disease , arrhythmia, valve disease

System	Manifestations
Vascular	Rheumatoid vasculitis (<1%, long-standing seropositive disease, hypocomplementaemia): nail-fold infarcts, leg ulcers, digital gangrene, mononeuritis multiplex
Neurologic	Cervical (atlantoaxial) myelopathy from C1–C2 subluxation; entrapment (carpal tunnel); sensorimotor neuropathy
Haematologic	Anaemia of chronic disease, thrombocytosis (acute-phase), Felty's syndrome , T-cell large granular lymphocyte (T-LGL) leukaemia, 2–4× increased lymphoma risk (diffuse large B-cell type)
Renal	Membranous nephropathy, secondary (AA) amyloidosis
Skeletal / endocrine	Osteoporosis ($\approx 2\times$ risk; fragility fractures), hypoandrogenism

- ▶ **Subcutaneous nodules** are the prototypic extra-articular lesion (reported in ~20–40%), strongly correlate with RF seropositivity; may enlarge with long-term methotrexate.
- ▶ **Cardiovascular disease is the leading cause of death** in RA, with coronary and carotid atherosclerosis exceeding that predicted by traditional risk factors — driven by systemic inflammation; overall **mortality is $\sim 2\times$ the general population**.

Felty's syndrome and related associations

- ▶ **Felty's syndrome** = clinical triad of **neutropenia + splenomegaly + nodular (severe, seropositive) RA**; <1% of patients, late in disease; declining with aggressive therapy. Must be distinguished from T-LGL leukaemia, which shares neutropenia/splenomegaly but may appear *early*.
- ▶ **Lymphoma**: risk rises with high disease activity and Felty's syndrome.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — RA hand deformities**: outline of a hand labelling MCP swelling with ulnar deviation, swan-neck deformity (PIP hyperextension + DIP flexion), **boutonnière deformity** (PIP flexion + DIP hyperextension), **Z-thumb deformity**, wrist/ulnar-styloid subluxation (piano-key), and DIP-sparing.
- ▶ **Diagram 2 — Whole-body extra-articular map**: a body figure with labelled pointers — **Eye** (keratoconjunctivitis sicca, episcleritis, scleritis); **Lung** (pleural effusion, ILD–UIP/NSIP, pulmonary nodules, Caplan's); **Heart** (pericarditis, IHD, myocarditis); **Neuro** (cervical myelopathy, mononeuritis multiplex); **Haematologic** (anaemia, Felty's,

lymphoma); **Skin** (nodules, vasculitis, pyoderma gangrenosum); **Renal** (amyloidosis, membranous nephropathy); **Skeletal** (osteoporosis).

Clinical / Diagnostic significance

- ▶ A score $\geq 6/10$ on ACR/EULAR criteria in a patient with synovitis warrants **early DMARD therapy** — *treat-to-target* aiming for low disease activity/remission (assessed by DAS28, CDAI, SDAI, RAPID3).
- ▶ **Anti-CCP** is the most useful single test to distinguish RA from RF-positive mimics (hepatitis C arthropathy, Sjögren's, SLE) and predicts erosive, extra-articular disease.
- ▶ Atlantoaxial subluxation mandates **cervical-spine assessment before intubation/surgery** — risk of compressive myelopathy.
- ▶ Any RA patient with **one joint inflamed out of proportion** to the rest needs arthrocentesis to exclude **septic arthritis**.
- ▶ Management: **methotrexate** is the anchor DMARD (with folate); add sulfasalazine/hydroxychloroquine (*triple therapy*) or biologics (TNF inhibitors, **abatacept**, **rituximab**, **tocilizumab/sarilumab**) or **JAK inhibitors** (tofacitinib, baricitinib, upadacitinib). Screen for **latent TB and hepatitis B/C** before biologics/JAK inhibitors. High-dose steroids are reserved for severe extra-articular disease (ILD, necrotising scleritis, vasculitis).

High-yield exam pointers

- ▶ **2010 ACR/EULAR score $\geq 6/10$ = definite RA**; four domains — joints, serology, acute-phase reactants, duration.
- ▶ **Anti-CCP specificity $\approx 95\%$** , RF sensitivity $\approx 75\%$ but poorly specific; both positive = worse prognosis.
- ▶ These are **classification, not diagnostic, criteria** — designed for early disease.
- ▶ Commonest extra-articular lesion = **subcutaneous nodule**; commonest pulmonary lesion = **pleuritis/effusion** (exudative).
- ▶ **Felty's triad** = neutropenia + splenomegaly + nodular RA ($<1\%$).
- ▶ **Caplan's syndrome** = rheumatoid pulmonary nodules + pneumoconiosis (silica/coal).
- ▶ **Cervical myelopathy** from atlantoaxial subluxation; thoraco-lumbar spine spared.
- ▶ **Cardiovascular disease = commonest cause of death**; overall mortality $\sim 2\times$.
- ▶ RA carries a **2–4 $\times$ increased risk of lymphoma** (diffuse large B-cell).
- ▶ ANCA may be positive but **anti-MPO/anti-PR3 negative**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e — "Rheumatoid Arthritis"** (ACR/EULAR 2010 classification criteria [Table 370-1], extra-articular manifestations [Fig. 370-2], laboratory/imaging features, Felty's syndrome, prognosis).
- ▶ **CMDT 2026 — "Rheumatoid Arthritis" (Rheumatologic, Immunologic & Allergic Disorders)** for the classification-criteria reproduction (Table 23-5), current treat-to-target management, DMARD/biologic/JAK-inhibitor regimens, and pre-biologic screening.
- ▶ *Coverage note:* The 1987 ACR seven-item criteria are not enumerated in the corpus (Harrison cites only that the 1987 set was "revised"); they are included as universally accepted standard internal-medicine knowledge and clearly labelled as historical.



Discuss the risk factors for disease flares in patients with SLE, how do you classify severity of flare

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease driven by autoantibodies and immune-complex deposition, with a characteristically **relapsing–remitting course** — roughly 70% of patients follow a pattern of flares and remissions. A **flare** is a measurable increase in disease activity (clinical and/or serological) above the patient's prior stable state that warrants escalation or intensification of therapy. Recognising the triggers of a flare allows preventive counselling, while grading flare severity is the central decision node that dictates whether treatment is purely symptomatic, intensified with steroid-sparing immunosuppression, or escalated to high-dose/pulse glucocorticoids and aggressive immunosuppression.

What constitutes a "flare"

- ▶ An *increase* in disease activity over baseline — new organ involvement or worsening of existing involvement — sufficient to require a change in treatment, distinct from chronic irreversible **damage** (which does not respond to immunosuppression).
- ▶ Flares may be **clinical** (e.g., arthritis, rash, serositis, nephritis, cytopenia, neuropsychiatric) and/or **serological** (rising anti-dsDNA titre, falling C3/C4).
- ▶ Most SLE patients have active disease despite therapy or have frequent flares requiring treatment adjustment; the treatment goal is remission or a low disease-activity state on the least possible therapy.

Risk factors / triggers for disease flares

Grouped by mechanism (all faithful to the source corpus unless flagged):

Category	Specific risk factors
Environmental / physical	Ultraviolet (UV) light / sun exposure — induces apoptosis, self-stimulatory nucleic acids, keratinocyte activation and DNA-methylation change (photosensitive patients flare rapidly after first major UV exposure); crystalline silica ; toxins (mercury, diet)
Infections	Viral infection, especially Epstein–Barr virus (EBV) , induces the type-1 interferon response and can precipitate activity
Hormonal / reproductive	Pregnancy and the postpartum period — disease can flare in any trimester; oestrogen-containing contraceptives/HRT are avoided in active or moderate–severe SLE (thrombosis and flare risk); active disease at conception predicts more flares
Drug / treatment-related	Non-adherence to therapy; discontinuation of hydroxychloroquine (HCQ) ; too-rapid glucocorticoid tapering/withdrawal; drug-induced lupus activity from offending agents
Lifestyle	Cigarette smoking — causes autoantigen release, worsens disease and interferes with antimalarial efficacy
Serological / disease-intrinsic	Rising anti-dsDNA titres and falling C3/C4 complement herald impending activity, especially nephritis; high prior disease activity; persistently active disease despite therapy
Host factors	Non-White ethnicity and low socioeconomic status (worse/more severe disease and poorer access to care)

Key prevention pearls embedded in the corpus: **HCQ prevents flares**, prolongs survival and reduces flares during pregnancy and postpartum — hence it is recommended for *all* patients unless contraindicated; daily sunscreen, smoking cessation and adherence are foundational.

Serological predictors of an impending flare

- ▶ Anti-dsDNA antibodies are produced by short-lived plasmablasts and track disease activity; a rising titre signals reactivation.
- ▶ **C3 and C4** fall during high activity (consumed by immune-complex formation); the **anti-dsDNA↑ / complement↓** combination specifically predicts active lupus **nephritis**.
- ▶ Quarterly monitoring of UPCr/eGFR, CBC and complement/anti-dsDNA is advised because renal and haematological flares can be clinically *silent*.

- ▶ Caveat (well recognised): a subset of patients have persistently high anti-dsDNA and low complement without clinical flare (“serologically active, clinically quiescent”) — treat the patient, not the number alone.

Classification of flare / disease-activity severity

Severity is graded both by **validated composite indices** (for trials and longitudinal monitoring) and by a practical **categorical mild/moderate/severe** scheme that drives therapy.

A. Validated disease-activity instruments

- ▶ **SLEDAI / SLEDAI-2K** (SLE Disease Activity Index) — weighted score summing active manifestations across organ systems; underpins treat-to-target targets (LLDAS, DORIS remission).
- ▶ **BILAG** (British Isles Lupus Assessment Group) — an organ-by-organ “physician’s intention-to-treat” categorical index grading each system: **A = severe** activity (needs high-dose steroids/immunosuppression), **B = moderate**, **C = mild/stable**, **D = previously involved, now inactive**, **E = never involved**.
- ▶ **SELENA–SLEDAI Flare Index (SFI)** — purpose-built flare instrument that categorises flares as **mild/moderate vs severe** using the change in SLEDAI plus clinical descriptors and the Physician Global Assessment (see Coverage note).
- ▶ Composite trial endpoints derived from these: **SRI** (SLE Responder Index) and **BICLA** (BILAG-based Composite Lupus Assessment); **CLASI** for cutaneous activity; **SLICC/ACR Damage Index** measures accrued damage (not activity).

B. EULAR categorical severity (the bedside, therapy-driving classification)

Severity	Defining features	SLEDAI	BILAG	Typical first-line therapy
Mild	Constitutional symptoms; mild arthritis; rash $\leq 9\%$ BSA; platelets $50\text{--}100 \times 10^9/\text{L}$	≤ 6	BILAG C or ≤ 1 BILAG B	HCQ $\pm$ short low-dose glucocorticoid; NSAIDs; topicals
Moderate	Moderate–severe (“RA-like”) arthritis; rash $9\text{--}18\%$ BSA; platelets $20\text{--}50 \times 10^9/\text{L}$; serositis	$7\text{--}12$	≥ 2 BILAG B	HCQ + GC + steroid-sparing agent (MTX/AZA/MMF); belimumab/anifrolumab add-on
Severe	Major organ-threatening disease (cerebritis, myelitis,	>12	≥ 1 BILAG A	Pulse/high-dose GC (IV methylprednisolone $125\text{--}1000\text{ mg/day} \times 1\text{--}3\text{ d}$) + MMF or

Severity	Defining features	SLEDAI	BILAG	Typical first-line therapy
	pneumonitis, mesenteric vasculitis); platelets $<20 \times 10^9/L$; TTP-like / acute haemophagocytic syndrome; rash $>18\%$ BSA			cyclophosphamide $\pm$ rituximab

C. Treat-to-target reference states (the “no-flare” goals against which a flare is judged):

- ▶ **Low disease-activity state (LLDAS):** clinical SLEDAI ≤ 4 , on HCQ, stable immunosuppressive/biologic, with prednisone ≤ 5 mg/day.
- ▶ **DORIS remission:** clinical SLEDAI = 0, with prednisone ≤ 5 mg/day and stable maintenance therapy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Flare risk-factor wheel:** central hub “SLE FLARE” with labelled spokes — *UV light/sun, EBV/infection, Pregnancy & postpartum, Non-adherence / HCQ withdrawal, Rapid steroid taper, Smoking, Oestrogen (OCP/HRT), Rising anti-dsDNA / falling C3–C4*. Annotate “HCQ + sunscreen + adherence = flare prevention”.
- ▶ **Severity ladder (3-tier bar):** three ascending blocks labelled **MILD** (SLEDAI ≤ 6 / BILAG C), **MODERATE** (SLEDAI 7–12 / ≥ 2 BILAG B), **SEVERE** (SLEDAI >12 / ≥ 1 BILAG A); side-label the matching platelet count, %BSA rash and first-line drug for each tier; add a baseline line for “LLDAS / DORIS remission”.

Clinical / Diagnostic significance

- ▶ **Distinguish flare from infection:** in active SLE the ESR rises but CRP is usually normal — a high CRP without serositis/arthritis should raise suspicion of **infection** (a major mimic in an immunosuppressed patient).
- ▶ **Distinguish flare from damage:** activity is reversible with immunosuppression; damage (e.g., glucocorticoid-induced cataract, avascular necrosis, ESRD) is not — escalating immunosuppression for damage only adds toxicity.
- ▶ **Renal flare** is often silent: a UPCr rising above 0.5 and/or falling eGFR with active sediment (haematuria, cellular casts) should prompt renal biopsy; class III/IV ($\pm V$) nephritis needs aggressive therapy.

- ▶ **Pregnancy planning:** conceive when disease is quiescent for ≥ 6 months, continue **HCQ**, use AZA/tacrolimus if immunosuppression is needed, and avoid MMF, methotrexate, cyclophosphamide and warfarin.
- ▶ **Severity grade determines therapy intensity:** mild $\rightarrow$ HCQ $\pm$ brief low-dose steroid; moderate $\rightarrow$ add a steroid-sparing agent $\pm$ biologic; severe/organ-threatening $\rightarrow$ pulse methylprednisolone plus MMF/cyclophosphamide $\pm$ rituximab, with the steroid tapered to ≤ 5 mg/day as fast as feasible.

High-yield exam pointers

- ▶ SLE is **relapsing–remitting** in $\sim 70\%$; a flare = increase in activity requiring treatment change, *not* fixed damage.
- ▶ **Top modifiable flare triggers:** UV light, infection (EBV), pregnancy/postpartum, **HCQ discontinuation / non-adherence**, smoking, oestrogens, rapid steroid taper.
- ▶ **HCQ prevents flares**, improves survival and is recommended for *all* SLE patients (≤ 5 mg/kg/day; annual retinal screening).
- ▶ **Anti-dsDNA $\uparrow$ + C3/C4 $\downarrow$** predicts a flare, especially **nephritis**.
- ▶ Severity is graded by **SLEDAI** (≤ 6 mild, 7–12 moderate, >12 severe) and **BILAG** (A severe, B moderate, C mild, D inactive, E never involved).
- ▶ **SELENA–SLEDAI Flare Index** grades flares as mild/moderate vs severe; **SRI/BICLA** are composite trial endpoints; **SLICC/ACR Damage Index** measures damage, not activity.
- ▶ **Severe flare = organ-threatening** (CNS, renal, pulmonary, mesenteric vasculitis, platelets $<20 \times 10^9/L$) $\rightarrow$ IV methylprednisolone pulse + MMF/cyclophosphamide $\pm$ rituximab.
- ▶ **Treat-to-target:** aim for **LLDAS** (SLEDAI ≤ 4 , prednisone ≤ 5 mg/day) or **DORIS remission** (SLEDAI 0).
- ▶ **CRP normal in pure lupus flare** — a raised CRP points to infection or serositis.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Systemic Lupus Erythematosus” (risk factors/environmental triggers, anti-dsDNA/complement monitoring, EULAR mild/moderate/severe activity figure, SLEDAI/BILAG/SRI/BICLA, LLDAS/DORIS targets, pregnancy and flare prevention with HCQ); “Antiphospholipid Syndrome” (flare-related triggers of catastrophic APS).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic, & Allergic Disorders: Systemic Lupus Erythematosus” (waxing–waning course, severity-matched therapy, CRP-vs-infection pearl, HCQ flare prevention, glucocorticoid dosing for mild vs severe disease).
- ▶ **Rook's Textbook of Dermatology, 10e** — “Lupus Erythematosus and Antiphospholipid Syndrome” (relapsing–remitting epidemiology, disease-activity indices)

SELENA/SLEDAI/SLEDAI-2K/BILAG/CLASI, UV- and smoking-induced flares, anti-dsDNA/complement as predictors).

Coverage note: The corpus names and uses the SLEDAI, BILAG, SELENA, SRI, BICLA, CLASI and SLICC/ACR indices and provides the EULAR categorical mild/moderate/severe activity cut-offs (used as the main severity table here), but it does **not** spell out the numeric thresholds of the *SELENA-SLEDAI Flare Index* (e.g., SLEDAI change >3 for mild/moderate vs >12 for a severe flare, with Physician Global Assessment descriptors) or the full BILAG-2004 organ glossary. The SFI mild/moderate-vs-severe framing and the BILAG A–E category meanings given above are standard, universally accepted rheumatology, included for completeness and flagged here as not detailed verbatim in the available chapters.



Disease-Modifying Antirheumatic Drugs

Asked in: Paper III Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Disease-modifying antirheumatic drugs (DMARDs) are agents that, unlike pure analgesics or NSAIDs, **slow or arrest the structural (radiographic) progression** of inflammatory arthritis in addition to relieving symptoms. They are the cornerstone of management of **rheumatoid arthritis (RA)** and are also used in other immune-mediated arthritides (psoriatic arthritis, SLE, vasculitis). They are conventionally divided into **conventional synthetic (csDMARDs)**, **biologic (bDMARDs)** and **targeted synthetic (tsDMARDs)** classes. They share a characteristically **delayed onset of action** (≈ 6 –12 weeks for csDMARDs) and require structured laboratory monitoring for toxicity.

Classification of DMARDs

Class	Sub-group	Representative agents
Conventional synthetic (csDMARD)	—	Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine
Biologic (bDMARD)	TNF- α inhibitors	Infliximab, Etanercept, Adalimumab, Golimumab, Certolizumab pegol
	IL-6 receptor blockers	Tocilizumab, Sarilumab
	IL-1 receptor antagonist	Anakinra
	T-cell co-stimulation blocker	Abatacept (CTLA-4-Ig)
	Anti-CD20 (B-cell depletion)	Rituximab

Class	Sub-group	Representative agents
Targeted synthetic (tsDMARD)	JAK inhibitors	Tofacitinib, Baricitinib, Upadacitinib

- ▶ **Biosimilars** — agents engineered to have the same active properties as a licensed reference biologic, with similar efficacy and toxicity (available for infliximab, etanercept, adalimumab); they reduce cost.
- ▶ *Methotrexate* is the **DMARD of first choice** and the “**anchor drug**” for most combination regimens.
- ▶ *Hydroxychloroquine*, although DMARD-like, has **not** been shown to delay radiographic progression and so is **not strictly a true DMARD**; it is used for early/mild disease or as an adjunct.

Conventional synthetic DMARDs (csDMARDs)

- ▶ **Methotrexate (MTX)** — a **folate antagonist (dihydrofolate reductase inhibitor)**; at the low *weekly* doses used in RA its anti-inflammatory action is mediated chiefly by **promoting adenosine release**. Onset 4–6 weeks; about one-third of patients reach low disease activity on monotherapy. Given **10–25 mg once weekly orally or subcutaneously** (CMDT: start 7.5–15 mg/week, titrate to a maximal oral dose of ~20 mg/week). **Folic acid 1 mg/day** (or weekly leucovorin) is co-prescribed to reduce stomatitis, cytopenias, GI and hepatic toxicity. SQ route is used when oral is poorly tolerated or absorption is limiting.
- ▶ **Leflunomide** — inhibits **dihydro-orotate dehydrogenase**, blocking *de novo* pyrimidine synthesis; efficacy similar to MTX as monotherapy or in combination. Dose **10–20 mg/day** orally. Very long half-life with active metabolite detectable for up to ~2 years (cholestyramine washout if rapid elimination needed, e.g., pregnancy planning).
- ▶ **Sulfasalazine** — reduces joint inflammation and **retards radiographic progression** (RCT-proven). Start **500 mg twice daily**, maintenance **1000–1500 mg twice daily**. Check G6PD before starting (haemolysis risk).
- ▶ **Hydroxychloroquine** — antimalarial, **not immunosuppressive**, low toxicity; **200–400 mg/day** (≤ 5 mg/kg) to limit retinal toxicity. Mainly used within “**oral triple therapy**” (MTX + sulfasalazine + hydroxychloroquine).

Biologic DMARDs (bDMARDs)

Biologics are **protein therapeutics** targeting cytokines or cell-surface molecules; the **TNF inhibitors** (first approved 1999) revolutionised RA care. Most are used **in combination with background methotrexate**, typically after an inadequate response to MTX.

Target / mechanism	Agent	Dosing (representative)
TNF- α — chimeric mAb	Infliximab	3 mg/kg IV at wk 0, 2, 6, then every 8 wk (up to 10 mg/kg q4wk)
TNF- α — soluble TNF-R2-Fc fusion	Etanercept	50 mg SQ weekly
TNF- α — humanized mAb	Adalimumab	40 mg SQ every other week
TNF- α — humanized mAb	Golimumab	50 mg SQ monthly
TNF- α — pegylated Fab' fragment	Certolizumab pegol	400 mg SQ wk 0, 2, 4 $\rightarrow$ 200 mg every other week
IL-6 receptor mAb	Tocilizumab / Sarilumab	Tocilizumab 4–8 mg/kg IV monthly <i>or</i> 162 mg SQ; Sarilumab 200 mg SQ every other week
IL-1 receptor antagonist	Anakinra	100 mg SQ daily (limited use; lower efficacy)
T-cell co-stimulation (CTLA-4-Ig blocks CD28–CD80/86)	Abatacept	Weight-based IV q4wk <i>or</i> 125 mg SQ weekly
CD20 B-cell depletion	Rituximab	1000 mg IV $\times$ 2 (days 0 and 14); repeat $\sim$ q24 weeks

- ▶ **TNF inhibitors** reduce signs/symptoms, **slow radiographic damage**, and improve function/quality of life.
- ▶ **Abatacept** blocks the CD28–CD80/86 co-stimulatory signal to T cells.
- ▶ **Rituximab** (anti-CD20) is approved for **refractory RA** (TNF-inhibitor failure) with MTX; **more effective in seropositive disease**. Rare risk of **progressive multifocal leukoencephalopathy (PML)** ($\sim$ 1:25,000) and blunting of vaccine response.
- ▶ **IL-6R blockers** are effective as monotherapy or with MTX; raise **LDL cholesterol** and carry a risk of **GI perforation** (avoid in diverticulitis/recent peptic ulcer).
- ▶ **Biologics should not be combined with one another** (additive infection risk without added benefit).

Targeted synthetic DMARDs — JAK inhibitors

- ▶ **Mechanism** — small oral molecules inhibiting Janus kinases (JAK1, JAK2, JAK3, Tyk2), which transduce intracellular signals from cytokine receptors (common γ -chain cytokines IL-2/-4/-7/-9/-15/-21, IFN- γ , IL-6, IL-12/-23) via the JAK–STAT pathway.
 - *Tofacitinib* — JAK1/JAK3 inhibitor; **5 mg twice daily** (or 11 mg XR daily).
 - *Baricitinib* — JAK1/JAK2 inhibitor; **2 mg daily**.

- *Upadacitinib* — selective JAK1 inhibitor; **15 mg daily**.
- ▶ Advantage: **oral** route; used as monotherapy or with MTX.
- ▶ **Safety signal** — an FDA **black-box warning** (from an RCT vs TNF inhibitors in MTX-treated patients) of increased **serious infection, herpes zoster, thrombosis/VTE, major adverse cardiovascular events (MACE), malignancy and death**, greatest in the **elderly**.

Adverse effects, screening and monitoring

Drug	Serious toxicity	Baseline screen	Monitoring
Methotrexate	Hepatotoxicity, myelosuppression, interstitial pneumonitis; teratogenic (Pregnancy category X)	CBC, LFTs, viral hepatitis panel, CXR	CBC, creatinine, LFTs every 2–3 months
Leflunomide	Hepatotoxicity, myelosuppression; teratogenic	CBC, LFTs, viral hepatitis panel	LFTs periodically
Sulfasalazine	Granulocytopenia, haemolysis (G6PD deficiency)	G6PD level , CBC, LFTs	CBC every 2–4 wk ×3 months, then q3 months
Hydroxychloroquine	Irreversible retinal damage , cardiotoxicity	Eye exam (esp. >40 y)	OCT + visual fields every 12 months
TNF inhibitors	Serious bacterial/fungal infection, reactivation of latent TB , demyelination, drug-induced lupus	TB screening (PPD or IGRA) , hepatitis panel	Monitor for infection/injection or infusion reactions
Rituximab	Infection, hepatitis B reactivation , PML, infusion reaction	Viral hepatitis panel, CBC	CBC at intervals
JAK inhibitors	Infection (zoster), thrombosis, MACE, malignancy, transaminitis, dyslipidaemia	TB screening, varicella vaccination	CBC, LFTs, lipids at intervals

- ▶ **Latent TB** must be screened (PPD/IGRA) before any biologic or JAK inhibitor; if positive, **treat LTBI for ≥1 month** before starting.
- ▶ TNF inhibitors are **contraindicated** in active infection, **chronic hepatitis B**, and NYHA class III/IV heart failure.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **DMARD molecular-target schematic of the rheumatoid synovium** — draw a synovial joint with infiltrating immune cells and arrows to each drug target. Labels: *TNF- α* (infliximab/etanercept/adalimumab/golimumab/certolizumab), *IL-6 / IL-6R* (tocilizumab/sarilumab), *IL-1 / IL-1Ra* (anakinra), *CD20 B cell* (rituximab), *T-cell co-stimulation CD28-CD80/86* (abatacept/CTLA-4-Ig), *intracellular JAK1/2/3-Tyk2* $\rightarrow$ *STAT* (tofacitinib/baricitinib/upadacitinib).
- ▶ **Treat-to-target algorithm** — flow boxes: *Early RA diagnosis* $\rightarrow$ *Methotrexate + folic acid (anchor)* $\pm$ *short glucocorticoid bridge* $\rightarrow$ *Reassess at 3–6 months (DAS28 / CDAI / SDAI)* $\rightarrow$ if target not met $\rightarrow$ *Triple csDMARD therapy or Add TNF inhibitor $\pm$ MTX or Non-TNF biologic $\pm$ MTX* $\rightarrow$ *Switch class / JAK inhibitor* $\rightarrow$ *Goal: low disease activity or remission.*

Clinical / Diagnostic significance

- ▶ **Treat-to-target (“T2T”)** — the guiding principle: aim for **low disease activity or clinical remission**, with **frequent reassessment** using composite indices (DAS28, SDAI, CDAI, RAPID3) and rapid step-up of therapy when targets are unmet. *ACR/EULAR provisional remission*: tender joints ≤ 1 , swollen joints ≤ 1 , CRP ≤ 1 mg/dL, patient global ≤ 1 — **or** SDAI ≤ 3.3 .
- ▶ **Sequencing** — begin with **methotrexate**; if inadequate at 3–6 months, escalate to a combination (**oral triple therapy** = MTX + sulfasalazine + hydroxychloroquine) **or** add a TNF / non-TNF biologic $\pm$ MTX. MTX + anti-TNF is superior to MTX alone for symptoms and for retarding structural damage. Triple therapy is **non-inferior to MTX + etanercept** and is economical.
- ▶ **Switching** — anti-TNF failure may respond to a **different mechanism** (abatacept, rituximab, IL-6R blocker, JAK inhibitor); evidence suggests switching to abatacept can beat a second anti-TNF.
- ▶ **Glucocorticoid bridging** — low–moderate dose prednisone (5–10 mg/day) gives rapid control until DMARDs act; chronic use is minimised (osteoporosis — consider bisphosphonate prophylaxis).
- ▶ **Pregnancy** — **methotrexate and leflunomide are contraindicated (teratogenic)**; **hydroxychloroquine and sulfasalazine are the safest**; anti-TNF agents are generally acceptable but usually stopped in the third trimester.
- ▶ **Comorbidity/mortality** — RA excess mortality is largely **cardiovascular**; controlling inflammation plus CV risk-factor management improves outcomes. In resource-limited settings, **TB and viral hepatitis reactivation** drive screening practice.

High-yield exam pointers

- ▶ DMARD = drug that **slows radiographic progression**, not just symptoms; csDMARDs act in 6–12 weeks.
- ▶ **Methotrexate = anchor/first-choice DMARD**; weekly dosing + **folic acid**; key toxicities = hepatotoxicity, cytopenias, **pneumonitis**, teratogenicity.

- ▶ **Hydroxychloroquine is not a true DMARD** (no radiographic benefit); main risk = **retinal toxicity** → annual OCT/visual fields, dose ≤ 5 mg/kg.
- ▶ **Oral triple therapy** = MTX + sulfasalazine + hydroxychloroquine.
- ▶ **Five TNF inhibitors**: infliximab, etanercept, adalimumab, golimumab, certolizumab; screen **latent TB** first; avoid in chronic HBV and **class III/IV heart failure**.
- ▶ **Abatacept** = CTLA-4-Ig (T-cell co-stimulation block); **Rituximab** = anti-CD20 (better in **seropositive RA**, risk of HBV reactivation/PML); **Tocilizumab/Sarilumab** = IL-6R (raise LDL, GI perforation).
- ▶ **JAK inhibitors** (tofacitinib, baricitinib, upadacitinib) are **oral tsDMARDs**; **black-box warning** for thrombosis, MACE, malignancy, infection.
- ▶ **Do not combine two biologics**; remission target = **SDAI ≤ 3.3** .

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Rheumatoid Arthritis” (Treatment section; Table 370-2 *DMARDs Used for the Treatment of Rheumatoid Arthritis*; Table 370-3 *ACR/EULAR Provisional Definition of Remission*).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic, & Allergic Disorders” (Rheumatoid Arthritis — synthetic and biologic DMARD dosing, monitoring, combination/triple therapy).
- ▶ Mechanistic notes for methotrexate (dihydrofolate reductase inhibition) and leflunomide (dihydro-orotate dehydrogenase inhibition) and the csDMARD/bDMARD/tsDMARD classification are universally accepted standard internal medicine, consistent with the cited chapters.



Drug-Induced Lupus

Asked in: Paper III Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Drug-induced lupus (DIL)* is an autoimmune phenomenon in which a positive antinuclear antibody (ANA) and clinical features resembling systemic lupus erythematosus (SLE) arise as a consequence of continuous exposure to a particular drug, and characteristically resolve after the offending agent is withdrawn. It accounts for roughly **6–12% of all lupus cases**. Compared with idiopathic SLE it is generally milder, *rarely involves the kidney or brain*, lacks the strong female predominance, and is serologically dominated by **antihistone antibodies**. Recognising DIL is important because it is largely reversible — the single most effective “treatment” is to stop the culprit drug.

Epidemiology and offending drugs

- ▶ DIL was first described with **hydralazine** in 1954; since then **more than 100 drugs** have been implicated as potential triggers.
- ▶ The **highest incidence is with the antiarrhythmic procainamide**, where the risk has been reported to be as high as ~30%. With **hydralazine taken for a year or longer the incidence is ~5–8%**; for most other implicated drugs the risk is considerably **lower than 1%**.
- ▶ DIL has a **nearly equal sex ratio** (unlike the strong female predominance of SLE), and typically affects an **older age group**, reflecting the age at which the culprit cardiovascular/anti-infective drugs are prescribed.
- ▶ *Drugs with definite associations: hydralazine, procainamide, isoniazid, minocycline*, with methyl dopa and chlorpromazine less commonly.

Risk / drug class	Representative agents
High risk	Procainamide (~30%), hydralazine (~5–8% if ≥1 yr)
Antiarrhythmics / antihypertensives	Procainamide, quinidine, hydralazine, methyl dopa, ACE inhibitors, beta-blockers, hydrochlorothiazide
Anti-infectives	Isoniazid, minocycline, rifampin, nitrofurantoin
Anticonvulsants	Phenytoin, carbamazepine
Antithyroid	Propylthiouracil
Psychotropics	Chlorpromazine, lithium
Others	Sulfasalazine, proton-pump inhibitors, NSAIDs, oral contraceptives
Biologics	Anti-TNF- α agents (especially infliximab , etanercept), interferon- α

- ▶ **Drug-induced subacute cutaneous lupus erythematosus (SCLE)** is a related but distinct entity — *more than one-third* of SCLE is drug-induced; **hydrochlorothiazide** is a classic cause, with terbinafine, PPIs, calcium-channel blockers, ACE inhibitors and TNF inhibitors also implicated.

Pathogenesis

- ▶ Drug exposure provokes a **loss of self-tolerance**, generating ANA and SLE-like clinical features; in many cases simple **discontinuation of the drug is sufficient** for symptoms to abate.
- ▶ **Pharmacogenetic susceptibility** — the **slow-acetylator phenotype**: hydralazine, procainamide and isoniazid are metabolised by hepatic N-acetyltransferase 2 (NAT2). *Slow acetylators* accumulate the parent drug and develop DIL **earlier, more frequently and at lower cumulative doses** than fast acetylators (universally accepted internal-medicine teaching).
- ▶ Proposed mechanisms include drug-induced **disruption of central tolerance**, **impaired DNA methylation in T cells**, and **oxidative/reactive-metabolite modification of self chromatin** (the

histone–DNA complex), exposing cryptic antigens — explaining the dominance of **antihistone antibodies**.

- ▶ **Biologic-induced lupus** (anti-TNF, IFN- α) is mechanistically distinct: TNF inhibitors can induce **antibodies to dsDNA but usually not antihistone antibodies**, and clinically produce a lupus-like syndrome in only ~0.5–1%.

Clinical features

- ▶ Typically an **abrupt onset weeks to several months after starting the drug**, with constitutional and musculoskeletal/serosal symptoms predominating:
 - **Fever, arthralgia and myalgia, arthritis**
 - **Serositis** — pleuritis (pleuritic chest pain, effusion) and pericarditis
 - **Cutaneous rash** (including photosensitive eruptions; drug-induced SCLE as a variant)
- ▶ **Severe organ involvement is characteristically absent** — *renal* (nephritis) and *CNS/neuropsychiatric* disease are rare, distinguishing DIL from SLE.
- ▶ **Cytopenias** may occur but are typically **mild**.
- ▶ Symptoms **resolve within several weeks to a few months of stopping the offending agent**.

Feature	Drug-induced lupus	Idiopathic SLE
Sex ratio	Nearly equal	Strong female predominance
Typical age	Older (drug-exposed)	Younger (15–45 yr)
Renal / CNS disease	Rare	Common, prognosis-defining
Severity	Generally milder	Variable, can be severe
ANA	Positive (often before symptoms)	Positive ($\geq 95\%$)
ANA pattern	Usually homogeneous	Variable (often speckled/homogeneous)
Antihistone Ab	Positive in ~75–95%	~70% (not specific)
Anti-dsDNA / anti-Sm	Usually absent (dsDNA may occur with anti-TNF)	dsDNA & Sm characteristic
Complement (C3/C4)	Usually normal	Often low in active disease
Course on drug withdrawal	Resolves	Persists (chronic)

Investigations and serology

- ▶ ANA is **positive in essentially all symptomatic patients**, characteristically in a **homogeneous** pattern, and the ANA frequently **appears before symptoms**.

- ▶ **Antihistone antibodies** are the serologic hallmark — present in ~75% (Harrison) up to ~95% (CMDT) of DIL. *Important caveat:* antihistone antibodies are also seen in the majority of idiopathic SLE, so by themselves they **do not distinguish** DIL from SLE.
- ▶ **Antibodies to dsDNA, Sm, RNP, SS-A (Ro) and SS-B (La)** are characteristically rare in DIL — their presence should raise suspicion for true SLE. *Exception:* **TNF inhibitors can induce anti-dsDNA antibodies.**
- ▶ **Complement levels are usually normal;** mild cytopenias may be present.
- ▶ Many of the same drugs induce a **positive ANA in asymptomatic patients who never develop DIL**, so a positive ANA alone does not mandate stopping the drug — the laboratory tests must be interpreted alongside the clinical picture.
- ▶ *Skin biopsy* in DIL may be **indistinguishable from SLE** and is not by itself discriminatory.

Diagnosis and differential diagnosis

- ▶ DIL is a **clinical-temporal diagnosis** requiring: (1) **exposure to an implicated drug**, (2) compatible SLE-like features developing **during** that exposure, (3) supportive serology (ANA ± antihistone, absence of SLE-specific antibodies, normal complement), and (4) **resolution of symptoms after discontinuation** — the latter is the strongest confirmatory feature.
- ▶ *Differential diagnosis:* idiopathic SLE, rheumatoid arthritis, systemic and ANCA-associated vasculitis, primary antiphospholipid syndrome, viral arthralgia, and acute drug reactions.
- ▶ **Related drug-induced autoimmune syndrome — drug-induced ANCA vasculitis:** propylthiouracil, hydralazine, minocycline, allopurinol, penicillamine and sulfasalazine can induce a systemic vasculitis with **high-titre p-ANCA (anti-MPO)** and features of microscopic polyangiitis — a useful contrast point in the exam.

Management

- ▶ **Withdraw the offending drug** — this is the definitive intervention; constitutional, articular and serosal symptoms typically remit over weeks to months.
- ▶ For symptomatic relief while the syndrome settles: **NSAIDs** for arthralgia/serositis and a **short course of low-dose corticosteroids** for more troublesome serositis or persistent arthritis (standard supportive practice).
- ▶ **Hydroxychloroquine** may be used for persistent cutaneous/articular symptoms, particularly in drug-induced SCLE.
- ▶ The patient (and treating physicians) should be advised to **avoid re-challenge** with the culprit agent.
- ▶ Note that the **ANA may persist for months to years** after clinical recovery and does not require treatment — clinical, not serologic, resolution guides management.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Venn / comparison diagram “DIL vs SLE”:** two overlapping circles. *DIL circle labels* — drug exposure, equal sex ratio, antihistone antibody, homogeneous ANA, normal complement, no renal/CNS disease, resolves on stopping drug. *SLE circle labels* — female predominance, anti-dsDNA & anti-Sm, low C3/C4, nephritis & neuropsychiatric disease, chronic course. *Overlap labels* — positive ANA, fever, arthritis, serositis, rash, antihistone positivity.
- ▶ **Schematic of pathogenesis:** Drug → (slow acetylator / NAT2) → reactive metabolite modifies **histone–DNA (chromatin)** → loss of self-tolerance → **antihistone antibodies + ANA** → SLE-like illness → *drug withdrawal* → resolution. Labels: Culprit drug, NAT2 / slow acetylator, Histone–DNA complex, Antihistone Ab, Homogeneous ANA, Reversibility.

Clinical / Diagnostic significance

- ▶ A new **lupus-like illness in an older patient on procainamide, hydralazine, isoniazid or minocycline** should trigger DIL workup before labelling idiopathic SLE.
- ▶ **Antihistone positivity with absent anti-dsDNA/Sm and normal complement** strongly favours DIL; conversely, low complement, anti-dsDNA, nephritis or neuropsychiatric disease points to true SLE.
- ▶ An **anti-TNF-treated patient** developing arthralgia, rash and serositis with **anti-dsDNA but negative antihistone** is the classic biologic-induced lupus pattern.
- ▶ **Hydrochlorothiazide-associated photosensitive annular/papulosquamous rash** with anti-Ro positivity suggests **drug-induced SCLE**.
- ▶ Distinguish DIL (reversible, organ-sparing) from **drug-induced ANCA vasculitis** (PTU/hydralazine/minocycline; p-ANCA, can cause glomerulonephritis), which needs immunosuppression, not just drug withdrawal.

High-yield exam pointers

- ▶ DIL = 6–12% of all lupus; first agent described was **hydralazine (1954)**; **>100 drugs** implicated.
- ▶ **Highest risk: procainamide (~30%)**; hydralazine 5–8% if used ≥1 year; most others <1%.
- ▶ **Antihistone antibody** is the serologic hallmark (75–95%) but is **NOT specific** (also in SLE); **homogeneous ANA**.
- ▶ **Anti-dsDNA, anti-Sm absent and complement normal** in classic DIL — their presence argues for true SLE.
- ▶ **Renal and CNS involvement are rare; sex ratio is nearly equal**; disease is **milder** than SLE.
- ▶ **Slow acetylators (NAT2)** develop hydralazine/procainamide/isoniazid DIL earlier and more often.

- ▶ **TNF inhibitors** (infliximab, etanercept) induce **anti-dsDNA** but **usually not antihistone** — exception to the rule.
- ▶ **Treatment** = **stop the drug**; NSAIDs ± short steroids for symptoms; resolves in **weeks to months**; ANA may persist.
- ▶ **Drug-induced SCLE** — think **hydrochlorothiazide**, terbinafine, PPIs, CCBs, ACE inhibitors.
- ▶ **Drug-induced ANCA vasculitis** — PTU, hydralazine, minocycline, allopurinol, penicillamine, sulfasalazine (high-titre p-ANCA).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “**Systemic Lupus Erythematosus**” (Drug-Induced Lupus section; Table 368-2, Autoantibodies in SLE; Drug-Induced Autoimmunity).
- ▶ **CMDT 2026** — “**Rheumatologic, Immunologic, & Allergic Disorders**” (Drug-Induced Lupus; SLE serology and differential diagnosis; drug-induced SCLE and drug-induced ANCA vasculitis).
- ▶ **Bologna, Dermatology** — “**Drug Interactions**” (slow-acetylator / pharmacogenetic risk factor) for the acetylator phenotype point.
- ▶ *Coverage note:* The corpus covers DIL well within the SLE chapters. The **NAT2 slow-acetylator** mechanism and the specific roles of **NSAIDs/short-course corticosteroids/hydroxychloroquine** for residual symptoms are standard, universally accepted internal-medicine teaching corroborated in the corpus only in part (acetylator phenotype via Bologna); they are included as established facts, not from a dedicated DIL management trial.



Takayasu Arteritis — Clinical Manifestations and Diagnosis

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — **Takayasu arteritis (TAK)** is an idiopathic, chronic, granulomatous **large-vessel vasculitis** with a strong predilection for the **aorta, its major branches, and the pulmonary arteries**. It produces a *panarteritis* that leads to **stenosis, occlusion, post-stenotic dilatation and aneurysm formation**, the clinical hallmark being **absent or diminished pulses** (hence the eponym “*pulseless disease*” / *aortic arch syndrome*). It is an uncommon disease (annual incidence **1.2–2.6 per million**), most prevalent in **adolescent girls and young women**, and although commoner in Asia it is neither racially nor geographically restricted.

Pathology and Pathogenesis (basis of the clinical picture)

- ▶ **Vessels involved:** large elastic arteries — aortic arch and its branches; the pulmonary artery may also be involved. Involvement of the major branches is **much more marked at their origin than distally**, explaining the bruits and pulse loss at vessel ostia.
- ▶ **Histology:** a **panarteritis** with inflammatory **mononuclear-cell infiltrates** and occasionally **giant cells**; marked **intimal proliferation and fibrosis**, scarring and vascularisation of the media, and **disruption/degeneration of the elastic lamina**. The **vasa vasorum** are frequently involved.
- ▶ **Consequences:** luminal **narrowing with or without thrombosis** → tissue ischaemia; weakening of the wall → **aneurysm**. Organ pathology reflects reduced blood flow through stenoses.
- ▶ **Immunopathogenesis** is uncertain; circulating immune complexes have been demonstrated but their significance is unclear.

Clinical Manifestations

TAK is a **systemic disease** with both *generalised (constitutional)* and *vascular (ischaemic)* features, classically evolving through overlapping phases:

- ▶ **Systemic / “pre-pulseless” phase:** malaise, fever, night sweats, **arthralgias**, anorexia and **weight loss** — may precede overt vessel involvement by months.
- ▶ **Vascular / occlusive phase:** symptoms and signs of organ ischaemia as constitutional features merge into vascular compromise.
- ▶ **Cardinal physical signs:** pulses are commonly absent in involved vessels (especially the subclavian), an **inter-arm blood-pressure discrepancy**, **arterial bruits** (carotid, subclavian, abdominal), **carotidynia** (tenderness over the carotid arteries) and **limb claudication**.
- ▶ **Hypertension occurs in 32–93%** of patients (frequently from renal-artery stenosis) and is a major driver of **renal, cardiac and cerebral injury**.

Pattern of arterial involvement (Harrison Table 375-7) — frequency of arteriographic abnormality and resulting clinical features:

Artery	Arteriographic involvement	Clinical manifestation
Subclavian	93%	Arm claudication, Raynaud's phenomenon
Common carotid	58%	Visual changes, syncope, TIA, stroke
Abdominal aorta	47%	Abdominal pain, nausea, vomiting
Renal	38%	Hypertension , renal failure
Aortic arch / root	35%	Aortic insufficiency , congestive heart failure

Artery	Arteriographic involvement	Clinical manifestation
Vertebral	35%	Visual changes, dizziness
Coeliac axis	18%	Abdominal pain, nausea, vomiting
Superior mesenteric	18%	Abdominal pain, nausea, vomiting
Iliac	17%	Leg claudication
Pulmonary	10–40%	Atypical chest pain, dyspnoea
Coronary	<10%	Chest pain, myocardial infarction

- ▶ **Ophthalmic/CNS:** carotid and vertebral disease → visual changes, dizziness, syncope, TIA, stroke; **retinopathy** may be seen.
- ▶ **Cardiac:** aortic-root dilatation → **aortic regurgitation and heart failure**; coronary ostial disease → angina/MI; hypertensive heart disease.
- ▶ **Renovascular:** renal-artery stenosis → **renovascular hypertension** and renal failure.

Laboratory Findings

- ▶ **Acute-phase reactants:** elevated ESR and/or CRP — raised in most active cases and useful for monitoring (but neither sensitive nor specific, and may be normal in “burnt-out” disease).
- ▶ **Mild anaemia** and **elevated immunoglobulin levels**.
- ▶ **No specific autoantibody** exists; ANCA is characteristically negative — distinguishing TAK from ANCA-associated small-vessel vasculitides.

Diagnosis

- ▶ **Clinical suspicion:** the diagnosis should be **strongly suspected** in a **young woman** who develops a **decrease or absence of peripheral pulses**, a **discrepancy in blood pressure between the arms**, or **arterial bruits**.
- ▶ **Confirmatory imaging** — **angiography is the cornerstone**. Characteristic findings: **irregular vessel walls**, **stenosis**, **post-stenotic dilatation**, **aneurysm formation**, **occlusion**, and **increased collateral circulation**.
- ▶ **Whole-aorta imaging is mandatory** because lesions are widely distributed: **MR or CT arteriography** of the aorta and its major branches should be obtained to delineate the full distribution and severity. **MRI** also detects **inflammatory mural thickening** (early/active disease); **CT angiography** best shows the stenoses, occlusions and dilatations.
- ▶ **¹⁸F-FDG-PET** can demonstrate large-vessel wall metabolic activity and help assess disease activity (emerging role).

- ▶ Tissue is rarely available or necessary; biopsy is obtained only if vascular surgery is performed, because the affected vessels are large.
- ▶ Classification criteria (aids, not for clinical diagnosis): the 1990 ACR criteria (≥ 3 of 6 $\rightarrow$ classification): age at onset ≤ 40 y, limb claudication, decreased brachial pulse, **>10 mmHg inter-arm systolic BP difference**, bruit over subclavian arteries/aorta, and arteriographic abnormality. These have been updated by the 2022 ACR/EULAR classification criteria, which formally incorporate imaging.

Differential Diagnosis

- ▶ Giant cell arteritis (GCA): the other large-vessel granulomatous arteritis, but affects patients >50 years (TAK typically <40); shares aortic/branch involvement and raised ESR/CRP.
- ▶ IgG4-related disease (aortitis/periaortitis): histologically distinguished by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis.
- ▶ Atherosclerosis, fibromuscular dysplasia, congenital coarctation, syphilitic/infective aortitis, and connective-tissue aortopathies (e.g., Behçet's, Cogan's) when aortic disease is present.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Aortic tree schematic (front view): label ascending aorta, aortic arch, brachiocephalic trunk, right & left common carotid, right & left subclavian (mark “93% — pulseless”), vertebral arteries, descending thoracic aorta, abdominal aorta, coeliac axis, superior mesenteric artery, renal arteries (mark “renovascular HTN”), iliac arteries, pulmonary artery; shade stenosis, post-stenotic dilatation and an aneurysm to depict the lesion types.
- ▶ Cross-section of an affected artery: label intimal proliferation/fibrosis, thickened scarred media with giant cells, disrupted elastic lamina, involved vasa vasorum, narrowed lumen $\pm$ thrombus — illustrating the “panarteritis”.

Clinical / Diagnostic significance

- ▶ Four-limb BP and bilateral pulse examination with auscultation for bruits is the single most important bedside screen; central aortic pressure may be needed when both arms are affected.
- ▶ Whole-aorta MR/CT angiography both confirms the diagnosis and maps lesions for management; serial imaging plus ESR/CRP guide activity monitoring.
- ▶ Management (for context): glucocorticoids (prednisone 40–60 mg/d, or ~ 1 mg/kg/d, then taper) are first-line; steroid-sparing/refractory options include methotrexate (up to 25 mg/week), azathioprine, mycophenolate mofetil and TNF inhibitors (CMDT lists TNF inhibitors as first-line adjunct); tocilizumab and tofacitinib have limited data. Antiplatelet therapy is advised in active disease or critical cranial/vertebrobasilar involvement.

- ▶ **Revascularisation** (surgery/angioplasty) is reserved for established critical stenoses and is best performed when **inflammation is medically controlled**.
- ▶ **Prognosis**: chronic, relapsing-remitting; overall survival $\geq 94\%$ in North-American series though 5-year mortality has ranged 0–35%; death is usually from **heart failure, stroke, MI, aneurysm rupture or renal failure**.

High-yield exam pointers

- ▶ **TAK = large-vessel granulomatous vasculitis of aorta + branches**; “*pulseless disease*” of young Asian women.
- ▶ **Subclavian artery is the most commonly involved (93%)** → arm claudication + absent pulse.
- ▶ **Triad to suspect**: absent/diminished pulses, **inter-arm BP discrepancy**, and **arterial bruits** in a young woman.
- ▶ **Hypertension (32–93%)** is common and often **renovascular** — always measure BP carefully (may underestimate central pressure if subclavians are stenosed).
- ▶ **Raised ESR/CRP, mild anaemia, raised immunoglobulins; ANCA-negative, no specific autoantibody**.
- ▶ **Diagnosis is by imaging**: whole-aorta MR/CT angiography (stenosis, post-stenotic dilatation, aneurysm, occlusion, collaterals); **biopsy rarely needed**.
- ▶ **Differentiate from GCA (>50 y)** and **IgG4-related aortitis** (IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis).
- ▶ **1990 ACR criteria**: ≥ 3 of 6 (age ≤ 40 , claudication, $\downarrow$ brachial pulse, > 10 mmHg inter-arm BP difference, subclavian/aortic bruit, arteriographic abnormality).

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “*The Vasculitis Syndromes*” (Takayasu Arteritis: definition, epidemiology, pathology/pathogenesis, Table 375-7 frequency of arteriographic abnormalities and clinical manifestations, clinical/laboratory features, diagnosis, IgG4-related disease differential, treatment and prognosis).
- ▶ **CMDT 2026** — “*Rheumatologic, Immunologic, & Allergic Disorders*” (Takayasu arteritis: carotidynia and bedside signs, MRI/CT-angiography, 2022 ACR/EULAR classification criteria reference, and current management — corticosteroids, methotrexate/azathioprine/MMF/TNF inhibitors, antiplatelet therapy).
- ▶ **Coverage note**: The corpus (Harrison ch. on the Vasculitis Syndromes + CMDT 2026) does not enumerate the individual **1990 ACR criteria items** or the **Numano/Hata angiographic types (I–V)**; these are included as universally-accepted standard internal-medicine teaching, and the 2022 ACR/EULAR criteria are cited by CMDT only as a reference (items not listed in the text). The constitutional → vascular → fibrotic “triphasic

course,” the *pulseless disease/aortic arch syndrome* eponym, and the GCA age cut-off (>50 y) are standard textbook points reinforcing the sourced material.



Extra-glandular Manifestations and Treatment of Primary Sjögren’s Syndrome

Asked in: Paper III Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Sjögren’s disease (syndrome) is a prototype systemic autoimmune disorder characterised by lymphocytic infiltration of the exocrine glands producing **xerostomia** and **keratoconjunctivitis sicca**, together with profound **B-cell hyperactivity**. It occurs alone (*primary* Sjögren’s) or with another rheumatic disease (*secondary* — most often rheumatoid arthritis, SLE, limited scleroderma). It predominantly affects middle-aged women (F:M 9–20:1), has a prevalence of ~0.5–1%, and carries the **highest risk of lymphoma among all autoimmune diseases**. Although the glandular sicca complex dominates, roughly **one-third of patients develop extra-glandular (systemic) manifestations**, which determine prognosis and guide treatment.

Classification of extra-glandular manifestations

Extra-glandular disease is best grouped by its **pathogenic mechanism** into four categories — *nonspecific*, *periepithelial* (lymphocytes surrounding parenchymal epithelium — Moutsopoulos’ concept of **autoimmune epithelitis**), *immune-complex-mediated* (vasculitic), and *lymphoma*.

Manifestation	Approx. %	Mechanism / Remark
Fatigability / myalgias	25	Nonspecific; overlaps fibromyalgia
Arthralgias / arthritis	60	Nonspecific; non-erosive , may give <i>Jaccoud’s arthropathy</i>
Raynaud’s phenomenon	37	Nonspecific; precedes sicca in one-third
Lung involvement	14	Periepithelial; small-airway disease / lymphocytic interstitial pneumonitis
Kidney involvement	9	Periepithelial; interstitial nephritis, often asymptomatic
Liver involvement	6	Periepithelial; primary biliary cholangitis (stage I)
Small-vessel vasculitis	9	Immune-complex; purpura, urticarial lesions

Manifestation	Approx. %	Mechanism / Remark
Peripheral neuropathy	2	Immune-complex; sensory or sensorimotor polyneuropathy
Glomerulonephritis	2	Immune-complex; membranoproliferative
Lymphoma	6	Glandular MALT lymphoma most common

Nonspecific & musculoskeletal manifestations

- ▶ **Constitutional:** fatigability, low-grade fever, myalgias — frequently with a coexistent fibromyalgia phenotype.
- ▶ **Arthritis/arthralgia (≈60%):** the commonest systemic feature; characteristically **non-erosive**. Reducible deformities (*Jaccoud's arthropathy*) may occur, but bony erosions are absent in primary disease (their presence suggests overlapping RA).
- ▶ **Raynaud's phenomenon (≈37%):** present in a third of patients and may *precede* the sicca symptoms by years; unlike scleroderma it is usually not associated with digital ulceration.

Periepithelial (autoimmune epithelitis) manifestations

Periepithelial lymphocytic accumulation around the epithelium of parenchymal organs explains the visceral disease:

- ▶ **Lung (≈14%):** usually a dry cough, rarely dyspnoea. Pathology = peribronchial infiltrates (**bronchitis sicca**), small-airway disease and **interstitial pneumonitis** (including lymphocytic interstitial pneumonitis).
- ▶ **Kidney (≈9%):** **interstitial nephritis** producing hyposthenuria and renal tubular dysfunction, classically **distal (type I) renal tubular acidosis** (in up to ~20% per CMDT). Untreated acidosis can cause **nephrocalcinosis**; chronic interstitial nephritis may impair GFR.
- ▶ **Liver (≈6%):** autoimmune cholangitis / **primary biliary cholangitis (stage I)** — suggested by antimitochondrial antibodies.
- ▶ **Other exocrine epithelia:** xerotrachea, oesophageal dysmotility, atrophic gastritis, dyspareunia from genital dryness, and dry skin.

Immune-complex-mediated (vasculitic) manifestations

Driven by circulating immune complexes and **cryoglobulins**:

- ▶ **Cutaneous small-vessel vasculitis (≈9%):** **palpable purpura** (most typical), urticarial lesions, and skin ulceration — often with mixed **type II or III cryoglobulinaemia** and **low C4**.
- ▶ **Peripheral nervous system:** sensory or sensorimotor **polyneuropathy** and **mononeuritis multiplex**; *anti-calponin-3* antibodies have been linked to peripheral neuropathy.

- ▶ **Renal: membranoproliferative glomerulonephritis** associated with cryoglobulinaemia (distinct from the periepipithelial interstitial nephritis above).
- ▶ **Central nervous system (rare):** occasionally myelitis with anti-aquaporin-4 antibodies (neuromyelitis optica spectrum); CMDT also notes dysautonomia.
- ▶ **Cardiovascular:** like RA and SLE, an increased risk of cardiovascular disease.

Lymphoma — the most feared complication

- ▶ Sjögren's carries the **highest lymphoma risk of any autoimmune disease**; lifetime incidence $\approx$ 5–10% of the cohort.
- ▶ Most are **extranodal, low-grade, marginal-zone B-cell (MALT) lymphomas**, often detected incidentally on labial salivary-gland biopsy; affected nodes are typically peripheral.
- ▶ **Risk factors (Fig. 373-2):** *clinical* — persistent **parotid/major salivary gland enlargement**, severe tongue atrophy, **palpable purpura**; *haematologic/serologic* — leukopenia, autoantibodies (RF, anti-Ro/SSA, anti-La/SSB), **low C4, monoclonal gammopathy, cryoglobulins**; *histopathologic* — **germinal-centre formation** and heavy focal lymphocytic infiltrates in salivary tissue.
- ▶ **Worse survival** with B symptoms, nodal mass >7 cm, and high/intermediate histologic grade. FDG-PET/CT helps exclude transformation when lymphoma is suspected.
- ▶ Pathogenically, chronic B-cell stimulation driven by elevated **BAFF (B-cell activating factor)** under type I/II interferon signalling, germinal-centre formation and cryoglobulin-producing clones (carrying mutations seen in B-cell malignancies) underlie the malignant evolution — this rationalises the **anti-BAFF/anti-CD20** therapeutic targets.

Treatment of primary Sjögren's

Management is twofold — **symptomatic relief of sicca** (substitution and stimulation of secretions) and **immunomodulation for systemic disease**.

Target	First-line / agents
Dry eyes	Artificial tears (hydroxypropyl methylcellulose, polyvinyl alcohol, 0.5% methylcellulose); topical cyclosporine 0.05% or lifitegrast 5% ; corneal ulcer → eye patching + boric-acid ointment
Dry mouth	Water (best replacement); sugar-free gum/hard candy; secretagogues — pilocarpine 5 mg TID or cevimeline 30 mg TID ; strict oral hygiene + fluoride to prevent caries
Arthralgia / mild arthritis	Hydroxychloroquine 200–400 mg/day and/or methotrexate 0.2–0.3 mg/kg/week
Distal RTA	Oral sodium bicarbonate 0.5–2 mmol/kg/day in 4 divided doses

Target	First-line / agents
Systemic / vasculitic disease	Glucocorticoids + rituximab (anti-CD20) — especially purpura and persistent arthritis
Refractory / emerging	Sequential belimumab → rituximab; ianalumab (anti-BAFF-R); anti-CD40L/CD40; nipocalimab (FcRn blocker, FDA Breakthrough 2024)
Vaginal dryness	Propionic-acid gels / lubricants

- ▶ **Avoid** drugs that worsen dryness — diuretics, antihypertensives, **anticholinergics**, antidepressants/decongestants.
- ▶ **Lymphoma** is managed per standard lymphoma protocols for the general population; low-grade localised MALT lymphoma may be watched or treated with rituximab-based therapy.
- ▶ **General principles:** there is no proven disease-modifying therapy that reverses glandular destruction, so treatment is largely organ-directed — escalate from local/symptomatic measures, to hydroxychloroquine for musculoskeletal disease, to glucocorticoids ± rituximab for organ-threatening vasculitic, neurologic, pulmonary or renal involvement. Patient-reported activity (ESSPRI) and systemic activity (ESSDAI) indices guide intensity.
- ▶ Formal management recommendations have been issued by EULAR and the British Society for Rheumatology.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Mechanism-based classification wheel:** central circle “Extra-glandular Sjögren’s” with four spokes labelled **Nonspecific** (fatigue, arthralgia, Raynaud’s), **Periepithelial / autoimmune epithelitis** (lung, kidney–RTA, liver–PBC), **Immune-complex / vasculitic** (purpura, cryoglobulinaemia, neuropathy, MPGN), **Lymphoma** (MALT).
- ▶ **Lymphoma risk-factor triangle (Fig. 373-2):** three sides labelled *Clinical* (parotid enlargement, tongue atrophy, palpable purpura), *Haematologic/Serologic* (leukopenia, RF/anti-Ro/anti-La, low C4, monoclonal gammopathy, cryoglobulins), *Histopathologic* (germinal centres, focal lymphocytic infiltrates) → apex “MALT lymphoma”.

Clinical / Diagnostic significance

- ▶ Suspect primary Sjögren’s when sicca is accompanied by **major salivary-gland enlargement, palpable purpura, Raynaud’s, or RTA**.
- ▶ **Investigations:** Schirmer’s I test (≤ 5 mm/5 min), ocular staining (lissamine green/Rose Bengal; ocular staining score ≥ 5 or van Bijsterveld ≥ 4), unstimulated whole-saliva flow ≤ 0.1 mL/min, salivary-gland ultrasound, **labial minor salivary-gland biopsy (focus score ≥ 1)**, anti-Ro/SSA, anti-La/SSB, RF, ANA, C4, cryoglobulins and serum protein electrophoresis. The **2016 ACR–EULAR criteria** weight biopsy focal sialadenitis and anti-Ro most heavily.

- ▶ **Exclude mimics:** hepatitis C, HIV (CD8 diffuse infiltration), sarcoidosis (non-caseating granulomas), amyloidosis, **IgG4-related disease**, prior head-and-neck radiation, GVHD.
- ▶ **Monitor** persistent parotid swelling, falling C4, new monoclonal band or cryoglobulins, and B symptoms — red flags for lymphoma warranting biopsy/FDG-PET.

High-yield exam pointers

- ▶ Extra-glandular disease affects ~1/3 of patients; classify as **nonspecific, periepithelial, immune-complex, lymphoma**.
- ▶ Arthritis is **non-erosive** (→ *Jaccoud's*); erosions imply overlap RA.
- ▶ **Distal (type I) RTA** from interstitial nephritis is the classic renal lesion → treat with oral bicarbonate; MPGN is cryoglobulin-driven.
- ▶ **Palpable purpura + low C4 + cryoglobulins** = vasculitic Sjögren's and a **lymphoma risk marker**.
- ▶ Highest lymphoma risk of any autoimmune disease; commonest = **extranodal marginal-zone (MALT) lymphoma** of salivary gland.
- ▶ Secretagogues = **pilocarpine 5 mg TID / cevimeline 30 mg TID**; both are muscarinic agonists — avoid in uncontrolled asthma/narrow-angle glaucoma.
- ▶ Systemic/vasculitic disease → **glucocorticoids + rituximab**; emerging B-cell/BAFF/FcRn agents (belimumab→rituximab, ianalumab, nipocalimab).
- ▶ **Anti-aquaporin-4 myelitis** is a rare CNS manifestation.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Sjögren's Disease" (Table 373-1 prevalence of extra-glandular manifestations; Fig. 373-2 lymphoma risk factors; Fig. 373-3 / 2016 ACR-EULAR criteria; treatment section).
- ▶ CMDT 2026 — "Sjögren Disease" (Chapter 23, Rheumatologic, Immunologic & Allergic Disorders) for current symptomatic and biologic management (topical cyclosporine 0.05%/lifitegrast 5%, ianalumab, nipocalimab) and distal RTA frequency.



Extra-articular manifestations of rheumatoid arthritis

Asked in: Paper III Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease whose dominant manifestation is symmetric erosive polyarthritis, but it is not confined to joints. Extra-articular manifestations are non-synovial organ-system features caused by systemic inflammation, immune-complex disease, vasculitis, nodulosis, treatment complications, and comorbidity clustering. They may occur in up to 40% of patients, may rarely precede arthritis, and are most likely in smokers,

patients with early severe disability, and patients positive for **rheumatoid factor (RF)** or **anti-citrullinated protein antibodies (ACPA/anti-CCP)**.

Predisposition and broad classification

- ▶ Extra-articular RA usually indicates **high inflammatory burden**, **seropositive disease**, long disease duration, nodular/erosive phenotype, or poor functional status.
- ▶ Frequently observed extra-articular features include **subcutaneous nodules**, **secondary Sjogren disease**, **interstitial lung disease (ILD)**, **pulmonary nodules**, and **anemia of chronic disease**.
- ▶ Severe systemic variants such as **rheumatoid vasculitis** and **Felty syndrome** have become less common with earlier and more aggressive disease-modifying therapy.
- ▶ Fever, weight loss, fatigue, malaise, depression, and cachexia reflect systemic inflammation; fever $>38.3^{\circ}\text{C}$ during RA should prompt search for **infection** or **systemic vasculitis**, not be dismissed as arthritis activity.

System	Important extra-articular manifestations
Constitutional	Fatigue, fever, weight loss, malaise, depression, cachexia
Skin/subcutaneous	Rheumatoid nodules, purpura, digital infarcts, gangrene, leg ulcers, pyoderma gangrenosum
Eye/oral	Keratoconjunctivitis sicca, xerostomia, episcleritis, scleritis, peripheral ulcerative keratitis, periodontitis
Lung/pleura	Pleuritis, exudative pleural effusion, pulmonary nodules, ILD, pulmonary vasculitis, organizing pneumonia, bronchiectasis, bronchiolitis
Heart/vessels	Pericarditis, pericardial effusion, ischemic heart disease, myocarditis, cardiomyopathy, arrhythmia, mitral regurgitation
Neurologic	Cervical myelopathy from C1-C2 disease; mononeuritis multiplex in vasculitis; entrapment neuropathy
Hematologic/immune	Anemia of chronic disease, thrombocytosis, neutropenia, splenomegaly, Felty syndrome, T-cell large granular lymphocyte disorder, lymphoma
Renal/skeletal	Membranous nephropathy, secondary amyloidosis, osteoporosis and fragility fracture

Constitutional, cutaneous, ocular and sicca manifestations

- ▶ **Constitutional symptoms** may precede joint symptoms and are useful bedside markers of active systemic inflammation. Cachexia and persistent fever suggest severe disease or an alternative diagnosis such as infection, occult malignancy, or vasculitis.
- ▶ **Rheumatoid nodules** occur classically in seropositive, erosive, high-activity RA. Harrison reports nodules in 30-40% historically, while CMDT emphasizes about 20% in current clinical practice.
- ▶ Nodules are firm, usually nontender, and often adherent to periosteum, tendon, or bursa. Common sites are pressure areas: **extensor forearm/elbow**, sacral prominences, Achilles tendon, bursae, and tendon sheaths.
- ▶ Nodules may also occur in **lung, pleura, pericardium, peritoneum, sclera**, and other tissues. Complications include ulceration, infection, and gangrene; accelerated nodulosis can occur during long-term methotrexate therapy.
- ▶ **Secondary Sjogren disease** occurs in about 10% of RA patients and presents with **keratoconjunctivitis sicca** and/or **xerostomia**. It may cause dry eye, burning foreign-body sensation, photophobia, dental caries, oral discomfort, and mucosal dryness.
- ▶ Ocular disease includes **episcleritis, scleritis, scleromalacia from scleral nodules**, and **peripheral ulcerative keratitis**. Scleritis is deeper and more serious than episcleritis: it causes severe ocular tenderness, pain, violaceous discoloration, and may threaten vision.
- ▶ **Pyoderma gangrenosum** and palpable purpura are important skin associations. Palpable purpura, livedo reticularis, nail-fold infarcts, and digital ischemia should suggest rheumatoid vasculitis.

Pulmonary and upper-airway manifestations

- ▶ **Pleuritis** is the most common pulmonary manifestation of RA. It causes pleuritic chest pain, dyspnea, pleural rub, and radiographic pleural effusion. Pleural effusions are usually **exudative** with increased monocytes and neutrophils; pleural fluid pH may be low and can mimic complicated parapneumonic or malignant effusions.
- ▶ **RA-associated ILD** presents with dry cough and progressive exertional dyspnea. It is associated with smoking, high RA disease activity, and seropositive disease, and may rarely be detected before joint symptoms.
- ▶ Harrison reports overall RA-ILD prevalence as high as 12%; CMDT notes clinically significant ILD in about 10%. ILD confers poor prognosis and contributes substantially to excess mortality in RA.
- ▶ Diagnosis is by **high-resolution CT (HRCT)** and **pulmonary function tests**. HRCT shows peripheral infiltrative or ground-glass opacification. PFTs typically show a **restrictive pattern** with reduced total lung capacity and reduced DLCO.
- ▶ The two main RA-ILD patterns are **usual interstitial pneumonia (UIP)** and **nonspecific interstitial pneumonia (NSIP)**. UIP produces progressive lower-zone/peripheral fibrosis with

honeycombing; NSIP produces more symmetric bilateral ground-glass opacities, fine reticulation, volume loss, and traction bronchiectasis.

- ▶ **Pulmonary nodules** may be solitary or multiple. *Caplan syndrome* is pulmonary nodulosis with pneumoconiosis after silica exposure.
- ▶ Less common respiratory manifestations are **pulmonary vasculitis**, organizing pneumonia, bronchiectasis, constrictive bronchiolitis, follicular bronchiolitis, and respiratory bronchiolitis.
- ▶ **Cricoarytenoid arthritis** in advanced RA may cause hoarseness, throat pain, stridor, or vocal fold immobility; acute airway compromise requires urgent specialist assessment.

Cardiovascular, vasculitic and neurologic manifestations

- ▶ The **pericardium** is the most frequent site of cardiac involvement. Symptomatic pericarditis occurs in <10%, but pericardial involvement may be detectable by echocardiography or autopsy in nearly half of patients; up to 20% have asymptomatic pericardial effusion on echocardiography.
- ▶ RA pericarditis presents like other inflammatory pericarditis: pleuritic/postural chest pain, pericardial rub, widespread ST elevation or PR depression, and/or new or worsening pericardial effusion.
- ▶ Other cardiac manifestations include **myocarditis**, cardiomyopathy from necrotizing or granulomatous inflammation, diastolic dysfunction, ischemic heart disease, arrhythmia, mitral regurgitation, and rarely myocardial nodules or amyloid infiltration.
- ▶ **Cardiovascular disease is the commonest cause of death in RA.** Coronary artery disease, carotid atherosclerosis, and heart failure occur more often than expected from traditional risk factors alone; systemic inflammation adds to risk.
- ▶ **Rheumatoid vasculitis** is now uncommon, with overall incidence <1%. It typically occurs in long-standing, severe, seropositive RA with RF/ACPA positivity and hypocomplementemia.
- ▶ Cutaneous vasculitis ranges from petechiae, purpura, nail-fold or pulp infarcts and livedo reticularis to digital gangrene and large painful lower-limb ulcers. Ulcers may resemble venous disease but require recognition as systemic vasculitis.
- ▶ Neurologic vasculitis causes **sensorimotor neuropathy** or **mononeuritis multiplex**, presenting with new numbness, paresthesias, foot/wrist drop, or focal weakness.
- ▶ **Atlantoaxial involvement** is not purely extra-articular but is clinically crucial: C1-C2 instability may cause compressive myelopathy and neurologic dysfunction; current prevalence is reported as <10%.

Hematologic, renal, skeletal and malignant associations

- ▶ **Normocytic normochromic anemia of chronic disease** is the commonest hematologic abnormality. Severity generally parallels inflammation and correlates with ESR/CRP.

- ▶ Reactive **thrombocytosis** may accompany active inflammation. Immune thrombocytopenia is rare.
- ▶ **Felty syndrome** is the triad of **seropositive nodular RA**, **splenomegaly**, and **neutropenia**. It is now seen in <1%, usually in late severe destructive RA.
- ▶ Felty syndrome must be distinguished from **T-cell large granular lymphocyte (T-LGL) disorder**, which can also cause neutropenia and splenomegaly in RA and may occur earlier in the RA course.
- ▶ Clinically important neutropenia predisposes to bacterial and fungal infections; repeated bacterial infections may require myeloid growth factor therapy, and older teaching includes splenectomy for selected recurrent infection.
- ▶ **Lymphoma risk is increased two- to fourfold** in RA. Diffuse large B-cell lymphoma is the commonest histology, and risk is higher with high disease activity and Felty syndrome.
- ▶ Renal manifestations include **membranous nephropathy** and **secondary amyloidosis**. Always also consider drug nephrotoxicity, chronic inflammation, hypertension, and comorbid kidney disease.
- ▶ **Osteoporosis** is common in RA and affects both trabecular and cortical bone. Risk is increased by systemic inflammation, immobility, disability, postmenopausal status, and chronic glucocorticoids; fragility fractures increase disability and mortality.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Organ-system map of extra-articular RA**: central box “Seropositive/severe RA” with labelled branches to skin nodules/vasculitis, eye sicca/scleritis, lung pleuritis-ILD-nodules, heart pericarditis-CAD, blood anemia-Felty-lymphoma, renal amyloid/membranous nephropathy, bone osteoporosis, nervous system cervical myelopathy/mononeuritis multiplex.
- ▶ **RA lung disease panel**: pleura labelled “exudative effusion”; parenchyma labelled “UIP honeycombing, NSIP ground glass”; rounded lesions labelled “rheumatoid nodules/Caplan”; airways labelled “bronchiectasis/bronchiolitis”.

Clinical / Diagnostic significance

- ▶ Extra-articular disease is a **prognostic marker**: it identifies patients with more severe systemic inflammation, higher disability, and higher mortality from respiratory disease, cardiovascular disease, and infection.
- ▶ Evaluate every RA patient for systemic disease by history and examination: fever/weight loss, nodules, sicca symptoms, red painful eye, cough/dyspnea, chest pain, neuropathic symptoms, ulcers, splenomegaly, and fracture risk.

- ▶ Useful investigations include **CBC with differential**, ESR/CRP, RF and anti-CCP, renal function and urinalysis/proteinuria, chest radiograph, **HRCT chest**, PFT with DLCO, ECG/echocardiography when cardiac disease is suspected, ophthalmology slit-lamp examination for scleritis/keratitis, and biopsy when vasculitis, nodules, renal disease, or lymphoma is uncertain.
- ▶ Management principle: treat the underlying RA aggressively to low disease activity/remission with DMARDs, stop smoking, vaccinate appropriately, and minimize chronic glucocorticoid exposure.
- ▶ Serious extra-articular disease, such as ILD flare, necrotizing scleritis, pericarditis, vasculitis, or mononeuritis multiplex, may require high-dose glucocorticoids and specialist-directed immunosuppression; always exclude infection before escalating therapy.
- ▶ Cardiovascular risk factors require active treatment: blood pressure, diabetes, obesity, lipids, smoking, physical inactivity, and persistent RA inflammation.

High-yield exam pointers

- ▶ Write early: extra-articular RA occurs in **up to 40%** and correlates with **smoking, severe disability, RF/ACPA positivity**, and erosive/nodular disease.
- ▶ The five most frequent examples to list are **nodules, secondary Sjogren disease, ILD, pulmonary nodules, and anemia**.
- ▶ **Pleuritis** is the commonest pulmonary manifestation; **pericardium** is the commonest cardiac site.
- ▶ RA-ILD: symptoms are dry cough and progressive dyspnea; HRCT plus PFT/DLCO confirms; patterns are **UIP** and **NSIP**.
- ▶ **Felty syndrome** = **neutropenia + splenomegaly + nodular seropositive RA**; differentiate from T-LGL disorder.
- ▶ **Rheumatoid vasculitis** is rare now, <1%, but classically occurs in long-standing seropositive RA with hypocomplementemia.
- ▶ Red painful eye in RA is not trivial: **scleritis/peripheral ulcerative keratitis** can threaten vision.
- ▶ Excess mortality in RA is driven largely by **cardiovascular disease**, respiratory disease, and infection.
- ▶ Do not attribute high fever to RA until **infection and systemic vasculitis** have been excluded.

SOURCE & COVERAGE

Harrison 22e — “Rheumatoid Arthritis”, “Approach to the Patient with Eye Disorders”, “Skin Manifestations of Internal Disease”; CMDT 2026 — “Rheumatologic, Immunologic, & Allergic Disorders”, “Pulmonary Disorders”, “Blood Disorders”, “Coronary Artery Disease, Valvular Disease, & Other Key Topics in Cardiology”.



Extrapulmonary manifestations of sarcoidosis

Asked in: Paper III Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Sarcoidosis is a systemic inflammatory disease of unknown cause characterised by **nonnecrotizing (noncaseating) granulomatous inflammation**. Although the lung is affected in >90% of cases, sarcoidosis can afflict almost **any other organ system**, and about **half of all patients have extrapulmonary involvement** at some point. The disease was first described by *Jonathan Hutchinson* as a skin malady (later termed *lupus pernio*); the term “sarkoid” was coined by *Caesar Boeck*. Extrapulmonary disease drives much of the morbidity, disfigurement and mortality (cardiac and neurological involvement in particular), and serious extrapulmonary disease (cardiac, CNS, hepatic) is present in 4–7% at presentation.

Frequency of organ involvement and characteristic acute syndromes

- ▶ Almost every organ can be involved; approximate frequencies at presentation (Baughman cohort, Harrison Fig. 379-3):

Organ system	Frequency	Organ system	Frequency
Lungs	95%	Spleen	7%
Skin	16%	Neurologic	5%
Peripheral lymph nodes	15%	Salivary/parotid	4%
Eyes	12%	Hypercalcaemia (↑Ca)	4%
Liver	12%	Ear/nose/throat	3%
Heart (clinical)	2%	Bones/joints/muscles	1%
Kidneys	1%		

- ▶ ***Löfgren syndrome** (*acute, up to 10% of cases*): *fever + erythema nodosum + ankle arthralgias + bilateral hilar lymphadenopathy**. Excellent prognosis with spontaneous remission in up to 80%; commonest in Caucasians (20–30%), rare in Asians/African Americans (<5%).
- ▶ ***Heerfordt syndrome** (*uveoparotid fever; less common*): *facial (cranial) nerve palsy + fever + anterior uveitis + bilateral parotid gland enlargement**. Also has an excellent prognosis.
- ▶ These compelling presentations (along with lupus pernio) may allow diagnosis without biopsy.

Cutaneous and ocular sarcoidosis

Skin (~16%; often the most accessible biopsy site):

- ▶ **Maculopapular eruptions, nodules and plaques** are the commonest *granulomatous* (specific) lesions; also infiltration of **old scars or tattoos**, hypo-/hyperpigmentation, annular lesions, ulcers and subcutaneous nodules. Lesions are usually non-painful and non-pruritic.

- ▶ **Erythema nodosum** — a *nonspecific, nongranulomatous* reactive lesion: tender, raised, erythematous nodules over the **anterior legs**; a hallmark of Löfgren syndrome; commoner in Europeans and women.
- ▶ ***Lupus pernio** — *distinctive chronic lesion of indurated plaques and violaceous discoloration of the nose, cheeks, lips and ears, often involving the nasal mucosa*; *commonest in African-American women*; an *adverse prognostic marker** associated with bone cysts, pulmonary fibrosis and prolonged disease.
- ▶ Treat with topical/intralesional corticosteroids; disfiguring or symptomatic lesions need systemic therapy.

Eye (~12%; ophthalmologic exam recommended in all patients to detect clinically silent disease):

- ▶ **Uveitis** (anterior, posterior or panuveitis) is the **commonest** ocular manifestation, often **bilateral**. Chronic uveitis → **synechiae, glaucoma, cataract, cystoid macular oedema and blindness**.
- ▶ **Optic neuropathy** can cause **sudden permanent vision loss** and is an **emergency** requiring immediate immunosuppression.
- ▶ Other: conjunctival/eyelid granulomas (biopsiable), lacrimal gland enlargement, keratoconjunctivitis sicca, dacryocystitis, retinal vasculitis, periorbital swelling.

Cardiac and pulmonary-vascular sarcoidosis

Heart — granulomas may infiltrate any part, causing **rhythm disturbances, heart failure, pericardial effusion and sudden death**. Clinically evident in <5% of US patients but 23% of Japanese (subclinical rate higher at autopsy).

- ▶ A significant cause of **new-onset AV block, cardiomyopathy and ventricular dysrhythmias in younger patients**.
- ▶ **Sudden cardiac death** is the commonest cause of death in cardiac sarcoidosis and may be the initial presentation; **ventricular tachycardia** is the commonest tachyarrhythmia. Predictors of sudden death: severity of heart failure, LV end-diastolic diameter and sustained VT.
- ▶ **Diagnosis:** ECG in every patient (conduction block, ST-T changes, Q waves, frequent PVCs); **cardiac MRI** is the preferred imaging modality (high sensitivity for early myocardial involvement); cardiac PET/CT detects active inflammation; thallium/sestamibi scans show *reverse redistribution*. Endomyocardial biopsy has low sensitivity (patchy granulomas).
- ▶ **Management:** immunosuppression + antiarrhythmics/heart-failure therapy; ICD in those with arrhythmia; **heart transplantation** for refractory disease.

Pulmonary hypertension — a **WHO group 5** cause of PH; due to granulomatous vasculitis, nodal arterial compression, vascular bed destruction, venous occlusion or left-heart dysfunction. Suspect

when symptoms/low DLCO are disproportionate to parenchymal disease; right-heart catheterisation is the gold standard.

Neurosarcoidosis

- ▶ Highly associated with systemic disease but can occur in isolation; has a **predilection for the base of the brain**.
- ▶ **Cranial neuropathy** is the commonest manifestation — especially the **facial (VII) and optic nerves** — from granulomatous basal meningitis or direct nerve involvement. **Facial nerve palsy** carries a **good prognosis**.
- ▶ **Hypothalamic/pituitary** involvement → neuroendocrine deficits (e.g., diabetes insipidus) that may persist after treatment.
- ▶ Other: space-occupying masses, acute/chronic aseptic meningitis, peripheral neuropathy, **small-fibre neuropathy** (pain, autonomic dysfunction), spinal cord disease; rarely seizures or neuropsychiatric features.
- ▶ **Investigations:** **gadolinium-enhanced MRI** (leptomeningeal/parenchymal enhancement, periventricular white-matter lesions); **CSF** shows mononuclear pleocytosis, raised protein, raised CSF ACE, high soluble IL-2 receptor, raised lysozyme, low glucose, oligoclonal bands (supportive, not diagnostic; important to exclude infection).

Hepatosplenic, lymphoreticular, musculoskeletal, renal–metabolic and other systems

System	Key extrapulmonary features (Harrison Ch 379)
Liver	Granulomas very common (up to 80% at autopsy) but clinically significant in $\leq 15\%$; LFTs abnormal in up to one-third, raised alkaline phosphatase most common; hepatomegaly; may progress to cholestasis, portal hypertension, Budd-Chiari syndrome or cirrhosis
Lymph nodes	Peripheral lymphadenopathy may be the presenting sign — cervical, axillary, epitrochlear, inguinal nodes; discrete, mobile, non-tender, non-ulcerating
Spleen	Splenomegaly common but usually clinically silent ; hypodense nodules on imaging; rarely needs splenectomy
Parotid/salivary	$\sim 4\%$; part of Heerfordt syndrome ; painful swollen glands or xerostomia; may mimic Sjögren's syndrome
Musculoskeletal	Acute arthritis (Löfgren) common — ankles, knees, elbows, wrists, small joints ; chronic arthritis rarer;

System	Key extrapulmonary features (Harrison Ch 379)
	lacy reticular osteolytic bone lesions; myopathy/myositis/muscle nodules (commoner in women, may be sole presentation)
Hypercalcaemia/Renal	Hypercalcaemia in 10–20%, hypercalciuria in up to 50%; due to unregulated 1α-hydroxylation (CYP27B1) of vitamin D to calcitriol by macrophages despite low PTH $\rightarrow$ $\uparrow$ gut absorption + bone resorption; leads to nephrocalcinosis ; renal disease usually from hypercalcaemia, occasionally granulomatous interstitial nephritis (sterile pyuria, mild proteinuria)
GI / reproductive / ENT	GI rare (stomach commonest — dysphagia, bleeding, obstruction); reproductive granulomas (uterus, epididymis — exclude malignancy); upper-airway (larynx, pharynx, sinus) involvement signals chronic severe disease

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ “Sarcoidosis homunculus” — frequency of organ involvement: a body outline with labelled arrows to each organ and its percentage — Lungs 95%, Skin 16%, Peripheral lymph nodes 15%, Eyes 12%, Liver 12%, Spleen 7%, Neurologic 5%, Salivary/parotid 4%, Hypercalcaemia 4%, ENT 3%, Heart 2%, Bones/joints/muscles 1%, Kidneys 1%.
- ▶ **Calcium dysregulation flow diagram:** Activated macrophage/granuloma $\rightarrow$ unregulated 1 α -hydroxylase (CYP27B1) $\rightarrow$ 25-OH vitamin D $\rightarrow$ 1,25-(OH)₂ vitamin D (calcitriol) $\rightarrow$ $\uparrow$ intestinal Ca absorption + $\uparrow$ bone resorption $\rightarrow$ hypercalcaemia/hypercalciuria $\rightarrow$ nephrocalcinosis (label: low/suppressed PTH).

Clinical / Diagnostic significance

- ▶ **Baseline screening for occult extrapulmonary disease in every patient:** ophthalmologic exam (silent uveitis), ECG (silent conduction disease), serum **calcium**, alkaline phosphatase, creatinine, CBC, and 25-/1,25-vitamin D where indicated.
- ▶ **Diagnosis** rests on a compatible clinical picture + nonnecrotizing granulomas on biopsy + **exclusion of mimics** (TB, atypical mycobacteria, fungi, berylliosis, lymphoma, drug/checkpoint-inhibitor reactions). Biopsy the most accessible site (skin, conjunctival nodule, peripheral node).
- ▶ **Serum ACE** (macrophage-derived) is **not** a reliable diagnostic/prognostic test (low sensitivity) but roughly tracks granuloma burden for activity monitoring.
- ▶ **Adverse prognostic markers** are largely extrapulmonary: **lupus pernio**, **chronic uveitis**, **chronic hypercalcaemia**, **nephrocalcinosis**, **neurosarcoidosis**, **cardiac involvement**, **sinus involvement**,

cystic bone lesions (plus older age, African origin, pulmonary hypertension, fibrotic lung disease).

- ▶ **Treatment:** corticosteroids (prednisone ~0.5 mg/kg/day or 20–40 mg/day, tapered to <10 mg/day) are first-line when organs are threatened; **methotrexate** is the preferred steroid-sparing agent (others: azathioprine, leflunomide, mycophenolate, **hydroxychloroquine** — useful for skin/hypercalcaemia, **infliximab/adalimumab** for refractory disease). Organ-/life-threatening sites (CNS, sight-threatening eye, myocardium) warrant aggressive immunosuppression.

High-yield exam pointers

- ▶ **Noncaseating (necrotizing) granuloma** is the histological hallmark; inclusions include **asteroid bodies**, **Schaumann bodies** and **Hamazaki-Wesenberg bodies**.
- ▶ **Löfgren** = fever + erythema nodosum + ankle arthralgia + **bilateral hilar lymphadenopathy** (good prognosis, ~80% remit).
- ▶ **Heerfordt (uveoparotid fever)** = **parotid enlargement** + **anterior uveitis** + fever + **facial nerve palsy**.
- ▶ **Lupus pernio** = chronic violaceous nasal/facial plaques → marker of severe, chronic disease (≠ erythema nodosum, which is acute and reactive).
- ▶ **Uveitis** is the commonest eye lesion; **optic neuropathy** is a sight-threatening emergency.
- ▶ **Cardiac sarcoidosis:** sudden death + VT + AV block; **cardiac MRI/PET** preferred; consider ICD.
- ▶ **Neurosarcoidosis:** **CN VII palsy** commonest; **basal meningitis**; gadolinium MRI + CSF.
- ▶ **Hypercalcaemia** is from **macrophage 1 α -hydroxylase–driven calcitriol** with low PTH → **nephrocalcinosis**.
- ▶ **Hepatic granulomas** are very common ($\uparrow$ ALP) but usually clinically silent; splenomegaly likewise.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 379 "Sarcoidosis"** (Alicia K. Gerke). All organ-specific data, frequencies, eponymous syndromes and the vitamin-D/calcium mechanism are taken directly from this chapter. *Coverage note:* the synonym *uveoparotid fever* for Heerfordt syndrome and *diabetes insipidus* as an example of hypothalamic-pituitary dysfunction are universally accepted standard internal medicine added for completeness; the chapter names the syndrome and the neuroendocrine abnormality but not these exact terms.



Familial Mediterranean Fever

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — Familial Mediterranean fever (FMF) is the prototype of the hereditary recurrent (periodic) fevers — a group of monogenic **autoinflammatory** diseases driven by dysregulated *innate* immunity (myeloid effector cells and germline pattern-recognition receptors) rather than by high-titre autoantibodies or antigen-specific T cells. It is characterised by recurrent, self-limited episodes of fever accompanied by **serosal (peritoneal/pleural), synovial or cutaneous inflammation**, and, if untreated, the eventual development of systemic **AA amyloidosis**. It is caused by gain-of-function mutations in the *MEFV* gene encoding **pyrin**, and is exquisitely responsive to lifelong oral colchicine.

Epidemiology and Genetics

- ▶ **Populations:** First recognised among **Armenians, Arabs, Turks, and non-Ashkenazi (North African, Iraqi) Jews**; with genetic testing now documented in Ashkenazi Jews, Italians and other Mediterranean/Middle-Eastern groups, and occasionally in those without known Mediterranean ancestry.
- ▶ **Gene:** *MEFV* on chromosome **16p13.3**; product is a **781-amino-acid, ~95-kDa protein, pyrin** (marennostin), expressed in granulocytes, eosinophils, monocytes, dendritic cells, and synovial/peritoneal fibroblasts.
- ▶ **Inheritance:** Classically **autosomal recessive**, but clear-cut clinical cases occur with only a *single* demonstrable mutation, and certain rare mutations show **dominant** inheritance. Only ~70% of clinically typical patients have two identifiable mutations *in trans* (gain-of-function with a gene-dosage effect).
- ▶ **Carrier frequency** is as high as **1:10** in affected populations — a selective advantage is postulated, with population-genetic evidence implicating **bubonic plague pandemics** in selecting for founder mutations that arose in the Middle East in Biblical times.
- ▶ A positive **family history** is elicited in only ~50% of cases (small families).
- ▶ **Genotype–phenotype:** Most severe disease-associated mutations lie in **exon 10. M694V homozygosity** (especially in non-Ashkenazi Jews) → earlier onset and higher frequency of arthritis, erysipeloid rash and amyloidosis. The **E148Q** variant (exon 2), common in Asian populations, more often raises overall inflammation than causes overt FMF and may increase penetrance of an exon-10 mutation when present *in cis*.

Pathophysiology — the pyrin inflammasome

- ▶ Pyrin's N-terminal 92 amino acids form the **PYRIN domain (PYD)**, a homotypic protein–interaction motif also found in **cryopyrin (NLRP3)**.
- ▶ Via an intermediary adaptor (ASC), pyrin nucleates a macromolecular **pyrin inflammasome** that activates **caspase-1** (IL-1 β –converting enzyme), driving secretion of **IL-1 β and IL-18** and **gasdermin-D–mediated pyroptotic cell death**.

- ▶ Physiologically, bacterial toxins that inactivate **RhoA GTPase** (blocking cytoskeletal assembly) trigger pyrin inflammasome activation as host defence; FMF mutations are **gain-of-function**, lowering the activation threshold and producing sterile, IL-1 β -driven inflammation.
- ▶ (CMDT additionally notes deficiency of a serosal protease that normally inactivates IL-8 and complement C5a, contributing to the neutrophil-rich serositis.)

Clinical features — the acute attack

- ▶ **Onset:** Often in early infancy; **90% have had their first attack by age 20**. In infants, fever (even febrile seizures/hyperpyrexia) may be the sole manifestation.
- ▶ **Duration:** Typical episodes last **24–72 h** (arthritis somewhat longer); frequency varies from every few days to remissions of years. Triggers include physical exertion, emotional stress and menses; pregnancy is often associated with remission.

Site	Manifestation
Fever	Nearly always present; abrupt, high-grade
Abdomen (>90%)	Sterile peritonitis — pain, guarding, rebound, absent bowel sounds, air–fluid levels; neutrophil-rich exudate at laparotomy; <i>ascites rare</i> ; mimics surgical acute abdomen → “needless laparotomy”
Pleura	Unilateral, sharp, stabbing chest pain; exudative neutrophilic effusion; pleural thickening after repeated attacks
Joints	Acute monoarthritis of knee/ankle/hip; large sterile neutrophil-rich effusion <i>without</i> commensurate erythema/warmth; radiographic change rare; chronic hip/knee arthritis (~5% pre-colchicine); chronic sacroiliitis can occur irrespective of HLA-B27
Skin	Erysipelas-like erythema — raised, tender, on dorsum of foot/ankle/lower leg (most often in M694V homozygotes)
Muscle	Exercise-induced (non-febrile) myalgia common; rare protracted febrile myalgia lasting weeks
Other	Acute unilateral scrotal inflammation (prepubertal boys); rare pericarditis; aseptic meningitis (controversial)

- ▶ **Associations:** Increased frequency of IgA vasculitis (**Henoch-Schönlein purpura**) and **polyarteritis nodosa**; the M694V mutation is a risk factor for **Behçet’s syndrome** and **ankylosing spondylitis**.

- ▶ **Laboratory (during attacks):** Elevated ESR, CRP, leukocytosis, thrombocytosis (in children), raised fibrinogen, haptoglobin and immunoglobulins; transient albuminuria/haematuria.

AA (secondary) amyloidosis — the major long-term threat

- ▶ Caused by tissue deposition of a fragment of **serum amyloid A (SAA)**, an acute-phase reactant, in **kidneys, adrenals, intestine, spleen, lung and testes**; the kidney is affected first → nephrotic-range proteinuria and progressive renal failure.
- ▶ **Suspect when proteinuria persists between attacks; confirm by renal or rectal biopsy** (Congo-red apple-green birefringence).
- ▶ **Risk factors:** M694V homozygosity, positive family history (independent of mutation status), SAA1 genotype, male sex, **non-compliance with colchicine/IL-1 inhibitor**, and national origin (amyloid risk parallels infant-mortality rate).
- ▶ Now largely *preventable* with adherent colchicine prophylaxis.

The hereditary recurrent fevers — differentiation (exam table)

Feature	FMF	TRAPS	HIDS / MKD	CAPS (FCAS / MWS / NOMID)
Gene / protein	MEFV / pyrin	TNFRSF1A / p55 TNF receptor	MVK / mevalonate kinase	NLRP3 / cryopyrin
Inheritance	Recessive (or dominant)	Dominant	Recessive	Dominant (NOMID often <i>de novo</i> /mosaic)
Attack length	1–3 days	Often >7 days	3–7 days	Minutes–3 days (NOMID continuous)
Distinctive clue	Erysipeloid erythema; serositis	Migratory myalgia + overlying erythema; periorbital oedema/conjunctivitis	Cervical adenopathy, oral ulcers, palm/sole rash; ↑urinary mevalonate	Cold-induced urticarial rash (FCAS); sensorineural deafness (MWS); aseptic meningitis (NOMID)
Treatment	Colchicine ; IL-1 inhibitors if refractory	Glucocorticoids, IL-1 inhibitors, etanercept	IL-1 inhibitors; NSAIDs for fever	IL-1 inhibitors (anakinra/canakinumab/rilonacept)

(TRAPS = *TNF-receptor-associated periodic syndrome / familial Hibernian fever*; HIDS/MKD = *hyperimmunoglobulinaemia D / mevalonate kinase deficiency*; CAPS = *cryopyrin-associated periodic syndromes*.)

Diagnosis

- ▶ **Largely clinical** in experienced hands; validated clinical criteria sets perform well where pre-test probability is high. Core features: recurrent short (<72 h) febrile serositis episodes in an at-risk ethnic group, family history, and a **therapeutic response to colchicine**.
- ▶ **Genetic testing** (*MEFV* sequencing) is a useful adjunct in ambiguous cases; the expert-curated **Infevers** registry catalogues pathogenic mutations vs benign polymorphisms. Note: a single or no mutation does **not** exclude FMF.
- ▶ **Differential diagnosis**: other hereditary recurrent fevers; **PFAPA** (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis — commonest periodic fever of childhood); systemic-onset JIA / adult Still's disease; porphyria; **hereditary angio-oedema**; inflammatory bowel disease; and gynaecological disorders in women.

Treatment

- ▶ **Daily oral colchicine is first-line** — it reduces attack frequency/severity and **prevents amyloidosis** in compliant patients; intermittent dosing at attack onset is *inferior* and unproven for amyloid prevention.
- ▶ **Adult dose 1.2–1.8 mg/day** (CMDT: 0.6 mg 2–3 times daily): substantial benefit in ~two-thirds, some improvement in >90%; children need lower (non-weight-proportional) doses.
- ▶ **Side effects**: bloating, cramps, **lactose intolerance**, **diarrhoea** — minimised by low starting dose, dose-splitting, simethicone and dairy avoidance. In **renal insufficiency/elderly**, watch for **colchicine myoneuropathy** (proximal weakness, raised CK).
- ▶ **Cautions**: **never give IV colchicine to a patient already on oral colchicine** (fatal toxicity); **cyclosporine** blocks hepatic colchicine excretion via the **MDR1** transporter (toxicity post renal transplant). Colchicine is **continued in pregnancy** (FMF-attack miscarriage risk outweighs fetal risk) though it may marginally raise trisomy-21 risk if taken at conception.
- ▶ **Colchicine-resistant/intolerant disease** → **IL-1 inhibitors**: **canakinumab** (anti-IL-1 β monoclonal, monthly SC; FDA-approved for FMF on phase-3 data), **rilonacept** (IL-1 receptor fusion protein, weekly SC), **anakinra** (recombinant IL-1 receptor antagonist, daily SC; may also reduce established amyloid). Bone-marrow transplantation has an unacceptable risk–benefit ratio.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pyrin inflammasome cascade**: *MEFV* mutation → mutant pyrin (PYD) + adaptor ASC → assembled **pyrin inflammasome** → **caspase-1** activation → **IL-1 β / IL-18** secretion + **gasdermin-D** → **pyroptosis** → recurrent sterile serositis/fever. Side-label the trigger: bacterial toxin → **RhoA GTPase inactivation**. Show colchicine and anti-IL-1 agents (anakinra/canakinumab/rilonacept) as the therapeutic blockade points.

- ▶ “Spot map” of FMF organ involvement: stick-figure with labels — *Serosa* (peritonitis, pleurisy), *Joint* (acute monoarthritis – knee/ankle), *Skin* (erysipeloid erythema – dorsum of foot), *Scrotum* (acute scrotal inflammation), and *Kidney* → AA amyloidosis (proteinuria) as the long-term complication.

Clinical / Diagnostic significance

- ▶ Consider FMF in any patient of Mediterranean/Middle-Eastern origin with **recurrent self-limited fever + serositis** and unexplained acute abdomens — early diagnosis prevents repeated negative laparotomies.
- ▶ **Persistent inter-attack proteinuria mandates work-up for AA amyloidosis** (renal/rectal biopsy); it is the leading cause of morbidity/mortality and is preventable.
- ▶ A **colchicine therapeutic trial** can be diagnostically confirmatory when genetics are equivocal.
- ▶ Lifelong adherence is the single most important determinant of outcome; counsel that colchicine is continued through pregnancy.

High-yield exam pointers

- ▶ *MEFV* gene (16p13.3) → **pyrin** → gain-of-function → over-active **pyrin inflammasome** → IL-1 β .
- ▶ Autosomal **recessive** (mostly); carrier frequency up to **1:10**; **90% present before age 20**.
- ▶ Attack = **24–72 h** of fever + **sterile peritonitis/pleuritis, monoarthritis, erysipeloid erythema**; resolves spontaneously.
- ▶ **M694V homozygote** = severe phenotype → arthritis, rash, **amyloidosis**.
- ▶ Main complication = **AA amyloidosis** (SAA deposition, renal-first, nephrotic proteinuria) — preventable by colchicine.
- ▶ **Colchicine 1.2–1.8 mg/day** is first-line and *amyloid-protective*; **IL-1 inhibitors** (canakinumab/anakinra/rilonacept) for refractory cases.
- ▶ **Never give IV colchicine to a patient on oral colchicine.**
- ▶ Differential: TRAPS, HIDS/MKD, CAPS, PFAPA, adult Still’s, hereditary angio-oedema.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Familial Mediterranean Fever and Other Hereditary Autoinflammatory Diseases” (Kastner); and “Amyloidosis” (AA amyloidosis / SAA, colchicine).
- ▶ **CMDT 2026** — “Gastrointestinal Disorders” (Familial Mediterranean fever; ascites differential) and “Amyloidosis” management note.



Fibromyalgia

Asked in: Paper III Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Fibromyalgia (FM) is characterised by **chronic widespread musculoskeletal pain and tenderness**. Although defined primarily as a *pain syndrome*, patients also commonly report associated **neuropsychological symptoms** — fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression. Available evidence implicates the **central nervous system (CNS)** as key to maintaining the pain and other core symptoms. FM belongs to a group of **chronic primary / chronic overlapping pain conditions** and carries substantial negative consequences for physical and social functioning.

Epidemiology and risk factors

- ▶ **Worldwide prevalence** ~2% — approximately 4% in women and <1% in men; data are similar across world regions and socioeconomic classes.
- ▶ **Sex ratio:** in clinical settings women >> men at ~8:1; in population studies the ratio is closer to 3:1 (subjective criteria applied to populations raise prevalence and shift the sex ratio).
- ▶ Markedly higher in **rheumatic disease** — up to 30% of patients with rheumatoid arthritis or SLE have comorbid FM; FM occurs in ~10–30% of patients with degenerative or inflammatory rheumatic disorders (these act as peripheral pain generators).
- ▶ **Additional risk factors:** sleep disturbances, physical inactivity, and overweight or obesity.

Clinical manifestations

- ▶ **Pain and tenderness:** patients classically report “*pain all over*.” Widespread pain is operationalised as being present **above and below the waist, on both sides of the body, and involving the axial skeleton** (neck, back, or chest). The pain is poorly localised, difficult to ignore, severe, and reduces functional capacity.
- ▶ **Duration:** pain present **most of the day on most days for at least 3 months**.
- ▶ **Evoked pain sensitivity (hyperalgesia/allodynia):** elevated sensitivity may be detected clinically by pain from a **blood-pressure cuff** or **skin-roll tenderness**. Formal **tender-point examination** uses the thumbnail to exert ~4 kg/m² pressure (the amount producing blanching of the thumbnail tip) over defined musculotendinous sites; the older **ACR criteria required 11 of 18 tender points**. Tenderness is a continuous variable, so a strict categorical threshold is not essential.
- ▶ **Peripheral pain generators / triggers:** arthritis, bursitis, tendinitis, neuropathies; more subtle ones include **joint hypermobility** and **scoliosis**. Myalgias may be triggered by infectious, metabolic, or psychiatric conditions.
- ▶ **Neuropsychological symptoms:** fatigue (highly prevalent), stiffness, **non-restorative sleep** (difficulty falling/staying asleep, early-morning awakening, waking unrefreshed; may include

restless legs syndrome, sleep-disordered breathing, frank sleep apnea), and cognitive dysfunction (“fibro-fog” — impaired attention/concentration, word-retrieval difficulty, short-term memory loss with age-appropriate processing speed). Lifetime prevalence of mood disorders approaches 80% — screen for depression by querying depressed mood and anhedonia (depression is neither necessary nor sufficient for diagnosis).

- **Overlapping syndromes (chronic overlapping pain conditions):** myalgic encephalitis/chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes.
- **Psychosocial:** onset and exacerbation often during perceived stress; high prevalence of prior interpersonal violence — consider PTSD.

Diagnostic criteria (2016, after Wolfe et al.)

The newer criteria eliminate tender-point counting and rely on patient-reported widespread pain and symptom burden, using the Widespread Pain Index (WPI, 0–19) and Symptom Severity Score (SSS, 0–12).

Component	Detail
WPI (0–19)	Number of body regions with pain/tenderness over the past week
SSS (0–12)	Fatigue + trouble thinking/remembering + waking unrefreshed (each 0–3); plus abdominal pain/cramps, depression, headache over 6 months (each 0/1)
Threshold	WPI ≥ 7 and SSS ≥ 5 OR WPI 4–6 and SSS ≥ 9
Generalised pain	Pain in ≥ 4 of 5 regions (jaw, chest, and abdomen not counted)
Chronicity	Symptoms present at a similar level for ≥ 3 months

Differential diagnosis and investigations

Because musculoskeletal pain is so common, the differential is broad; inflammatory causes are identifiable by specific history, examination, and laboratory/radiographic tests.

Category	Conditions to exclude
Inflammatory	Polymyalgia rheumatica; inflammatory arthritis (RA, spondyloarthritis); connective tissue disease (SLE, Sjögren’s)
Infectious	Hepatitis C, HIV, Lyme disease, parvovirus B19, Epstein-Barr virus

Category	Conditions to exclude
Non-inflammatory	Degenerative joint/spine/disk disease; myofascial pain syndromes; bursitis, tendinitis, repetitive strain injuries
Endocrine	Hypo-/hyperthyroidism, hyperparathyroidism
Neurologic	Multiple sclerosis, neuropathic pain syndromes
Psychiatric	Major depressive disorder
Drugs	Statins, aromatase inhibitors

- ▶ **Routine labs and radiographs are normal** in uncomplicated FM; testing aims to identify alternative diagnoses, pain generators, or comorbidities.
- ▶ **Routine screen:** ESR or CRP, CBC, TSH.
- ▶ **Guided by history/examination:** complete metabolic panel, ANA, anti-SSA/anti-SSB, rheumatoid factor and anti-CCP, CPK, viral (hepatitis C, HIV) and bacterial (Lyme) serologies, spine/joint radiographs.
- ▶ Use radiography **very sparingly** (only for suspected inflammatory arthritis); **avoid repeat testing**, and particularly **discourage MRI of the spine** unless there are features of inflammatory spine disease or neurologic symptoms.

Pathophysiology and genetics

- ▶ **Polygenic vulnerability** — multiple genes in pathways controlling **pain and stress responses**; notably genes for **metabolism, transport, and receptors of serotonin and other monoamines**, shared with mood disorders and other chronic pain conditions.
- ▶ **Central pain amplification:** psychophysical testing shows **altered sensory afferent pain processing and impaired descending noxious inhibitory control**, producing **hyperalgesia and allodynia**. Functional MRI demonstrates activation of brain pain regions to stimuli that are innocuous in healthy controls.
- ▶ Pain perception is modulated by **emotional and cognitive factors** (catastrophising, perceived loss of control) — the rationale for cognitive-behavioural treatment.
- ▶ Some patients have a **small-fibre neuropathy**; early reports suggest a possible **autoimmune** contribution and altered peripheral-blood gene/metabolic signatures (not yet diagnostic).

Treatment

Optimal management requires prompt diagnosis, assessment of pain/function/psychosocial context, patient education, and a goal of **improved function and quality of life rather than elimination of pain**. Illness behaviours (e.g., frequent visits) are discouraged.

Non-pharmacologic (first-line):

- ▶ **Physical conditioning / aerobic exercise** — the most consistently helpful strategy; begin at low intensity and advance slowly. Physically inactive patients do best with **supervised or water-based** programs; add **strength training** after aerobic goals are met.
- ▶ **FDA-approved devices**: a **laser therapy** device and a **TENS** device — an RCT showed TENS reduces movement-evoked pain and fatigue.
- ▶ **Meditative movement therapies** — qigong, yoga, Tai Chi; also consider acupuncture and hydrotherapy.
- ▶ **Cognitive-behavioural strategies** to improve sleep hygiene and reduce illness behaviour.

Pharmacologic — target afferent or descending pain pathways; use single agents that cover multiple symptom domains.

Drug class	Examples	Best symptom target
Muscle relaxant	Cyclobenzaprine	Pain + sleep disturbance
Sedating tricyclic antidepressant	Amitriptyline	Pain + sleep disturbance
$\alpha 2$ - δ ligands	Gabapentin, Pregabalin	Pain + sleep disturbance
SNRIs	Duloxetine, Milnacipran	Pain + fatigue/anxiety/depression

- ▶ **Treat any comorbid triggering condition.** Glucocorticoids and NSAIDs help inflammatory triggers but are **not effective against FM symptoms**.
- ▶ **Avoid strong opioids** — no demonstrated efficacy and adverse effects worsen both symptoms and function. **Tramadol** (an opioid with mild serotonin-noradrenaline reuptake inhibitor activity) shows some efficacy but is **generally discouraged** because of opioid-related adverse effects.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Body manikin for the Widespread Pain Index** — front-and-back human outline with the 19 WPI sites labelled: right/left jaw, neck, upper back, lower back, chest, right/left shoulder, right/left upper arm, right/left lower arm, right/left hip (buttock), right/left upper leg, right/left lower leg, plus abdomen — and the **5 generalised-pain regions** (Region 1 upper-left, Region 2 upper-right, Region 3 lower-left, Region 4 lower-right, Region 5 axial). Annotate threshold: **WPI ≥ 7 + SSS ≥ 5 OR WPI 4–6 + SSS ≥ 9 ; $\geq 4/5$ regions; ≥ 3 months.**
- ▶ **Schematic of central pain amplification** — labels: *peripheral pain generator* → *increased ascending afferent input* → *impaired descending noxious inhibitory control* → *CNS amplification* → *hyperalgesia & allodynia*, with side-boxes for *genetic/serotonin-monoamine vulnerability* and *stress / catastrophising*.

Clinical / Diagnostic significance

- ▶ FM is a **clinical diagnosis of central sensitisation**, not a diagnosis of exclusion requiring extensive imaging — over-investigation reinforces illness behaviour.
- ▶ **Recognise FM superimposed on rheumatic disease (RA, SLE)**: when pain extends beyond what the inflammatory disease explains, with neuropsychological symptoms and diffuse tenderness, treat **central pain** rather than escalating anti-inflammatory therapy.
- ▶ **Screen for and treat mood disorders, non-restorative sleep, and sleep apnea** — they drive disability and respond to dual-action agents.
- ▶ A **multimodal plan (education + exercise + a single rationally chosen drug + CBT)** outperforms drug monotherapy and is the examiner-favoured management answer.

High-yield exam pointers

- ▶ FM = **chronic widespread pain + tenderness ≥ 3 months**, with fatigue, unrefreshing sleep, cognitive (“fibro-fog”), anxiety/depression; a **CNS central-sensitisation disorder**.
- ▶ Prevalence $\sim 2\%$ ($\approx 4\%$ women, $< 1\%$ men); clinical F:M $\sim 8:1$; up to **30%** comorbidity with RA/SLE.
- ▶ **2016 criteria** use **WPI (0–19) + SSS (0–12)**; **tender points (11/18, 4 kg/m²)** are the **OLD ACR criteria**.
- ▶ Mechanism: **impaired descending inhibition + augmented afferent processing** $\rightarrow$ **hyperalgesia and allodynia**; serotonin/monoamine genes; some have **small-fibre neuropathy**.
- ▶ **Routine labs normal**; order ESR/CRP, CBC, TSH; avoid repeat testing and spine MRI.
- ▶ First-line is **non-pharmacologic** — **aerobic exercise is the single most helpful intervention**; TENS and a laser device are FDA-approved.
- ▶ Effective drugs: **pregabalin/gabapentin, duloxetine/milnacipran, amitriptyline, cyclobenzaprine**.
- ▶ **Avoid strong opioids; tramadol discouraged; glucocorticoids/NSAIDs ineffective for FM pain**.

SOURCE & COVERAGE

Harrison 22e — Ch 385 “Fibromyalgia” (L.J. Crofford). 2016 diagnostic criteria per Fig. 385-1 (Wolfe et al., *Semin Arthritis Rheum* 2016); differential diagnosis from Table 385-1; investigations from Table 385-2; drug classes from Table 385-3.

Coverage note: The plain-text extract reproduces the *names/classes* of effective drugs (Table 385-3) but not their **doses**; specific milligram regimens (e.g., pregabalin 300–450 mg/day, duloxetine 60 mg/day, milnacipran 50 mg BID, low-dose amitriptyline at night) and the statement that **pregabalin, duloxetine and milnacipran are the three FDA-approved agents for FM** are standard, universally accepted internal medicine added for completeness and are not verbatim in the provided chapter text. The WPI/SSS scoring breakdown is drawn from Fig. 385-1.



Gout

Asked in: Paper III Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Gout is a hyperuricemic metabolic disorder typically manifesting as **episodic inflammatory arthritis** with disabling pain, most often in middle-aged to elderly men and postmenopausal women. It arises from an **increased body pool of urate** due to chronic hyperuricemia, leading to supersaturation and crystallisation of **monosodium urate (MSU)** within joints and connective tissue, with subsequent inflammatory reactions to the crystals. Although chronic hyperuricemia is a prerequisite, only a minority of hyperuricemic individuals develop gout; additional pathophysiologic factors govern crystallisation and the inflammatory response. Humans are the only mammals to develop gout spontaneously, owing to evolutionary species-wide **loss of uricase** (which converts urate to highly soluble allantoin).

Urate metabolism and pathogenesis

- ▶ At physiologic pH, uric acid exists largely as **urate**, its ionised form, reflecting its weak acidity (**pKa 5.8**). Systemic urate reflects a balance of dietary intake, endogenous synthesis, and excretion.
- ▶ Supersaturation threshold: serum urate **>~6.85 mg/dL** favours MSU crystallisation, crystal growth, and tissue deposition.
- ▶ **Overproduction vs under-excretion** — hyperuricemia arises predominantly from **impaired renal urate excretion (90%)** or, less commonly, **overproduction (10%)**, with many cases involving both.
- ▶ **Renal handling**: ~two-thirds of daily urate is eliminated renally, one-third via the GI tract. In the proximal tubule, apical reabsorption is **sodium-dependent** via **URAT1** and **OAT10**; basolateral efflux is via the **GLUT9** transporter (the target of anti-uricosurics like *pyrazinoate (PZA)* and *nicotinate*). Intestinal urate efflux occurs through **ABCG2**, followed by degradation by gut bacteria (**intestinal uricolysis**).
- ▶ **Crystal-induced inflammation**: triggered crystal shedding from synovial tophi → phagocytosis of MSU by neutrophils; activation of resident synovial macrophages, mast cells, and the **NLRP3 inflammasome** → generation of **pro-IL-1 / IL-1β**, plus IL-6, IL-8, and TNF-α. Neutrophils mount a **respiratory burst** releasing lysosomal enzymes, superoxide anion, **leukotriene B4**, and IL-1.
- ▶ Untreated, gout progresses to **chronic gouty arthritis** with low-grade persistent synovitis, erosive deformities, and **tophi** (MSU deposits surrounded by granulomatous inflammation in proteoglycan-rich joints and tendons).

Etiology / classification of hyperuricemia

Mechanism	Causes (per Harrison)
Under-excretion (~90%)	Idiopathic; CKD/renal insufficiency; diuretics (thiazide, loop); low-dose aspirin; insulin-resistance syndrome
Overproduction (~10%)	Increased cell turnover with purine salvage — hematologic malignancies, psoriasis; chemotherapy; tissue hypoxia
Inherited metabolic (subset of overproduction)	PRPP synthetase superactivity (X-linked) → ↑PRPP, purine nucleotides, urate; HPRT deficiency — <i>Lesch-Nyhan syndrome</i> and variants (X-linked)

- ▶ **PRPP synthetase overactivity**: accelerated production of PRPP, purine nucleotides, and urate → gout and urate nephrolithiasis.
- ▶ **HPRT deficiency**: hypoxanthine cannot be recycled and is converted exclusively to urate; reduced IMP/GMP further drives hyperuricemia via loss of feedback inhibition of de-novo purine synthesis. The HPRT gene is on the **X chromosome** (>250 described mutations); homozygous males are affected, carrier (esp. postmenopausal) females may develop gout/stones.
Hyperuricemia in prepubertal boys should prompt consideration of these enzyme defects.
- ▶ **Modifiable risk factors**: obesity, Western diet, alcohol, fructose-rich foods/beverages, sedentary lifestyle, and diuretics.
- ▶ **Comorbidity cluster** (part of the insulin-resistance syndrome): obesity, hypertension, type 2 diabetes, myocardial infarction, stroke, CKD, and urate nephrolithiasis.

Clinical manifestations and stages

- ▶ **Acute gout flare**: usually **monoarticular** initially. The **1st metatarsophalangeal joint (podagra)** is involved in **70–90%** of cases, followed by tarsal joints, ankles, and knees; finger/wrist/elbow involvement is later (elderly, advanced disease). Oligo- and polyarticular flares develop over time.
- ▶ Flares characteristically begin at **night to early morning** and are among the most painful human conditions: the joint becomes warm, red, tender, and swollen, often mimicking cellulitis (**pseudocellulitis**). Untreated flares subside spontaneously within **1–2 weeks**.
- ▶ **Intercritical gout**: symptom-free intervals of varying length between flares.
- ▶ **Triggers**: purine-rich food, alcohol, diuretic use, **initiation of urate-lowering therapy (ULT)**, local trauma, and medical illness (congestive heart failure, respiratory/hypoxic conditions).
- ▶ **Chronic gouty arthritis** (after years of untreated flares): ongoing synovitis, **subcutaneous tophi**, deformity, and bony destruction; rarely gout manifests only as tophi or only as chronic arthritis.
- ▶ **Women** account for only **5–20%** of gout patients — usually postmenopausal/elderly, often with OA, hypertension, mild renal insufficiency, and diuretic use; premenopausal gout is rare.

Diagnosis

- ▶ **Definitive** = needle aspiration of joint or tophus with **polarising light microscopy**: MSU crystals are **needle/rod-shaped**, seen both intracellularly and extracellularly during flares, showing **strong negative birefringence** under compensated polarised light.
- ▶ **Synovial fluid**: cloudy/inflammatory with leukocytes typically **5000–75,000/μL**; may be thick, pasty, chalky. Always **Gram-stain and culture** to exclude septic arthritis, which can coexist with crystals. MSU crystals are demonstrable in the 1st MTP and clinically quiet knees, so **inter-critical arthrocentesis** is diagnostically useful.
- ▶ **Serum urate**: can be normal or low *during* an acute flare (inflammatory cytokines, e.g. IL-6, are uricosuric and lower urate ~2 mg/dL) — so seek **historical or post-flare** values; urate is almost always elevated at some point. Baseline workup: serum creatinine, LFTs, hemoglobin, WBC, HbA1c, and serum lipids (comorbidity screen and treatment monitoring).
- ▶ **Imaging**: musculoskeletal ultrasound shows the **double-contour sign** over articular cartilage (MSU deposition); **dual-energy CT** identifies MSU by chemical composition. Plain radiographs in advanced tophaceous gout show **cystic changes, well-defined erosions with sclerotic margins and overhanging bony edges**, and soft-tissue masses (absent in early disease).

Management

A. Acute flare — mainstay is early anti-inflammatory therapy (ice and rest are adjuncts); choice depends on comorbidities, concurrent drugs, and prior response.

Drug	Regimen (per Harrison)	Key caution
Colchicine	Low-dose: 1.2 mg at first sign, then 0.6 mg in 1 h, with subsequent-day dosing by response	Eliminated via P-glycoprotein (MDR1) and CYP3A4; reduce dose in renal disease, hepatorenal impairment, or with inhibitors (<i>clarithromycin, tacrolimus</i>)
NSAIDs	Indomethacin 25–50 mg tid; naproxen 500 mg bid; ibuprofen 800 mg tid; celecoxib 800 mg then 400 mg at 12 h, then 400 mg bid	Avoid in significant comorbidity (renal/GI/cardiac)
Glucocorticoids	Prednisone 30–50 mg/d initial, tapered; IM injection; intra-articular for one/few joints	Effective even in polyarticular gout
IL-1β blockade	Anakinra or canakinumab	When other options contraindicated or failed

B. Urate-lowering therapy (ULT) — corrects the central cause (chronic hyperuricemia); usually lifelong. **Target serum urate <5–6 mg/dL (300–360 μmol/L)**, a sub-saturation point, to prevent flares and dissolve tophi.

- **Indications:** ≥ 2 flares/year, severe/prolonged flares, or patient commitment; *always* if subcutaneous tophi, chronic gouty arthritis, or known uric-acid nephrolithiasis.
- **Allopurinol** (xanthine oxidase inhibitor) — **first-line**; single morning dose starting **100 mg/day or less**, titrating up to **800 mg/day**. In CKD start lower (e.g. **50 mg/day** if $\text{eGFR} < 30 \text{ mL/min}$) and titrate slowly. Risk of SCARs (**Stevens-Johnson syndrome, toxic epidermal necrolysis**) — risk factors are CKD, higher initial dose, and **HLA-B5801* carriage. **Screen for HLA-B5801*** before starting in Southeast Asian (except Japanese descent), Pacific Islander/Native Hawaiian, and Black patients; if positive, use an alternative agent. Mild cutaneous reactions in $\sim 2\%$.
- **Febuxostat** (xanthine oxidase inhibitor) — hepatic metabolism (glucuronidation/oxidation), **no dose adjustment in moderate–severe CKD**; usable in HLA-B*5801 carriers.
- **Uricosurics** — **probenecid** (second-line): 250 mg bid up to 3 g/day; needs good renal function (ineffective if creatinine $> 2 \text{ mg/dL}$ [$177 \mu\text{mol/L}$]). *Benzbromarone* (not in the US) is more effective in CKD.
- **Pegloticase** — pegylated uricase for refractory/intolerant patients; given with **methotrexate** to reduce immunogenicity (which causes loss of efficacy and infusion reactions).
- **Comorbidity drugs that also lower urate:** losartan, amlodipine, fenofibrate, and SGLT2 inhibitors (added cardiometabolic-renal benefit).
- **Flare prophylaxis at ULT initiation:** do not start ULT during an active flare; begin in the resolution phase with **colchicine 0.6 mg once–twice daily** or **naproxen 250 mg bid**, continued until normouricemic and flare-free for **3–6 months** or tophi resolve. Rapid urate lowering shedding MSU from tophi causes paradoxical flares.

Differential — Pseudogout (CPPD) vs Gout

Feature	Gout (MSU)	Pseudogout / CPPD
Crystal	Needle/rod-shaped, strongly negatively birefringent	Rhomboid/rod-shaped, weakly positively or non-birefringent
Typical joint	1st MTP (podagra), tarsus, ankle, knee	Knee (commonest), then wrist; podagra rarely
Radiograph clue	Erosions with overhanging edges, tophi	Chondrocalcinosis (linear/punctate cartilage calcification)
Key associations	Insulin-resistance syndrome, CKD, diuretics	Aging, OA, hyperparathyroidism , hemochromatosis , hypophosphatasia , hypomagnesemia ; <i>ANKH</i> gene

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Feature	Gout (MSU)	Pseudogout / CPPD
	▶ Pathogenesis-and-targets schematic (Fig. 384-1): boxes/arrows — <i>Risk factors</i> (obesity/insulin resistance, diet/alcohol, genes, diuretics & low-dose aspirin) → Chronic hyperuricemia / increased urate pool → $SU > \sim 6.85 \text{ mg/dL}$ → MSU crystallisation, crystal growth, tissue deposition → Recurrent acute crystal-induced flares → Chronic gouty arthritis (tophi). Annotate two therapeutic targets: Urate-lowering therapy (allopurinol, febuxostat, probenecid, uricase; target $< 5\text{--}6 \text{ mg/dL}$) acting on the urate pool, and Anti-inflammatory therapy (NSAIDs, colchicine, glucocorticoids) acting on the flare. Labels: <i>Risk factors, Chronic hyperuricemia, MSU crystallisation/deposition, Acute flare, Chronic tophaceous gout, ULT target $< 5\text{--}6 \text{ mg/dL}$, Anti-inflammatory therapy.</i> ▶ MSU crystal under compensated polarised light: draw needle-shaped crystal inside a neutrophil; label <i>intracellular MSU crystal, needle-shaped, strongly negative birefringence, leukocyte 5000–75,000/μL.</i>	

Clinical / Diagnostic significance

- ▶ Crystal-proven diagnosis (synovial fluid microscopy) is the gold standard and simultaneously **excludes septic arthritis**, which may coexist — never assume crystals exclude infection.
- ▶ Serum urate is unreliable *during* a flare; use historical/post-flare values for diagnosis and as the **ULT target** ($< 5\text{--}6 \text{ mg/dL}$).
- ▶ Treat-to-target ULT dissolves tophi and prevents flares but must be paired with **flare prophylaxis** and started outside active flares.
- ▶ Gout is a marker of **cardiometabolic-renal disease** — screen for and manage obesity, hypertension, diabetes, dyslipidemia, and CKD; favour agents with dual benefit (losartan, fenofibrate, SGLT2i).
- ▶ **HLA-B5801 pharmacogenomic screening*** before allopurinol in high-risk ethnicities prevents life-threatening SCARs.

High-yield exam pointers

- ▶ Hyperuricemia = **90% under-excretion, 10% overproduction**; supersaturation threshold $\sim 6.85 \text{ mg/dL}$; urate pKa 5.8.
- ▶ Renal transporters: reabsorption via **URAT1/OAT10** (apical, Na-dependent), efflux via **GLUT9**; gut efflux via **ABCG2**.
- ▶ **NLRP3 inflammasome** → **IL-1 β** drives the acute flare (rationale for anakinra/canakinumab).
- ▶ **Podagra (1st MTP)** in **70–90%**; flares nocturnal, self-limited in **1–2 weeks**; intercritical periods between attacks.

- ▶ Crystals: **needle-shaped, strongly negatively birefringent**, intra- and extracellular; synovial WBC 5000–75,000/ μ L.
- ▶ **Allopurinol first-line** (start 100 mg/d, up to 800 mg/d; 50 mg/d if eGFR <30); **febuxostat** safe in CKD and HLA-B*5801 carriers.
- ▶ Lesch-Nyhan = **HPRT deficiency** (X-linked); **PRPP synthetase superactivity** = X-linked overproduction.
- ▶ ULT prophylaxis: **colchicine 0.6 mg od–bid** continued until urate-normal and flare-free 3–6 months / tophi resolve.
- ▶ **Pseudogout** = CPPD, knee, weakly positive birefringence, chondrocalcinosis; check Ca/PO4/Mg/iron in patients <50 y.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 384 "Gout and Other Crystal-Associated Arthropathies" (Hyon K. Choi). Coverage note: All specifics above (drug doses, transporters, crystal morphology, HLA-B*5801, targets) are taken from this chapter; the gout topic is fully covered. The CPPD/pseudogout differential is drawn from the same chapter as supporting context for the differential diagnosis.



Granulomatosis with Polyangiitis (Wegener's Granulomatosis)

Asked in: Paper III Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Granulomatosis with polyangiitis (GPA, formerly *Wegener's granulomatosis*) is a distinct clinicopathologic entity characterised by **necrotising granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis**, with variable disseminated small-vessel vasculitis involving both small arteries and veins. It is one of the three **antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides** (with microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis) and is strongly linked to **cytoplasmic ANCA against proteinase-3 (PR3-ANCA/c-ANCA)**. Untreated generalised disease is almost uniformly fatal within ~1 year.

Epidemiology & nosology

- ▶ **Prevalence ~3 per 100,000** (Harrison); estimated incidence ~12 cases per million per year (CMDT). Extremely rare in Black compared with White patients.
- ▶ **Male : female = 1:1**; mean age of onset **40–60 years** (4th–5th decade), but ~15% of patients are <19 years; onset before adolescence is rare.

- ▶ Belongs to the **ANCA-associated vasculitides (AAV)** — small-vessel vasculitis group. Distinguished from microscopic polyangiitis by **granulomatous inflammation and upper-airway/pulmonary-nodular disease**.
- ▶ Classification frameworks: the **1992/2012 Chapel Hill Consensus Conference nomenclature** (renamed Wegener's → GPA) and the **2022 ACR/EULAR classification criteria (DCVAS)** used to classify, not diagnose.

Pathology & pathogenesis

- ▶ **Histopathologic triad of hallmarks:** (1) **necrotising vasculitis** of small arteries and veins; (2) **granuloma formation** (intra- or extravascular) — palisading histiocytes and giant cells around *geographic necrosis*; (3) **pauci-immune crescentic glomerulonephritis**.
- ▶ **Renal lesion:** earliest is a focal, segmental glomerulitis evolving into **rapidly progressive crescentic GN**; immunofluorescence shows scant immunoglobulin/complement — *pauci-immune* — differentiating it from immune-complex and anti-GBM disease. Granulomas are *rarely* seen on renal biopsy.
- ▶ **Lung:** multiple, bilateral, nodular or **cavitary** infiltrates; biopsy reveals necrotising granulomatous vasculitis (highest diagnostic yield, ideally thorascopic).
- ▶ **Immunopathogenesis:** aberrant **TH1-type** cell-mediated response ($\uparrow$ IFN- γ , $\uparrow$ TNF- α , $\uparrow$ IL-12) to an airway antigen; suggested role of **ANCA** — when neutrophils/monocytes are primed by TNF- α /IL-1, PR3 and myeloperoxidase translocate to the cell surface, bind circulating ANCA, and trigger **degranulation, reactive-oxygen-species release, and endothelial injury**. Chronic nasal carriage of *Staphylococcus aureus* is associated with higher relapse rates (causal role unproven).

ANCA serology

Feature	c-ANCA (PR3-ANCA)	p-ANCA (MPO-ANCA)
Antigen	Proteinase-3 (29-kDa serine proteinase, azurophilic granule)	Myeloperoxidase
Immunofluorescence	Diffuse granular cytoplasmic staining	Perinuclear staining
Association in GPA	>90% of active GPA ; specificity >90%	~10–25% of classic GPA
Caveats	Sensitivity falls to ~60–70% in inactive disease; up to 20% of GPA are ANCA-negative ("limited"/sinonasal disease)	Predominant in microscopic polyangiitis & EGPA

- ▶ Positive immunofluorescence should be **confirmed by antigen-specific enzyme immunoassay** for anti-PR3 or anti-MPO.

- ▶ **ANCA titres correlate poorly with disease activity** — a rising titre alone is *not* a harbinger of relapse (only ~43% relapse within 1 year of an ANCA rise) and should **not** by itself trigger escalation of immunosuppression.

Clinical manifestations (frequencies through disease course)

- ▶ **Upper airway (~95%)**: paranasal sinus pain/drainage, purulent or bloody nasal discharge, nasal mucosal ulceration → nasal septal perforation → ***saddle-nose deformity**; *serous otitis media (eustachian blockage)*; *subglottic stenosis (~16%)** causing airway obstruction.
- ▶ **Lung (85–90%)**: cough, haemoptysis, dyspnoea, pleuritic pain; up to 30% asymptomatic; endobronchial disease with atelectasis; **diffuse alveolar haemorrhage** (severe).
- ▶ **Renal (~77%)**: glomerulitis with proteinuria, haematuria, **red-cell casts** → rapidly progressive renal failure if untreated; dominates prognosis.
- ▶ **Eye (~52%)**: conjunctivitis, episcleritis, **scleritis**, granulomatous sclerouveitis, **retro-orbital mass** → **proptosis** (orbital pseudotumour).
- ▶ **Skin (~46%)**: palpable purpura, papules, vesicles, ulcers, subcutaneous nodules.
- ▶ **Nervous system (~23%)**: **mononeuritis multiplex**, cranial neuritis; rarely cerebral vasculitis/granuloma.
- ▶ **Cardiac (~8%)**: pericarditis, coronary vasculitis, rarely cardiomyopathy.
- ▶ **Constitutional**: fever, malaise, arthralgia, anorexia, weight loss; **migratory oligoarthritis** of large joints. *Newly acquired hypertension is rare* (unlike PAN). Increased risk of **venous thromboembolism (DVT/PE)**.

Investigations & diagnosis

- ▶ **Labs**: elevated ESR/CRP, normochromic anaemia, leukocytosis, mild hypergammaglobulinaemia, thrombocytosis (acute-phase); urinalysis with dysmorphic RBCs and **red-cell casts**.
- ▶ **ANCA (PR3/c-ANCA)**: predictive value ~90% with active glomerulonephritis, but only 30–60% with isolated sinus/lung disease — so biopsy is needed there to exclude infection/malignancy.
- ▶ **Imaging**: chest CT (more sensitive than CXR) — bilateral nodules, masses, **cavitation**, infiltrates; extensive sinusitis with bony erosion.
- ▶ **Tissue biopsy is the diagnostic gold standard**: necrotising granulomatous vasculitis. **Lung** offers highest yield; **renal** biopsy confirms pauci-immune GN; **nasal** biopsy often shows only inflammation.
- ▶ **Differential diagnosis**: microscopic polyangiitis, EGPA, anti-GBM (Goodpasture) disease, SLE, relapsing polychondritis, **cocaine/levamisole-induced midline destruction** (anti-elastase ANCA, granulocytopenia, facial skin erosion), extranodal NK/T-cell lymphoma (nasal type),

lymphomatoid granulomatosis, infections (histoplasmosis, endocarditis, rhinoscleroma, mucocutaneous leishmaniasis). *Midline lesions in GPA are never irradiated.*

Treatment (induction → maintenance, severity-stratified)

- ▶ **Principle:** two phases — **induction** of remission, then **maintenance**. *Severe* = organ/life-threatening (active GN is *always* severe even with normal creatinine; alveolar haemorrhage); *non-severe* = no immediate organ threat.
- ▶ **Glucocorticoids:** historically prednisone 1 mg/kg/day then taper; reduced-dose regimens are **non-inferior with fewer serious infections**; IV methylprednisolone 1000 mg/day × 3 days for fulminant/life-threatening disease.

Setting	Induction	Maintenance
Severe disease	Rituximab 375 mg/m ² weekly × 4 or cyclophosphamide (oral 2 mg/kg/day; or IV 15 mg/kg q2wk × 3, then q3wk) + glucocorticoids ± avacopan	Rituximab (e.g. 500 mg × 2 then 500 mg q6mo, or 1000 mg q4mo), azathioprine 2 mg/kg/day, methotrexate 20–25 mg/week, or mycophenolate mofetil — usually ≥2 years
Non-severe disease	Methotrexate (15 → 20–25 mg/week) or mycophenolate mofetil + glucocorticoids; rituximab optional	Same agent continued

- ▶ **Avacopan** — oral C5a-receptor inhibitor; FDA-approved add-on; achieved higher sustained remission than prednisone and allows rapid steroid withdrawal.
- ▶ **Cyclophosphamide** is renally cleared (dose-reduce in renal impairment); stop at **3–6 months** and switch to a maintenance agent; bladder toxicity and infertility risk (rituximab avoids these).
- ▶ **Plasma exchange (PLEX):** PEXIVAS showed **no benefit** for the composite of ESRD/death — *not routine*; reserve for **co-existing anti-GBM antibody** (and possibly severe creatinine >5.7 mg/dL or fulminant pulmonary haemorrhage). When used with rituximab, separate by ≥48 h.
- ▶ **Infection prophylaxis:** trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* with cyclophosphamide/rituximab; TMP-SMX may help isolated sinonasal disease but **never as sole therapy** for multiorgan GPA. **Subglottic stenosis** responds to mechanical dilation + intralesional glucocorticoid, not systemic immunosuppression alone.
- ▶ **Avoid:** etanercept (no benefit, increased solid tumours), belimumab and abatacept (no benefit on relapse).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **“Organ map of GPA”** — head-to-kidney schematic with labels: *Sinusitis, Nasal septal perforation, Saddle-nose deformity, Subglottic stenosis, Serous otitis media, Scleritis/episcleritis/proptosis, Bilateral cavitary lung nodules, Diffuse alveolar haemorrhage /*

pulmonary capillaritis, Pauci-immune crescentic glomerulonephritis (RBC casts), Palpable purpura, Mononeuritis multiplex.

- ▶ **ANCA immunofluorescence panel** — two neutrophils: left labelled *c*-ANCA — *diffuse granular cytoplasmic staining* = anti-PR3; right labelled *p*-ANCA — *perinuclear staining* = anti-MPO. Inset: *necrotising granulomatous vasculitis* — *geographic necrosis with palisading histiocytes and giant cells.*

Clinical / Diagnostic significance

- ▶ GPA is a leading cause of the **pulmonary–renal syndrome** (alongside microscopic polyangiitis, anti-GBM disease, SLE) — recognise haemoptysis + active urinary sediment as an emergency.
- ▶ **Renal involvement dominates prognosis**; early induction prevents irreversible crescentic GN and dialysis dependence.
- ▶ Treatment transformed survival: cyclophosphamide-based regimens give **>90% marked improvement**, **~75% complete remission**, **>80% 5-year survival**; but **50–70% relapse**, leaving residual damage (renal insufficiency, hearing loss, subglottic stenosis, saddle-nose, chronic sinus disease).
- ▶ A positive PR3-ANCA in a patient with sinusitis + lung nodules + microscopic haematuria is highly suggestive, but **tissue biopsy remains confirmatory**, especially in ANCA-negative or atypical cases.
- ▶ Successful **renal transplantation** is possible after remission in those who reached ESRD.

High-yield exam pointers

- ▶ **Classic triad**: upper airway + lower respiratory tract + glomerulonephritis.
- ▶ PR3-ANCA / *c*-ANCA in >90% of active GPA; antigen = **proteinase-3 (29 kDa)**; up to 20% ANCA-negative.
- ▶ **Pauci-immune crescentic GN** = renal hallmark; **necrotising granulomatous vasculitis** = histologic hallmark.
- ▶ **Saddle-nose deformity, subglottic stenosis (~16%), bilateral cavitary lung nodules** are signature lesions.
- ▶ **Lung biopsy = highest diagnostic yield**; ANCA titre does not track activity.
- ▶ **Induction**: rituximab *or* cyclophosphamide + glucocorticoids ± **avacopan (C5a-receptor inhibitor)**; **PLEX not routine** (PEXIVAS).
- ▶ **Maintenance**: rituximab / azathioprine / methotrexate ≥2 years; **TMP-SMX for PCP prophylaxis**.
- ▶ *Newly acquired hypertension favours PAN, not GPA*; GPA carries increased VTE risk.
- ▶ **Mimics to exclude**: cocaine/levamisole midline destruction, nasal NK/T-cell lymphoma.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “The Vasculitis Syndromes” (GPA definition, epidemiology, pathology/pathogenesis, ANCA biology, NIH clinical-manifestation frequencies, diagnosis, and detailed induction/maintenance regimens including avacopan and PEXIVAS).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic, & Allergic Disorders” (current ACR/Vasculitis Foundation and EULAR 2022 management approach, PR3/MPO-ANCA testing, PCP prophylaxis, saddle-nose and subglottic findings).
- ▶ *Coverage note:* the spec lists no dedicated rheumatology subspecialty textbook for this topic, so depth is drawn from Harrison 22e supplemented by CMDT 2026; both are cited above. The **2022 ACR/EULAR classification criteria** are named in CMDT but item-level point weights are not reproduced in the corpus, so they are referenced by name only and not fabricated.

**IgG4-Related Disease**

Asked in: Paper III Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — IgG4-related disease (IgG4-RD) is a chronic, immune-mediated **fibroinflammatory** condition characterised by a tendency to form **tumefactive (mass-like) lesions** that mimic malignancy, lymphoma, or infection. It can affect virtually any organ, shows the **same distinctive histopathology at every site**, and has a particular tropism for blood vessels of any calibre—so it is now regarded as a **variable-vessel vasculitis**. It unifies many conditions formerly considered organ-specific entities (e.g. lymphoplasmacytic sclerosing pancreatitis → type 1 autoimmune pancreatitis; Mikulicz's disease; Riedel's thyroiditis). Diagnosis rests on **careful correlation of clinical, serologic, radiologic and pathologic findings**—pathology alone is never sufficient.

Epidemiology

- ▶ Typically a **middle-aged to elderly man** — a sharp contrast to most classic autoimmune diseases, which favour young women.
- ▶ **Male predominance ~2:1** (CMDT: ~75% of patients are men, usually >50 years); male predominance is even more striking for internal-organ disease (pancreas, kidney, retroperitoneum), whereas head-and-neck disease (orbits, lacrimal, salivary glands) is closer to 1:1.
- ▶ Male patients are ~5 years older at diagnosis and have **higher serologic activity** (higher IgG4, hypocomplementaemia).

- Presentation is usually **subacute**; fever and high CRP are usually absent. Substantial weight loss can occur (exocrine pancreatic failure → maldigestion; endocrine failure → diabetes mellitus).

Pathology and pathophysiology

The histopathology is **consistent across all organs** and forms the diagnostic backbone:

Hallmark	Description
Dense lymphoplasmacytic infiltrate	B and T lymphocytes; B cells in germinal centres , with CD19/CD138/IgG4+ plasma cells radiating outward; CD4+ T cells most abundant and diffuse
Storiform fibrosis	“Woven mat / basket-weave” pattern (Latin <i>storea</i> = woven mat)
Obliterative phlebitis	Inflammatory obliteration of veins — vascular tropism is a hallmark; obliterative <i>arteritis</i> also seen, especially in lung
Mild–moderate tissue eosinophilia	Variable; some biopsies eosinophil-rich

- **Against the diagnosis** (atypical features): intense **neutrophilic** infiltration, leukocytoclasia, **granulomatous inflammation**, **multinucleated giant cells**, and **fibrinoid necrosis**.
- **Immunohistochemistry** is essential: IgG4+ plasma cells predominate; quantify by **IgG4+ cells/high-power field** *and* the **IgG4+/IgG+ plasma-cell ratio**. In late fibrotic (acellular) phases, the ratio and the fibrosis pattern matter more than absolute cell counts.
- **Pathophysiology** — despite the name, the IgG4 molecule is *not* the primary driver:
 - IgG4 undergoes **Fab-arm exchange** (half-molecules swap), binds antigen weakly, and has **low affinity for Fcγ receptors and C1q** → it is essentially **non-inflammatory** (poor complement fixation, ADCC, phagocyte activation). IgG4 may even be a **counter-regulatory** response.
 - A unique **CD4+ cytotoxic T lymphocyte (CD4+ CTL)**, oligoclonally expanded at tissue sites, is the proposed **major disease driver** — it secretes IFN-γ, TGF-β, IL-1 (driving storiform fibrosis) and **perforin, granzyme A/B, granulysin** (cytotoxicity).
 - **Oligoclonal plasmablast expansions** circulate in blood; continuous **B-cell/plasmablast antigen presentation** sustains the CD4+ CTLs — explaining why **B-cell depletion** is therapeutic.

Organ manifestations (key clinical syndromes)

Organ / region	Characteristic presentation
Pancreas	Type 1 autoimmune pancreatitis — obstructive painless jaundice, mass mimicking adenocarcinoma; “ sausage-shaped pancreas ” (diffuse enlargement, loss of lobularity), rim of hypoattenuation, irregular

Organ / region	Characteristic presentation
	main-duct narrowing; 20–50% with new glucose intolerance
Biliary tree / liver	IgG4-related sclerosing cholangitis — mimics primary sclerosing cholangitis & cholangiocarcinoma ; obstructive jaundice; can progress to hepatic failure within months
Salivary glands	Bilateral submandibular/parotid enlargement (Mikulicz's disease); chronic sclerosing sialadenitis
Orbit / periorbital	Painless lid/periorcular swelling, orbital pseudotumor , dacryoadenitis, orbital myositis (enlarged extraocular muscles); proptosis
Retroperitoneum	Retroperitoneal fibrosis — periaortic inflammation extending to iliac vessels; ureteric entrapment → hydronephrosis , post-obstructive uropathy, renal atrophy
Kidney	Tubulointerstitial nephritis (multiple/bilateral tumoral lesions; strong link with hypocomplementaemia); membranous glomerulonephropathy in a minority
Aorta / vessels	Lymphoplasmacytic aortitis , periaortitis, inflammatory aneurysm, dissection ; coronary arteritis (wall thickening, periarterial encasement, stenosis, aneurysm)
Lung	Inflammatory pseudotumor, paravertebral mass, central-airway disease, interstitial pneumonia, pleural thickening/effusion
Thyroid	Riedel's thyroiditis ; fibrosing variant of Hashimoto's
Meninges / pituitary	Hypertrophic pachymeningitis (dural thickening/enhancement, cranial neuropathies); hypophysitis → anterior hypopituitarism and/or central diabetes insipidus, thickened stalk
Lymph nodes	Generalised or localised lymphadenopathy (1–2 cm, non-tender); may be indolent for years

- Two unifying clinical themes: **allergic phenomena** (atopy, asthma, eczema, nasal polyps, sinusitis, peripheral eosinophilia) and **tumefactive pseudotumors** that mimic cancer.
- Multiorgan disease may be present at diagnosis or evolve over months–years; subclinical involvement of other organs is common.

Serology and diagnosis

- ▶ **Serum IgG4 is elevated in the majority** but ~30% have normal levels despite classic histology (these tend to have fewer organs involved; e.g. retroperitoneal fibrosis often has normal IgG4 because disease is already fibrotic). Elevation can reach **30–40× the upper limit of normal** in multi-organ disease.
- ▶ Serum IgG4 alone is **not** a reliable diagnostic or activity marker: levels fall with therapy but often do not normalise; remissions occur with persistently high IgG4, and relapses occur with normal IgG4. **Steadily rising IgG4 after a response** flags impending flare.
- ▶ **Prozone effect** — very high IgG4 can give a **falsely low** nephelometry result; correct by **serial dilution** of serum. Missing this is dangerous (these patients are at highest risk of multi-organ injury).
- ▶ **Histopathology cut-offs (standard reference values)**: consensus generally requires >40% IgG4+/IgG+ ratio plus organ-dependent IgG4+ cell counts (e.g. >10/HPF) together with storiform fibrosis and obliterative phlebitis.
- ▶ **Classification / diagnostic frameworks**:
 - **2019 ACR/EULAR classification criteria** — a 3-step approach: (1) an **entry criterion** (characteristic involvement of a typical organ), (2) **exclusion criteria** (clinical, serologic, radiologic, pathologic red flags for mimics), and (3) **eight weighted inclusion domains** (histology, immunostaining, serum IgG4, bilateral lacrimal/parotid/sublingual/submandibular glands, chest, pancreas/biliary tree, kidney, retroperitoneum); a total **≥20 points** classifies the patient as IgG4-RD.
 - **Japanese comprehensive diagnostic criteria** — organ enlargement/mass + serum IgG4 **≥135 mg/dL** + histology (>40% IgG4+/IgG+ ratio, >10 IgG4+/HPF); *definite* = all three, *probable* = organ + histology, *possible* = organ + serology.
 - **Type 1 AIP** is diagnosed using the **HISORt criteria** — Histology, Imaging, Serology, Other-organ involvement, Response to corticosteroid therapy.
- ▶ **Differential diagnosis**: sarcoidosis, Sjögren's (lacrimal enlargement), pancreatic cancer/cholangiocarcinoma, **lymphoma**, granulomatosis with polyangiitis (proptosis, destructive sinus lesions), chronic infections (HIV, HCV), primary sclerosing cholangitis. **Most patients undergo biopsy** mainly to exclude malignancy.

Treatment

- ▶ **Not every manifestation needs immediate therapy** — indolent disease (e.g. asymptomatic lymphadenopathy) may be **watched**, but monitoring is essential because organ-threatening disease can evolve, especially with rising IgG4. **Vital-organ involvement must be treated aggressively** (risk of end-stage liver disease, pancreatic failure, renal atrophy, aortic dissection/aneurysm, destructive sinonasal lesions).

- ▶ **Glucocorticoids = first line.** Harrison: **prednisone 40 mg/day**, tapered to discontinuation or to **5 mg/day maintenance over 2–3 months**. CMDT: **prednisone 0.6 mg/kg/day** tapered over weeks–months. Response is usually swift and striking, but **steroid-free remissions are uncommon** and steroid toxicity is high in this older, often diabetic population.
- ▶ **B-cell depletion — rituximab** is the key second-line agent (and increasingly used early with steroids) for relapsing or glucocorticoid-resistant disease: **two doses of 1 g IV ~15 days apart**, producing a swift fall in serum IgG4 (by limiting repletion of short-lived IgG4-producing plasma cells) and modulating CD4+ CTL function.
- ▶ **Conventional steroid-sparing agents — azathioprine, mycophenolate mofetil** (limited evidence) as alternatives.
- ▶ **Emerging / targeted therapy — inebilizumab** (anti-CD19, positive phase-3 MITIGATE trial; CMDT cites Stone et al, *NEJM* 2025) and **obexelimab**; anti-CD19 B-cell strategies may become first-line for high steroid-toxicity risk or organ-threatening disease.
- ▶ **Prognosis —** depends on the **degree of established fibrosis** (fibrotic organs respond poorly). Bisphosphonates and infection prophylaxis as standard with immunosuppression.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Histopathology of IgG4-RD (low-/high-power composite):** label — *dense lymphoplasmacytic infiltrate, germinal centre/lymphoid follicle, storiform (“basket-weave”) fibrosis, IgG4+ plasma cells (IHC), obliterative phlebitis (vein with obliterated lumen), eosinophils.*
- ▶ **Pathophysiology schematic:** *B cell/plasmablast (antigen presentation) → CD4+ cytotoxic T cell → arrows to IFN- γ , TGF- β , IL-1 (→ storiform fibrosis) and perforin/granzyme/granulysin (→ tissue injury); side box IgG4 plasma cell → IgG4 (Fab-arm exchange, non-inflammatory); therapy arrow rituximab/inebilizumab → B-cell depletion.*

Clinical / Diagnostic significance

- ▶ **Great mimic of malignancy —** pancreatic mass, cholangiocarcinoma, orbital/lung pseudotumor; recognising IgG4-RD prevents unnecessary major surgery (e.g. Whipple, thyroidectomy).
- ▶ **A trial of corticosteroid response** can be diagnostically useful in AIP (the “R” of HISORT), but a non-resolving “mass” still mandates biopsy to exclude cancer.
- ▶ **Renal involvement + hypocomplementaemia** and the **prozone effect** are practical traps every physician must know.
- ▶ Screen newly diagnosed patients for **occult multi-organ disease** (history, exam, cross-sectional imaging, IgG4) and for **secondary diabetes/exocrine insufficiency**.

High-yield exam pointers

- ▶ IgG4-RD = **fibroinflammatory, tumefactive, multi-organ “variable-vessel vasculitis.”**

- ▶ Pathology triad: storiform fibrosis + obliterative phlebitis + IgG4+ lymphoplasmacytic infiltrate (with eosinophils); ratio IgG4+/IgG+ >40%.
- ▶ Demographics: older man, ~2:1 male, subacute, afebrile.
- ▶ Classic syndromes: type 1 AIP (“sausage pancreas”), Mikulicz’s disease, Riedel’s thyroiditis, retroperitoneal fibrosis, hypertrophic pachymeningitis, orbital pseudotumor.
- ▶ ~30% have normal serum IgG4; beware the prozone effect (falsely low) — dilute the sample.
- ▶ IgG4 is non-inflammatory (Fab-arm exchange); the CD4+ cytotoxic T cell is the proposed driver.
- ▶ Classification: 2019 ACR/EULAR criteria (≥ 20 points); AIP $\rightarrow$ HISORt.
- ▶ Treatment: glucocorticoids first-line; rituximab for relapse/resistance; inebilizumab/obexelimab emerging; pathology alone never diagnostic — correlate clinically.

SOURCE & COVERAGE

- ▶ Harrison’s Principles of Internal Medicine, 22e — “IgG4-Related Disease” (clinical features, organ table, serology incl. prozone effect, pathology/pathophysiology, glucocorticoid + rituximab regimens, emerging anti-CD19 therapy).
- ▶ CMDT 2026 — “IgG4-Related Disease” (epidemiology, diagnosis, prednisone 0.6 mg/kg/day, rituximab/inebilizumab, azathioprine/mycophenolate) and “Liver, Biliary Tract & Pancreas Disorders” (type 1 autoimmune pancreatitis, imaging, HISORt criteria, prednisone 40 mg/day taper).
- ▶ Coverage note: The Harrison/CMDT corpus describes the pathology, serology and management in depth but does **not enumerate** the exact point weights of the 2019 ACR/EULAR criteria or the numeric histology/serology cut-offs (IgG4+/IgG+ >40%, >10 IgG4+/HPF, serum IgG4 ≥ 135 mg/dL); these are stated from the universally accepted ACR/EULAR and Japanese consensus criteria and are standard internal-medicine reference values.



Management of Hyperuricemia

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Hyperuricemia is a sustained elevation of serum urate above the saturation point of monosodium urate (MSU), i.e. $> \sim 6.85$ mg/dL, beyond which crystallization, growth and tissue deposition occur. Humans are uniquely susceptible because evolutionary loss of **uricase** (which converts urate to the highly soluble *allantoin*) raises baseline urate; at physiologic pH uric acid exists largely as urate (weak acid, pK_a 5.8). Hyperuricemia is the central prerequisite for gout and is tightly linked to the insulin-resistance/cardiometabolic-renal cluster, yet only a minority of hyperuricemic individuals ever

develop gout. Management therefore is *not* simply “lower the number” but a graded strategy: correct reversible causes, decide *who* needs lifelong urate-lowering therapy (ULT), drive serum urate to a sub-saturation target, and cover the patient against paradoxical flares.

Pathophysiologic basis that dictates treatment

- ▶ Serum urate reflects the **balance of dietary intake, endogenous synthesis and excretion**. Hyperuricemia arises predominantly from **impaired renal urate excretion** (~90%) and, less commonly, **overproduction** (~10%); many patients have both.
- ▶ **Overproduction** drivers: high cell turnover (hematologic malignancy, psoriasis, chemotherapy, tissue hypoxia) and inherited enzyme defects — **PRPP synthetase superactivity** and **HPRT deficiency** (*Lesch-Nyhan syndrome* and variants, X-linked).
- ▶ Two-thirds of urate is eliminated renally (proximal-tubule transporters **URAT1, OAT10, GLUT9, ABCG2**) and one-third via the gut (intestinal uricolysis) — these transporters are the targets of *uricosuric* drugs and explain anti-uricosuric effects of pyrazinolate/nicotinate.
- ▶ These mechanisms define the two drug strategies: **reduce production** (xanthine oxidase inhibitors), **increase excretion / degrade urate** (uricosurics, recombinant uricase).

Non-pharmacologic measures and reversible causes (first step)

- ▶ Pursue *before/alongside* drugs; in most patients hyperuricemia cannot be corrected by these alone, but they reduce drug dose and address comorbidity.
- ▶ **Weight control** (obesity/insulin-resistance syndrome), **healthy diet** with reduced purine load, **limitation of alcohol**, and **decreased fructose-rich foods and beverages**.
- ▶ **Stop/avoid urate-raising drugs where feasible** — **thiazide and loop diuretics**, low-dose aspirin.
- ▶ Treat the dense comorbidity burden (hypertension, type 2 diabetes, CKD, ischemic heart disease); some agents lower urate as a bonus — **losartan, amlodipine, fenofibrate, and SGLT2 inhibitors** — the last offering combined urate reduction plus cardio-renal benefit.

When to start urate-lowering therapy (ULT)

- ▶ **Goal:** correct the chronic hyperuricemia/expanded urate pool (the central cause of gout) — a commitment that is **usually lifelong**.
- ▶ Consider ULT when hyperuricemia is *not* correctable by risk-factor modification, judged by:
 - **≥2 gout flares per year**, or flares of marked severity/duration, and patient willingness for long-term therapy.
- ▶ **Absolute (always-treat) indications:** any patient with **subcutaneous tophi**, **chronic gouty arthritis**, or **known uric acid nephrolithiasis** — start ULT regardless of flare frequency.

Urate-lowering and acute-flare drugs

Drug	Class / mechanism	Dosing & target	Key cautions
Allopurinol	Xanthine oxidase inhibitor; <i>first-line</i> ULT	Single morning dose; start ≤ 100 mg/d, titrate to max 800 mg/d ; in CKD with eGFR <30 mL/min start 50 mg/d and titrate slowly	Mild cutaneous reaction $\sim 2\%$; rare SCARs (SJS, TEN) — risk $\uparrow$ with CKD, higher start dose, *HLA-B5801** carriage
Febuxostat	Xanthine oxidase inhibitor	Alternative XO inhibitor; hepatic metabolism (glucuronidation + oxidation) — no dose adjustment in moderate-severe CKD	Useful in HLA-B*5801 carriers / allopurinol intolerance
Probenecid	Uricosuric; <i>second-line</i>	Start 250 mg BD , increase up to 3 g/d to target; alone or with an XO inhibitor	Needs good renal function — ineffective if serum creatinine >2 mg/dL (177 μmol/L)
Benzbromarone	Uricosuric	More effective uricosuric in CKD	<i>Not available in the United States</i>
Pegloticase	Pegylated recombinant uricase (IV)	For patients who fail/cannot tolerate full doses of other agents	Combine with methotrexate to cut immunogenicity (anti-drug antibodies $\rightarrow$ loss of efficacy, infusion reactions)
Colchicine	Anti-inflammatory (flare Rx / prophylaxis)	Flare: 1.2 mg at first sign, then 0.6 mg in 1 h , then daily dosing; prophylaxis 0.6 mg OD-BD	Eliminated via P-glycoprotein (MDR1) & CYP3A4 — reduce dose in renal disease or with clarithromycin/tacrolimus
NSAIDs	Anti-inflammatory (flare Rx)	Indomethacin 25–50 mg TID; naproxen 500 mg BD; ibuprofen 800 mg TID; celecoxib 800 then 400 mg at 12 h, then 400 mg BD	Avoid with significant comorbidity (renal, GI, cardiac)
Glucocorticoids	Anti-inflammatory (flare Rx)	Prednisone 30–50 mg/d tapered; or IM; or intra-articular for 1–few joints	Useful when NSAIDs/colchicine contraindicated
Anakinra / canakinumab	IL-1 β blockade	Reserved for refractory flares	When standard agents fail/contraindicated

- ▶ **Target serum urate:** drive to a sub-saturation point — typically $<5\text{--}6\text{ mg/dL}$ ($300\text{--}360\text{ }\mu\text{mol/L}$) — to prevent recurrent flares and dissolve tophi. A lower target ($<5\text{ mg/dL}$) accelerates tophus dissolution.
- ▶ ***HLA-B5801 screening:** **allele carriage is high among** Southeast Asian (except Japanese descent), Pacific Islander/Native Hawaiian, and black* *patients*; *screen before allopurinol in these groups and, if positive, use an alternative agent** (e.g. febuxostat).

Initiating ULT and flare prophylaxis (the practical pitfall)

- ▶ **Do not start ULT during an active flare** — abruptly lowering urate can worsen the ongoing attack.
- ▶ ULT may be started **in the resolution phase or after a flare**, always **under anti-inflammatory prophylaxis** — e.g. colchicine 0.6 mg once–twice daily or naproxen 250 mg twice daily.
- ▶ **Start low, titrate slowly:** low starting dose with gradual up-titration reduces both SCAR risk and the **paradoxical mobilization flares** caused by MSU crystals shedding from dissolving synovial tophi during rapid urate reduction.
- ▶ **Continue prophylaxis** until the patient is **normouricemic and flare-free for 3–6 months**, or until tophi resolve.

Special situations (standard medicine — see Coverage note)

- ▶ **Asymptomatic hyperuricemia:** routine ULT is generally *not* indicated for an incidentally high urate without gout, tophi, or urate stones; manage lifestyle and reversible causes, and treat comorbidities.
- ▶ **Tumor lysis syndrome (overproduction state):** prevent/treat with vigorous **IV hydration**, **allopurinol** prophylaxis, and **rasburicase** (recombinant urate oxidase) for high-risk/established cases; rasburicase is **contraindicated in G6PD deficiency** (hemolysis/methemoglobinemia).
- ▶ **Secondary/overproduction hyperuricemia** (myeloproliferative disease, inherited enzyme defects): control the underlying disorder; XO inhibition is preferred over uricosurics to avoid stone formation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis-and-therapeutic-targets flow diagram** (after Fig. 384-1): boxes top-to-bottom — *Risk factors* (obesity/insulin resistance, diet/alcohol, genes, diuretics/low-dose aspirin) → **Chronic hyperuricemia / increased urate pool** → $\text{SU} > 6.85\text{ mg/dL}$ → **MSU crystallization, crystal growth, tissue deposition** → **Recurrent gout flares (acute crystal-induced inflammation)** → **Chronic gouty arthritis / tophi**. Add two side-arrows labelled “**Urate-lowering therapy (target SU $<5\text{--}6\text{ mg/dL}$): allopurinol, febuxostat, probenecid, uricase**” pointing at the hyperuricemia box, and “**Anti-inflammatory therapy: NSAIDs**,”

colchicine, glucocorticoids” pointing at the flare box, plus a “Dissolution → normal urate level” return arrow.

- ▶ **Treatment algorithm box:** label nodes — *Confirm hyperuricemia/gout* → *Lifestyle + stop diuretics* → *Indication for ULT?* (≥ 2 flares/yr, tophi, chronic arthritis, urate stones) → *Check HLA-B5801 in high-risk ethnicity* → *Allopurinol (or febuxostat) start-low titrate-to-target* → *Add colchicine/NSAID prophylaxis 3–6 months**.

Clinical / Diagnostic significance

- ▶ **Confirm before committing to lifelong therapy:** definitive diagnosis of gout rests on **needle-shaped, strongly negatively birefringent MSU crystals** in synovial fluid/tophus under polarized light; always culture fluid as septic arthritis can coexist.
- ▶ Serum urate may be **normal or low during an acute flare** (uricosuric effect of IL-6, ~2 mg/dL fall) — do not exclude gout on a single normal value; recheck after the flare and use it as the **therapeutic target**.
- ▶ **Baseline workup before/with ULT:** serum creatinine/eGFR, LFTs, hemoglobin, WBC count, HbA1c and lipids — to detect comorbidity, choose drug/dose, and monitor toxicity.
- ▶ **Imaging adjuncts:** musculoskeletal **ultrasound double-contour sign** and **dual-energy CT** detect urate deposition early; radiographic punched-out erosions with overhanging edges mark advanced tophaceous disease.
- ▶ ULT response is monitored by serial serum urate to the **<5–6 mg/dL** target; persistent failure to reach target should prompt adherence checks, dose escalation, or a switch/add of class.

High-yield exam pointers

- ▶ **Allopurinol is first-line ULT;** start ≤ 100 mg/d (50 mg/d if eGFR < 30), titrate up to **800 mg/d**, target serum urate **<5–6 mg/dL**.
- ▶ ***Screen HLA-B5801 before allopurinol in Southeast Asian/Pacific Islander/Native Hawaiian/black patients; if positive use febuxostat**.**
- ▶ **Febuxostat needs no dose adjustment** in moderate–severe CKD (hepatic metabolism).
- ▶ **Probenecid** (uricosuric, 2nd-line) is **ineffective if creatinine > 2 mg/dL**; **benzbromarone** works better in CKD but is unavailable in the US.
- ▶ **Pegloticase** (pegylated uricase) for refractory/tophaceous gout — give with **methotrexate** to limit immunogenicity.
- ▶ **Never start ULT during an acute flare;** begin in resolution phase under **colchicine/NSAID prophylaxis**, continued **3–6 months** until normouricemic and flare-free or tophi resolve.
- ▶ **Start low–go slow** to avoid SCARs (SJS/TEN) and paradoxical mobilization flares.
- ▶ **Always-treat indications:** tophi, chronic gouty arthritis, uric acid nephrolithiasis.

- ▶ Rasburicase for tumor-lysis hyperuricemia — **contraindicated in G6PD deficiency**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 384 "Gout and Other Crystal-Associated Arthropathies" (urate physiology, indications/targets for ULT, allopurinol/febuxostat/probenecid/benzbromarone/pegloticase dosing and cautions, flare prophylaxis, HLA-B*5801 screening, acute-flare agents).

Coverage note: The provided chapter addresses hyperuricemia management within the *gout* framework. It does **not** explicitly cover (a) the threshold/decision for treating purely **asymptomatic hyperuricemia**, or (b) **tumor lysis syndrome** prophylaxis (IV hydration, rasburicase, G6PD contraindication). These points are included only as **universally accepted standard internal medicine**, not drawn from Ch 384, and are flagged here accordingly.



Microscopic Polyangiitis

Asked in: Paper III 09/2025 · Paper III Nov 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — Microscopic polyangiitis (MPA) is a **pauci-immune, non-granulomatous, necrotizing vasculitis** of small vessels (capillaries, venules, arterioles) — with frequent involvement of small- and medium-sized arteries — that characteristically produces **necrotizing glomerulonephritis** and **pulmonary capillaritis**. The term *microscopic polyarteritis* was coined by Davson (1948) to denote the glomerulonephritis seen in some patients with polyarteritis nodosa; the 1992 Chapel Hill Consensus Conference formalised “microscopic polyangiitis” as a distinct entity defined by small-vessel necrotizing vasculitis with **few or no immune deposits**. It is one of the three ANCA-associated vasculitides (AAV), alongside granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA), and is the commonest cause of the **pulmonary–renal syndrome**.

Epidemiology & Nomenclature

- ▶ Incidence ~3–5 per 100,000; mean age of onset ~57 years; males slightly more often affected than females.
- ▶ Classified under the Chapel Hill category of *ANCA-associated small-vessel vasculitis* — grouped with GPA and EGPA because all share ANCA positivity and pauci-immune small-vessel vasculitis, but each retains a **distinct clinical phenotype** and should be regarded as a separate disease.
- ▶ The hallmark **distinguishing MPA from GPA is the absence of granulomatous inflammation**; absence of asthma/eosinophilia distinguishes it from EGPA, and the involvement of

venules/capillaries (and glomerulonephritis) distinguishes it from classic polyarteritis nodosa (PAN).

Etiopathogenesis (ANCA biology)

- ▶ **Pauci-immune lesion:** immunohistochemistry shows a *paucity of immunoglobulin deposition* in the vessel wall, implying immune-complex formation does **not** drive pathogenesis (contrast with cryoglobulinemic/IgA vasculitis).
- ▶ **ANCA** are autoantibodies against neutrophil/monocyte cytoplasmic granule proteins. Two patterns by indirect immunofluorescence:
 - **p-ANCA (perinuclear)** — target **myeloperoxidase (MPO)**; this is the **predominant association in MPA**.
 - **c-ANCA (cytoplasmic)** — target **proteinase-3 (PR3)**, a 29-kDa serine proteinase; predominant in GPA.
- ▶ **Pathogenic sequence:** TNF- α / IL-1 (or alternative-complement activation) **primes** neutrophils → MPO/PR3 **translocate to the cell surface** → circulating ANCA bind and activate the neutrophil → **degranulation, reactive-oxygen-species release, and adhesion to/killing of endothelial cells** → release of IL-1, IL-8 and further leukocyte recruitment → **necrotizing small-vessel injury**. Adoptive-transfer experiments in mice support a direct pathogenic role of anti-MPO.
- ▶ **Complement** (alternative pathway, generating **C5a**) is now recognised as central — the basis for the C5a-receptor antagonist **avacopan**.
- ▶ **Drug-induced MPA / MPO-ANCA vasculitis:** implicated agents include **propylthiouracil, hydralazine, allopurinol, penicillamine, minocycline, and sulfasalazine** — typically high-titre p-ANCA; withdrawal of the drug is the first therapeutic step.

Clinical and Laboratory Manifestations

- ▶ **Constitutional onset:** may be gradual (fever, weight loss, myalgia/arthritis) or **acute**.

Organ system	Manifestation in MPA
Renal	Necrotizing pauci-immune (crescentic) glomerulonephritis in $\geq 79\%$; frequently rapidly progressive (RPGN) → renal failure; haematuria, RBC casts, sub-nephrotic proteinuria
Pulmonary	Alveolar haemorrhage from pulmonary capillaritis in $\sim 12\%$ (haemoptysis may be first symptom); interstitial fibrosis mimicking UIP carries a poor prognosis
Neurological	Mononeuritis multiplex (vasculitic neuropathy)
Cutaneous	Palpable purpura , splinter haemorrhages, ulcers, vesiculobullous lesions

Organ system	Manifestation in MPA
GI	Mesenteric/visceral vasculitis (abdominal pain, bleeding)
NOT typical	Upper-airway destructive disease and pulmonary nodules are absent — their presence suggests GPA instead

- ▶ **Laboratory:** features of inflammation — raised ESR/CRP, anaemia, leukocytosis, thrombocytosis; ANCA positive in ~75%, predominantly anti-MPO (p-ANCA), though PR3-ANCA may occur. The renal lesion is a **segmental necrotizing glomerulonephritis**, often with intraglomerular thrombi/localised intravascular coagulation.

Diagnosis

- ▶ Based on **histologic evidence of vasculitis or pauci-immune glomerulonephritis** in a patient with a **compatible multisystem clinical picture**.
- ▶ **Tissue biopsy** (kidney, skin, nerve/muscle, or lung) remains essential — especially when the clinical picture is atypical — even though MPA is strongly ANCA-associated. Renal biopsy shows **focal segmental necrotizing GN with crescents and absent/scanty immune deposits on immunofluorescence** (pauci-immune).
- ▶ Exclude **mimics** (infective endocarditis, anti-GBM disease, SLE, cryoglobulinemia, cholesterol emboli, thrombotic microangiopathy) before committing to immunosuppression.

Differential Diagnosis (key separators)

Feature	MPA	GPA	EGPA	PAN
Vessel size	Small ($\pm$ medium)	Small–medium	Small–medium	Medium (muscular arteries)
Granulomas	Absent	Present (necrotizing)	Present (eosinophil-rich)	Absent
Dominant ANCA	MPO / p-ANCA (~75%)	PR3 / c-ANCA (>90%)	MPO in ~40–48%	ANCA-negative
Upper airway / nodules	Absent	Prominent (sinusitis, nasal, lung nodules/cavities)	Allergic rhinitis/sinus polyps; asthma	Absent
Glomerulonephritis	Common (RPGN)	Common	Less common	Absent (arteritis, not GN)
Lung haemorrhage	Common (capillaritis)	Common	Uncommon	Pulmonary arteries spared

Feature	MPA	GPA	EGPA	PAN
Distinctive clue	Pulmonary–renal syndrome	Saddle-nose, granulomas	Asthma + eosinophilia >1000/ μ L	HBV association, microaneurysms

Treatment

Trials enrol GPA and MPA together; MPA is managed identically to GPA (Harrison).

- ▶ **Severe (organ-/life-threatening) disease — Remission INDUCTION:**
 - Glucocorticoids + either cyclophosphamide OR rituximab.
 - Cyclophosphamide 2 mg/kg/day oral (reduce dose in renal impairment); or IV pulse 15 mg/kg $\times$ 3 doses every 2 weeks then every 3 weeks (similar remission, higher relapse than daily oral).
 - Rituximab (anti-CD20) 375 mg/m² weekly $\times$ 4 weeks — *non-inferior to cyclophosphamide* (RAVE/RITUXVAS), and superior in relapsing disease; preferred when fertility preservation matters or for relapse.
 - Glucocorticoid regimen: historically prednisone 1 mg/kg/day then taper; a **reduced-dose regimen** (PEXIVAS) is **non-inferior with fewer serious infections**. Life-threatening disease $\rightarrow$ IV methylprednisolone 1000 mg/day $\times$ 3 days.
 - Avacopan (oral C5a-receptor antagonist) — a glucocorticoid-sparing add-on; in the ADVOCATE trial achieved higher sustained remission at 52 weeks with markedly lower steroid exposure.
 - Plasma exchange (PLEX): **no benefit** on the composite of ESRD/death in the large PEXIVAS trial; reserve for **coexisting anti-GBM antibody**, and consider in selected fulminant cases (severe RPGN, creatinine >5.7 mg/dL — improved renal recovery at the cost of infection). Separate PLEX and rituximab by $\geq$ 48 h.
- ▶ **Remission MAINTENANCE** (after cyclophosphamide induction, switch at 3–6 months):
 - Rituximab (e.g. 500 mg $\times$ 2 then 500 mg every 6 months) — **lowest relapse rate**; or azathioprine 2 mg/kg/day; or methotrexate 15 $\rightarrow$ 20–25 mg/week; or mycophenolate mofetil 1 g BID (higher relapse). Continue $\geq$ 2 years; individualise duration (relapse risk rises after stopping).
- ▶ **Non-severe disease:** methotrexate or mycophenolate ($\pm$ rituximab) with lower-dose glucocorticoids.
- ▶ **Prognosis:** 5-year survival $\sim$ 74% with treatment; death from alveolar haemorrhage, renal, cardiac or GI disease. **Relapse in $\geq$ 34%** (25–50% across AAV). **Early diagnosis is the key prognostic determinant** — late diagnosis means more renal fibrosis and worse outcomes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pauci-immune crescentic glomerulus:** label *Bowman's capsule, cellular crescent compressing the tuft, segmental fibrinoid necrosis of capillary loops, ruptured GBM, and "negative" immunofluorescence (absent immune deposits).*
- ▶ **ANCA pathogenesis flow diagram:** label *TNF- α /IL-1 priming $\rightarrow$ MPO/PR3 surface translocation $\rightarrow$ ANCA binding $\rightarrow$ neutrophil activation (ROS, degranulation, C5a) $\rightarrow$ endothelial injury $\rightarrow$ necrotizing small-vessel vasculitis, with the avacopan block at the C5a receptor and rituximab block at CD20 B-cell.*

Clinical / Diagnostic significance

- ▶ Suspect MPA in any **pulmonary–renal syndrome** (haemoptysis/alveolar haemorrhage + RPGN with active urinary sediment); it is **several-fold commoner than anti-GBM disease** as a cause.
- ▶ A **p-ANCA/anti-MPO positive RPGN with pauci-immune crescentic GN on biopsy and no granulomata/no upper-airway destruction** strongly favours MPA over GPA.
- ▶ **Send anti-GBM with ANCA** in every pulmonary–renal presentation — “double-positive” patients (anti-MPO + anti-GBM) require **plasma exchange**.
- ▶ **Mononeuritis multiplex** with constitutional symptoms and renal involvement is a high-yield clue; nerve/muscle biopsy can confirm vasculitis.
- ▶ Always **exclude drug-induced MPO-ANCA vasculitis** (PTU, hydralazine, minocycline, allopurinol) — withdrawing the drug may suffice in limited disease.
- ▶ Monitor for **treatment-related infection** (the major cause of early mortality), hepatitis-B reactivation with rituximab, and cyclophosphamide-related bladder toxicity/infertility/malignancy.

High-yield exam pointers

- ▶ MPA = **pauci-immune, non-granulomatous, necrotizing small-vessel vasculitis**; *no granulomas* (vs GPA), *no asthma/eosinophilia* (vs EGPA), *glomerulonephritis present and pulmonary arteries involved* (vs PAN).
- ▶ **Davson 1948** coined “microscopic polyarteritis”; **Chapel Hill 1992** defined MPA.
- ▶ **ANCA positive in ~75%**, predominantly **anti-MPO / p-ANCA**.
- ▶ **Glomerulonephritis $\geq 79\%$, alveolar haemorrhage $\sim 12\%$; commonest cause of pulmonary–renal syndrome.**
- ▶ **Renal biopsy = focal segmental necrotizing crescentic GN, pauci-immune on IF.**
- ▶ **Induction = glucocorticoid + (cyclophosphamide or rituximab $375 \text{ mg/m}^2 \times 4$) $\pm$ avacopan; methylprednisolone pulse for life-threatening disease.**
- ▶ **PLEX no longer routine (PEXIVAS)** — reserve for **anti-GBM positivity / selected fulminant cases.**

- ▶ Maintenance with rituximab (lowest relapse) / azathioprine / methotrexate for ≥ 2 years.
- ▶ 5-yr survival $\sim 74\%$; relapse $\geq 34\%$; outcome hinges on early diagnosis.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "The Vasculitis Syndromes" (Microscopic Polyangiitis; ANCA biology; treatment of ANCA-associated vasculitis) and "Glomerular Diseases" (ANCA small-vessel vasculitis / pauci-immune crescentic glomerulonephritis).
- ▶ CMDT 2026 — "Rheumatologic, Immunologic, & Allergic Disorders" (Microscopic Polyangiitis — essentials, drug-induced MPO-ANCA, treatment) and "Kidney Disease" (rapidly progressive GN).

Coverage note: The corpus does not contain the 2022 ACR/EULAR MPA classification-criteria point scores, so these were deliberately not stated; the answer uses the Chapel Hill 1992 nomenclature, which is fully sourced. All numbers, drug doses, eponyms and percentages above are taken verbatim from the cited chapters.



Mixed connective tissue disease

Asked in: Paper III May 2022 — RGUHS MD General Medicine

Definition / Introduction — Mixed connective tissue disease (MCTD) is an *overlap syndrome* in which features of systemic sclerosis (SSc, usually limited cutaneous), systemic lupus erythematosus (SLE), polymyositis/dermatomyositis and rheumatoid arthritis coexist in the same patient, characteristically accompanied by high titres of autoantibody to U1-ribonucleoprotein (anti-U1-RNP). The defining initial presentation is Raynaud's phenomenon with "puffy" (swollen) fingers and myalgia. More broadly, an *overlap syndrome* is defined as typical SSc features coexisting with clinical and laboratory evidence of another autoimmune disease — most commonly polymyositis, Sjögren's syndrome, polyarthritis, autoimmune liver disease, or SLE. MCTD was first delineated by Sharp and colleagues (1972).

Pathogenesis and immunology

- ▶ Autoantibody-driven autoimmune connective-tissue disease; the serological hallmark is anti-U1-RNP, which produces a high-titre speckled antinuclear antibody (ANA) pattern on HEp-2 immunofluorescence.
- ▶ Anti-U1-RNP is directed against the U1 small nuclear ribonucleoprotein, chiefly the 70-kDa polypeptide (U1-70K) and the A and C proteins — a *standard-textbook* specificity not detailed in the provided chapter.

- ▶ The B-cell hyperactivity, TH2-polarised T-cell response, and endothelial/microvascular injury that underlie SSc are shared mechanisms relevant to MCTD: chronic **B-cell activation** (elevated BAFF/APRIL), profibrotic cytokines (TGF- β , IL-6, IL-13), and a vasculopathy driving **Raynaud's phenomenon and pulmonary arterial hypertension (PAH)**.
- ▶ Strong association with **HLA class II (notably HLA-DR4)** genotypes (*standard immunology, flagged below*), in contrast to the anti-Sm/anti-dsDNA-linked HLA associations of SLE.

Clinical features (multisystem)

- ▶ **Hallmark triad** to recall: **Raynaud's phenomenon + swollen/puffy hands ("sausage" fingers) + high-titre anti-U1-RNP**.
- ▶ Over time, **sclerodactyly, soft-tissue calcinosis (calcinosis cutis) and cutaneous telangiectasia** appear (scleroderma-spectrum features).
- ▶ **SLE-like features**: malar (butterfly) erythema, photosensitivity, serositis, cytopenias, alopecia.
- ▶ **Myositis**: proximal muscle weakness with raised muscle enzymes (polymyositis overlap).
- ▶ **Inflammatory arthritis/arthritis**: may be erosive; some patients are **seropositive (RF/anti-CCP)** with a rheumatoid-arthritis overlap.

Organ system	Characteristic MCTD manifestations
Vascular	Raynaud's phenomenon (early, near-universal); abnormal nailfold capillaroscopy; digital ischaemia
Skin/hands	Puffy fingers, sclerodactyly, calcinosis cutis, telangiectasia, malar rash, photosensitivity
Musculoskeletal	Inflammatory polyarthritis ($\pm$ erosive), myositis with proximal weakness
Pulmonary	PAH (leading cause of death), interstitial lung disease (ILD), pleuritis
Gastrointestinal	Oesophageal dysmotility, GERD, reduced lower-oesophageal-sphincter tone (<i>standard SSc-spectrum feature</i>)
Cardiac	Pericarditis/pericardial effusion, conduction defects, myocardial involvement
Renal	Membranous/mesangial nephropathy; severe diffuse glomerulonephritis and scleroderma renal crisis are relatively uncommon
Neurological	Trigeminal (sensory) neuropathy; aseptic meningitis (often NSAID-related) — <i>standard, flagged</i>

Autoantibodies and laboratory features

- ▶ **Anti-U1-RNP in high titre is required** for the diagnosis; by definition the speckled ANA is strongly positive.
- ▶ **Absence of anti-Sm and anti-dsDNA** in high titre helps distinguish MCTD from classic SLE (*standard serology, flagged*); anti-Sm, when strongly positive, points toward SLE rather than MCTD.
- ▶ **Other overlap-associated antibodies** recognised in the SSc chapter (useful for the differential of overlap syndromes):

Autoantibody	Pattern	Principal association
U1-RNP	Speckled	MCTD — PAH, inflammatory arthritis, myositis overlap
PM/Scl	Nucleolar	Calcinosis cutis, ILD, myositis overlap (SSc-polymyositis)
Ku	Speckled	SLE / myositis overlap
Ro52 / TRIM21	—	Overlap, older-age onset, ILD
Topoisomerase I (Scl-70)	Speckled	Diffuse SSc, ILD (not MCTD)
Centromere (ACA)	Discrete speckled	Limited SSc, isolated PAH (not MCTD)

- ▶ Supportive labs: raised acute-phase reactants, anaemia, hypergammaglobulinaemia, raised creatine kinase (if myositis), low complement (variable), abnormal nailfold videocapillaroscopy.
- ▶ **Screening for organ involvement:** pulmonary function tests with DLCO, high-resolution CT chest (ILD), transthoracic echocardiography ± right-heart catheterisation for PAH, ECG, and CK/EMG for myositis.

Diagnostic criteria and classification of overlap syndromes

- ▶ MCTD is listed among the **overlap syndromes** in the scleroderma-spectrum classification (alongside SSc/polymyositis overlap).
- ▶ Several validated **classification criteria sets** exist (*standard rheumatology — not detailed in the provided Harrison chapter*): **Sharp, Alarcón-Segovia, Kasukawa, and Kahn** criteria. All require **high-titre anti-U1-RNP** plus a defined combination of clinical features.

Criteria set	Core requirement
Alarcón-Segovia (most widely used)	Serologic: anti-U1-RNP $\geq 1:1600$ (haemagglutination) plus ≥ 3 of 5 clinical — hand oedema, synovitis, myositis, Raynaud's, acrosclerosis (synovitis or myositis required)
Kasukawa	Raynaud's or swollen fingers/hands + positive anti-RNP + at least one feature from each of the SLE-, SSc-, and PM-like categories

Criteria set	Core requirement
Sharp	Major + minor clinical criteria with high-titre anti-RNP and low anti-Sm
Kahn	Anti-U1-RNP + Raynaud's + ≥ 2 of synovitis, myositis, swollen fingers

Management

- **Manifestation-directed and largely glucocorticoid-responsive disease**; therapy is tailored to the dominant organ involvement (*treatment specifics below are universally-accepted standard medicine; the provided chapter details only musculoskeletal therapy*).
- **Arthralgia/arthritis & musculoskeletal disease**: short courses of NSAIDs, methotrexate, hydroxychloroquine, and cautious low-dose glucocorticoids; physical/occupational therapy to prevent contractures (grounded in the SSc chapter).
- **Raynaud's phenomenon**: cold avoidance, dihydropyridine calcium-channel blockers; PDE5 inhibitors/prostanoids for digital ulcers.
- **Myositis & severe inflammatory disease**: moderate-to-high-dose glucocorticoids with steroid-sparing agents (methotrexate, azathioprine, mycophenolate mofetil).
- **ILD**: mycophenolate mofetil or cyclophosphamide, with rituximab in refractory disease.
- **PAH** (the prognosis-determining complication): endothelin-receptor antagonists, PDE5 inhibitors, and prostacyclin analogues — early screening and treatment are essential.
- **GERD/oesophageal disease**: proton-pump inhibitors, prokinetics, lifestyle measures.

Prognosis and course

- Generally more favourable than diffuse SSc or severe SLE, with many manifestations responding to glucocorticoids.
- **Pulmonary arterial hypertension is the leading cause of mortality** in MCTD; progressive ILD and cardiac disease also drive poor outcomes.
- The disease may **evolve over time** — some patients differentiate into a more clearly defined SSc or SLE phenotype, fuelling the ongoing debate over whether MCTD is a truly distinct entity or a transitional/overlap state.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Venn diagram of overlap syndromes**: three overlapping circles labelled “SLE”, “Systemic sclerosis”, “Polymyositis” (with a smaller “RA” overlap), and the central intersection labelled “MCTD — anti-U1-RNP”. Annotate central shared features: *Raynaud's, puffy hands, arthritis, myositis*.

- ▶ **Pathophysiology flow diagram:** *Genetic susceptibility (HLA-DR4) → Anti-U1-RNP autoimmunity / B-cell activation → Endothelial injury & vasculopathy → branches to “Raynaud’s / digital ischaemia” and “Pulmonary arterial hypertension (leading cause of death)”*; parallel branch *TH2 cytokines (TGF- β , IL-6, IL-13) → “Fibrosis: sclerodactyly, ILD”*.

Clinical / Diagnostic significance

- ▶ **Anti-U1-RNP in high titre is the single most important diagnostic test**; a high-titre speckled ANA in a patient with Raynaud’s and puffy hands should prompt its measurement.
- ▶ Distinguishing MCTD from SLE matters prognostically: MCTD typically **sparcs the patient from severe diffuse lupus nephritis and severe CNS lupus**, but carries a **high risk of PAH** demanding lifelong echocardiographic surveillance.
- ▶ Recognising the **overlap antibody panel** (PM/Scl, Ku, Ro52) helps classify atypical connective-tissue disease and predicts ILD/myositis risk.
- ▶ Early detection and aggressive treatment of **PAH and ILD** are the key determinants of survival.

High-yield exam pointers

- ▶ MCTD = SSc + SLE + **polymyositis** + **RA features** + **high-titre anti-U1-RNP**; first described by Sharp (1972).
- ▶ **Speckled ANA, high-titre anti-U1-RNP**; classically **anti-Sm/anti-dsDNA negative** (helps separate from SLE).
- ▶ Earliest/most consistent clue: **Raynaud’s phenomenon + swollen “puffy” hands + myalgia**.
- ▶ Later scleroderma features: **sclerodactyly, calcinosis cutis, telangiectasia**.
- ▶ **PAH = leading cause of death**; screen with echocardiography $\pm$ right-heart catheterisation.
- ▶ **Glucocorticoid-responsive disease** — better prognosis than diffuse SSc; severe lupus nephritis and renal crisis are uncommon.
- ▶ Most widely used classification criteria: **Alarcón-Segovia**; others — Kasukawa, Sharp, Kahn.
- ▶ May **evolve into SSc or SLE**; debated as a distinct entity vs an overlap state.

SOURCE & COVERAGE

Harrison’s Principles of Internal Medicine, 22e — Ch 372 “Systemic Sclerosis (Scleroderma) and Related Disorders” (MCTD/overlap-syndrome section, Tables 372-2 and 372-4). **Coverage note:** The provided chapter covers MCTD only briefly within the scleroderma spectrum — it grounds the definition, overlap concept, anti-U1-RNP/speckled-ANA serology and its associations (PAH, inflammatory arthritis, myositis), the early Raynaud’s/puffy-hands/myalgia presentation, later sclerodactyly/calcinosis/telangiectasia, SLE-like skin features, the overlap-antibody panel

(PM/Scl, Ku, Ro52), and musculoskeletal therapy. Items added as *universally-accepted standard internal medicine* and flagged in-text — Sharp 1972 origin, anti-U1-70K/A/C antigen specificity, HLA-DR4 association, the named classification criteria (Sharp, Alarcón-Segovia, Kasukawa, Kahn) and their thresholds, oesophageal/neurological detail, and the manifestation-directed pharmacotherapy (Raynaud's, myositis, ILD, PAH) — fall outside the verbatim text of the provided chapter.



Neuropathic Joint Diseases

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — **Neuropathic joint disease* (Charcot joint, *neuro-osteoarthropathy*) is a progressive, destructive arthritis that develops in a joint deprived of normal pain sensation, proprioception, or both. With loss of these protective mechanisms the joint is subjected to repeated, unperceived trauma, leading to severe cartilage and bone damage with a characteristic mismatch between gross radiographic destruction and the relative absence of pain. First described by Jean-Martin Charcot in the knees of patients with *tabes dorsalis**, it is now seen most frequently in the foot and ankle of patients with diabetes mellitus.

Etiology and characteristic joint distribution

The distribution of joint involvement is determined by the underlying neurological disorder, because the affected joints correspond to the territory of sensory loss.

Underlying disorder	Typical joint(s) affected
Diabetes mellitus (most frequent cause)	Tarsal and tarsometatarsal joints; then metatarsophalangeal and talotibial
Tabes dorsalis (tertiary syphilis)	Knees, hips, ankles
Syringomyelia	Glenohumeral (shoulder), elbow, wrist (upper limb)
Leprosy, yaws	Feet, hands
Meningomyelocele	Ankle, foot
Congenital indifference / insensitivity to pain	Ankle, foot
Peroneal muscular atrophy (<i>Charcot-Marie-Tooth disease</i>)	Foot, ankle
Amyloidosis	Variable peripheral joints

- ▶ Harrison's *Table 386-2* lists diabetes mellitus, amyloidosis, tabes dorsalis, leprosy, meningocele, congenital indifference to pain, syringomyelia and peroneal muscular atrophy as the recognised associations.
- ▶ An arthritis resembling neuropathic disease has been reported after **frequent intra-articular glucocorticoid injections**, attributed to the analgesic effect promoting overuse of an already-damaged joint (steroid cartilage damage is more typical of animal models than humans).

Pathophysiology — two complementary mechanisms

- ▶ **Neurotraumatic theory ("German" theory)**: loss of deep pain, proprioception and protective neuromuscular reflexes allows cumulative *microtrauma* — ligament tears and bone fractures — to accumulate unchecked, producing progressive joint disorganisation.
- ▶ **Neurovascular theory ("French" theory)**: an abnormal **autonomic nervous system** drives dysregulated (increased) blood flow to the joint, causing active bone **resorption** and osteopenia; loss of bone, particularly in the diabetic foot, may be the *initial* finding.
- ▶ In diabetes, **peripheral neuropathy, autonomic neuropathy and trauma** act together; denervation of intrinsic foot muscles causes clawing of the toes and anterior displacement of the submetatarsal fat pads, altering biomechanics and raising plantar pressures.
- ▶ It is not understood why only a minority of patients with neuropathy go on to develop clinically evident neuropathic arthropathy.

Pathology: changes resemble a *severe osteoarthritic joint* — fragmentation and eventual loss of articular cartilage, **eburnation** of underlying bone, marginal osteophytes, and, with advanced disease, surface erosions, fractures, devitalised bone, intra-articular loose bodies and microscopic cartilage/bone fragments.

Clinical features

- ▶ Usually **begins in a single joint** and later involves others, depending on the neurological substrate.
- ▶ The joint becomes **progressively enlarged** from bony overgrowth and synovial effusion; it is classically *swollen, boggy and relatively painless*.
- ▶ May evolve with surprising **rapidity** — a totally disorganised joint with multiple bony fragments can appear within weeks to months.
- ▶ **Hallmark:** *far less pain than expected* from the degree of destruction; occasional sudden pain occurs from intra-articular fractures of osteophytes. Free-floating cartilage/bone fragments cause mechanical (locking) symptoms.

Diabetic (Charcot) foot — exam favourite:

- ▶ Estimated incidence in diabetes ~0.5%, typically in patients **≥50 years** who have had diabetes for several years.

- ▶ Onset often attributed to antecedent trauma (e.g. *twisting* the foot); may follow a foot fracture or dislocation.
- ▶ Foot and ankle become swollen; downward collapse of the tarsal bones produces convexity of the sole — the “**rocker-bottom**” foot.
- ▶ Large osteophytes protrude dorsally; **calluses** form over the metatarsal heads and may break down into infected **ulcers and osteomyelitis**.
- ▶ The destructive change at the tarsometatarsal joints is termed a **Lisfranc fracture-dislocation**; radiographs show resorption and tapering of the distal metatarsals.

Radiographic features, staging and differential diagnosis

- ▶ **Early imaging** mimics osteoarthritis: joint-space narrowing, subchondral sclerosis, osteophytes, periarticular fractures, joint subluxation and effusions.
- ▶ **Late:** marked destructive *and* hypertrophic changes — striking osteolysis, fragmentation, dislocation and bony sclerosis (“disorganisation”).
- ▶ A useful descriptive mnemonic for the classic atrophic-hypertrophic picture is the “**6 D’s**”: *Distension* (effusion), increased *Density* (sclerosis), *Debris* (loose bodies), *Disorganisation*, *Dislocation/subluxation*, and *Destruction*.
- ▶ **Eichenholtz staging** of the Charcot foot (orthopaedic standard): *Stage 0* — acute inflammatory/prodromal (hot, swollen, red foot, near-normal X-ray); *Stage 1* — development/fragmentation; *Stage 2* — coalescence (debris absorption, reduced warmth); *Stage 3* — consolidation/reconstruction (bony remodelling, stable but deformed foot).

Feature	Neuropathic joint	Osteomyelitis
Joint margins on X-ray	Distinct/well-defined	Blurred/ill-defined
Indium-111-labelled WBC scan	No increased uptake	Increased uptake
Technetium bone scan	Increased uptake	Increased uptake (<i>non-discriminatory</i>)
Synovial neutrophils	Few (non-inflammatory)	Increased

- ▶ **Diagnosis** rests on the clinical picture plus characteristic radiographs in a patient with a known **sensory neuropathy**.
- ▶ **Differential diagnosis:** osteomyelitis, avascular necrosis, advanced osteoarthritis, stress fractures and **calcium pyrophosphate deposition disease (CPPD)** — more than one may coexist.
- ▶ **Synovial fluid** is *non-inflammatory*, often xanthochromic or frankly bloody, and contains fragments of synovium, cartilage and bone; CPPD crystals favour a crystal arthropathy, whereas a high synovial neutrophil count raises concern for superadded osteomyelitis. Tissue culture is often needed to exclude infection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled lateral radiograph of a diabetic Charcot foot:** label *collapse/loss of the medial longitudinal arch, bony fragmentation and dislocation in the midfoot, tarsometatarsal (Lisfranc) destruction, dorsal osteophytes*, and the resulting “*rocker-bottom*” sole convexity.
- ▶ **Pathophysiology flow diagram:** *Sensory + autonomic neuropathy* → two limbs — (1) *Neurotraumatic*: loss of pain/proprioception → repeated microtrauma → ligament tears/fractures; (2) *Neurovascular*: autonomic dysregulation → increased blood flow → bone resorption/osteopenia — both converging on → *progressive joint destruction / disorganisation (Charcot joint)*.

Clinical / Diagnostic significance

- ▶ **Screening prevents disease:** patients who cannot feel the **5.07 Semmes-Weinstein monofilament** have lost protective sensation and are at risk of unperceived neuropathic injury; regular foot examination, protective inserts and orthotics are pivotal.
- ▶ **Acute Charcot foot is a clinical emergency in disguise** — a hot, swollen, red foot in a neuropathic diabetic is frequently misdiagnosed as cellulitis, gout or DVT; missing it allows progression to fixed rocker-bottom deformity and ulceration.
- ▶ Distinguishing neuropathic joint from **osteomyelitis** is the central diagnostic challenge in the diabetic foot and directs whether antibiotics/surgery are needed (use joint-margin definition, indium-111 WBC scan, MRI and tissue culture).
- ▶ Established joint damage does **not** reverse with control of the underlying disease, so *early* recognition is everything.

High-yield exam pointers

- ▶ *Charcot joint* = destructive arthropathy from loss of **pain + proprioception**; named after **Jean-Martin Charcot** (first described in *tabes dorsalis*).
- ▶ **Diabetes mellitus** is the commonest cause today (incidence ~0.5%); *tabes dorsalis* → **knee/hip**, *syringomyelia* → **shoulder/upper limb**, **diabetes** → **tarsometatarsal foot**.
- ▶ Two mechanisms: **neurotraumatic** (microtrauma) + **neurovascular** (autonomic-driven bone resorption).
- ▶ Classic paradox: **gross destruction with disproportionately little pain**; joint is enlarged, boggy, unstable.
- ▶ Diabetic foot signs: **rocker-bottom deformity, Lisfranc fracture-dislocation**, calluses → infected ulcers/osteomyelitis.
- ▶ Radiology “**6 D’s**”; **Eichenholtz** stages 0–3 for the Charcot foot.
- ▶ Neuropathic vs osteomyelitis: **distinct joint margins** and **negative indium-111 WBC scan** favour neuropathic; technetium scan does *not* discriminate.

- ▶ Synovial fluid **non-inflammatory**, often **bloody/xanthochromic**.
- ▶ Treatment: **non-weight-bearing for ≥8 weeks**, bracing/splinting (with vigilant skin surveillance), and **arthrodesis** for unstable joints (nonunion common); **no proven pharmacotherapy**.

Management

- ▶ **Primary aim — stabilise and offload the joint.** Treating the underlying disorder, even successfully, usually does not reverse established joint disease.
- ▶ **Acute Charcot foot:** early recognition with **strict non-weight-bearing/immobilisation (total-contact cast)** for **at least 8 weeks** may prevent severe deformity.
- ▶ **Bracing and splinting** assist weight-bearing and limit further trauma, but require close surveillance because the insensate patient cannot perceive pressure from a poorly fitted device.
- ▶ **Surgery: arthrodesis (fusion)** of an unstable joint — with or without orthobiologics — can improve function and reduce pain when conservative measures fail; **nonunion is frequent**, especially with inadequate immobilisation.
- ▶ **Aggressive foot care, ulcer prevention and glycaemic control;** CMDT notes that **pharmacotherapy has not demonstrated efficacy** for the arthropathy itself.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Arthritis Associated with Systemic Disease, and Other Arthritides” (Neuropathic Joint Disease section: etiology, *Table 386-2*, pathophysiology, clinical features, diagnosis vs osteomyelitis, treatment; *Fig. 386-1* diabetic Charcot foot).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic & Allergic Disorders” (Neurogenic Arthropathy / Charcot Joint; synovial-fluid differential) and “Diabetes Mellitus & Hypoglycemia” (Charcot foot arthropathy, rocker-bottom deformity, 5.07 Semmes-Weinstein monofilament).

Coverage note: The corpus (Harrison + CMDT) covers this topic well for an internal-medicine answer. Two items added for exam completeness are *not* verbatim in the cited corpus but are universally accepted standard teaching: the **Eichenholtz staging** of the Charcot foot and the radiographic “**6 D's**” mnemonic; the *neurotraumatic* (“German”) / *neurovascular* (“French”) theory labels are the conventional names for the two mechanisms that Harrison describes in full.



Palindromic Rheumatism

Asked in: Paper III Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Palindromic rheumatism (PR) is a relapsing-remitting inflammatory arthropathy characterised by **recurrent, abrupt, self-limiting attacks of acute arthritis and peri-**

arthritis that resolve completely within hours to a few days, leaving **no residual joint deformity and no radiographic erosions**. The term (Greek *palindromos*, “running back again”) was coined by *Hench and Rosenberg in 1944* to describe the “coming-and-going” pattern. It is best regarded not as a static disease but as an **abortive / pre-clinical phase of inflammatory arthritis**, since a substantial proportion of patients evolve into rheumatoid arthritis (RA) — making it an important exam differential for the patient with intermittent, undifferentiated arthritis.

Clinical features of the attack

- ▶ **Onset:** sudden, often peaking within a few hours; patient frequently well one moment and incapacitated the next. Attacks may begin at any time, including at night.
- ▶ **Joint pattern:** typically **monoarticular or oligoarticular (1–3 joints)** per attack; over time many joints are affected in succession. Commonly involved — **metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrists, knees, shoulders**; can also involve ankles, elbows, hips.
- ▶ **Peri-articular involvement:** a hallmark is **para-articular soft-tissue and tendon-sheath inflammation** (peri-arthritis) producing diffuse swelling beyond the joint line; transient subcutaneous nodules may appear during attacks.
- ▶ **Local signs:** affected joint becomes warm, red, tender and swollen — clinically mimicking gout or septic arthritis (pseudocellulitis-like appearance).
- ▶ **Duration:** attacks are **brief — hours to 2–3 days** (occasionally up to a week), then resolve **spontaneously and completely**.
- ▶ **Inter-critical period:** between attacks the patient is **entirely asymptomatic with a normal joint examination** — analogous to the intercritical phase of gout.
- ▶ **Frequency:** highly variable — from several attacks per week to only a few per year; the disease may run for years.
- ▶ **No systemic damage:** unlike RA, there is **no progressive deformity, no joint-space narrowing and no bony erosion**, which is the single most useful distinguishing feature.

Laboratory and imaging features

- ▶ **Acute-phase reactants (ESR, CRP)** are typically elevated **during an attack** and normalise in the inter-critical period.
- ▶ **Rheumatoid factor (RF):** positive in roughly half of patients; **anti-citrullinated peptide antibodies (ACPA / anti-CCP)** are positive in a significant minority. In RA, anti-CCP carries a diagnostic specificity approaching **95%**, so its presence in a patient with palindromic attacks strongly predicts evolution to RA.
- ▶ **Antinuclear antibody (ANA):** may be positive in the subset destined to develop a connective-tissue disease such as SLE.

- ▶ **Synovial fluid:** inflammatory (raised WBC, neutrophil-predominant) but **sterile and crystal-negative** — aspiration with **polarised-light microscopy** is essential to exclude crystal arthropathy (negatively birefringent needle-shaped monosodium urate of gout; weakly positively birefringent rhomboid calcium pyrophosphate of CPPD).
- ▶ **Radiographs:** characteristically **normal** even after years — absence of erosions distinguishes PR from established RA. (Subclinical synovitis may be seen on ultrasound/MRI in those progressing to RA.)

Natural history and risk of progression

Palindromic rheumatism is prognostically heterogeneous; broadly three outcomes are recognised:

Outcome	Approx. proportion	Comment
Evolution to rheumatoid arthritis	roughly one-third to one-half	Most important outcome; attacks become more frequent then merge into persistent symmetrical synovitis
Evolution to another connective-tissue disease	smaller subset	SLE, Sjögren's, Behçet's, systemic sclerosis-overlap reported
Persistent palindromic course or complete remission	remainder	Some have lifelong intermittent attacks; a minority remit fully

Predictors of progression to RA:

- ▶ **Seropositivity** — positive RF and especially positive **anti-CCP/ACPA** (high-titre carries greatest risk).
- ▶ **Female sex.**
- ▶ **Small-joint (hand/wrist) involvement.**
- ▶ **More frequent attacks** and longer disease duration.
- ▶ **Family history** of RA.

Diagnosis and differential diagnosis

- ▶ Diagnosis is **clinical and one of exclusion** — no internationally validated criteria exist. Commonly cited **proposed (Guerné–Weisman / Hannonen) criteria** require: recurrent sudden brief attacks of arthritis/peri-arthritis over **≥6 months**, **direct observation of at least one attack by a physician**, involvement of **≥3 different joint areas** across attacks, and **exclusion of other arthropathies**.
- ▶ A detailed **attack diary** documenting site, duration and complete resolution is invaluable.

Differential	Discriminating feature
Gout / CPPD (pseudogout)	Crystals on polarised microscopy; podagra, tophi; chondrocalcinosis on X-ray

Differential	Discriminating feature
Early rheumatoid arthritis	Symptoms persistent >6 weeks, symmetrical, erosions develop, high-titre anti-CCP
Reactive / spondyloarthritis	Antecedent infection, enthesitis, sacroiliitis, psoriasis, HLA-B27
SLE / other CTD	Multisystem features, ANA/anti-dsDNA, cytopenias
Familial Mediterranean fever & periodic fever syndromes	Recurrent fever + serositis, ethnic background, <i>MEFV</i> mutation
Whipple's disease / Behçet's	GI/oral-genital features; <i>Tropheryma whipplei</i> ; pathergy
Septic arthritis	Single hot joint, fever, positive Gram stain/culture

Management

- ▶ **Acute attack:** NSAIDs are first-line; **colchicine** and short courses of **oral or intra-articular glucocorticoids** are alternatives for severe attacks. Because attacks are brief, the aim is symptom control and shortening the episode.
- ▶ **Disease-modifying / prophylactic therapy** (for frequent attacks or seropositive patients at risk of RA):
 - **Hydroxychloroquine** is the most widely used agent — reduces attack frequency and is reported to **delay or prevent progression to RA**.
 - **Sulfasalazine** and **methotrexate** are options in refractory or clearly RA-evolving disease.
 - **Colchicine** prophylaxis benefits some patients (especially where crystal disease cannot be fully excluded).
- ▶ **Monitoring:** periodic clinical review with RF/anti-CCP and acute-phase reactants to detect early conversion to persistent RA, at which point full RA-directed DMARD therapy (e.g., methotrexate ± biologic) is instituted.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Timeline of disease activity (preferred):** an X-axis labelled “Time” with intermittent vertical spikes labelled “Acute attack (hours–days)” separated by flat baselines labelled “Complete inter-critical remission — normal joints, normal X-ray”; add an arrow at the right labelled “Progression to RA (persistent synovitis, erosions)”. Contrast with a second curve labelled “Established RA — sustained activity.”
- ▶ **Hand outline:** shade the MCP, PIP, and wrist joints labelled “common sites”, with a dashed halo around a joint labelled “para-articular / peri-arthritis swelling” to depict the characteristic soft-tissue involvement.

Clinical / Diagnostic significance

- ▶ PR is a “**window of opportunity**” — recognising seropositive PR identifies patients in a **pre-RA** state in whom early hydroxychloroquine/DMARD may modify natural history.
- ▶ **Joint aspiration with polarised microscopy** is mandatory at first presentation to exclude gout, pseudogout and sepsis, all of which can present identically.
- ▶ Documenting **complete radiographic and clinical resolution between attacks** is the key step that separates PR from early erosive RA and crystal arthropathy.
- ▶ Anti-CCP/RF status drives both prognosis and the decision to start prophylactic therapy.

High-yield exam pointers

- ▶ **Eponym:** *Hench and Rosenberg, 1944; palindromos* = “to run back again.”
- ▶ **Hallmark triad:** recurrent **brief** attacks + **complete** inter-critical remission + **no** erosions/deformity.
- ▶ **1–3 joints** per attack, peaks in hours, lasts **hours to 2–3 days**; MCP/PIP/wrist/knee favoured; **peri-articular** swelling typical.
- ▶ **Seropositivity (RF, anti-CCP) predicts progression to RA**; anti-CCP specificity ~95%.
- ▶ **One-third to one-half** evolve into RA; smaller subset to SLE/other CTD; rest remit or stay palindromic.
- ▶ **Hydroxychloroquine** reduces attack frequency and may prevent RA conversion; NSAIDs/colchicine/steroids abort acute attacks.
- ▶ **Always aspirate** to exclude gout, pseudogout and septic arthritis (a diagnosis of exclusion).
- ▶ Radiograph is **characteristically normal** — a discriminator from established RA.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Disorders of the Joints and Adjacent Tissues / Gout and Other Crystal-Associated Arthropathies” (palindromic rheumatism listed among mimics of acute crystal arthritis; synovial-fluid analysis, MSU/CPPD birefringence, crystal-exclusion principles) and “**Rheumatoid Arthritis**” (RF/anti-CCP performance and ~95% ACPA specificity, 2010 ACR–EULAR classification framework, differential diagnosis of early inflammatory arthritis, predictors of persistent/erosive disease).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic & Allergic Disorders” (management principles of inflammatory arthritis; hydroxychloroquine/DMARD use).

Coverage note: The Harrison/CMDT corpus does **not** carry a dedicated section on palindromic rheumatism — it appears only as a named differential of crystal arthritis in the gout chapter, with the RA chapter supplying the antibody, prognostic and differential-diagnosis framework. The disease-specific detail (attack characteristics, Hench–Rosenberg eponym, ~one-third-to-one-half

RA conversion, Guerne–Weisman proposed criteria, hydroxychloroquine prophylaxis) is therefore drawn from **universally accepted standard rheumatology** and aligned with the corpus where it overlaps; specific conversion percentages are approximate and vary between series.



Polyarthrititis

Asked in: Paper III Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — *Polyarthrititis* denotes inflammatory involvement of **four or more joints** (≥ 5 by some classifications), distinguishing it from *monoarthrititis* (one joint) and *oligo-/pauciarticular* disease (two or three joints). It is a syndrome, not a diagnosis, with a broad differential spanning immune-mediated, infective, crystal-induced, reactive and degenerative disorders. The diagnostic art lies in answering four cardinal questions — *Is it articular? Is it inflammatory? Is it acute or chronic? How many and which joints?* — and then refining by pattern (symmetry, distribution, temporal evolution) and extra-articular clues, so that “red flag” conditions are not missed while needless testing is avoided.

The diagnostic framework — four cardinal questions

- ▶ **Articular vs non-articular.** Articular disorders show *deep/diffuse pain, swelling (synovial proliferation, effusion or bony enlargement), limited active AND passive movement, crepitus, instability or deformity*. Non-articular/peri-articular lesions (bursitis, tendinitis, fibromyalgia) cause focal/point tenderness, pain on active but not passive motion, and lack true synovial swelling — a frequent masquerader of “polyarthrititis.”
- ▶ **Inflammatory vs non-inflammatory.** Inflammation is suggested by the cardinal signs (erythema, warmth, pain, swelling), **prolonged morning stiffness (often hours, ≥ 30 –45 min) that improves with activity**, systemic features (fever, rash, weight loss), and laboratory evidence — raised ESR/CRP, thrombocytosis, anaemia of chronic disease, hypoalbuminaemia. Non-inflammatory (e.g., osteoarthritis) shows brief *gel-phenomenon* stiffness (≤ 45 min, often < 15 min) worsened by activity, and normal inflammatory markers.
- ▶ **Acute (≤ 6 weeks) vs chronic (> 6 weeks).** Acute polyarthrititis tends to be infective, crystal-induced, reactive or viral; chronic polyarthrititis tends to be immune-mediated (RA, SLE) or degenerative.
- ▶ **Number and distribution of joints** — polyarticular (≥ 4), with attention to *which* joints (small vs large; upper vs lower; axial involvement), *symmetry*, and *temporal pattern*.

Causes of polyarthrititis (grouped)

Category	Representative diseases
Chronic inflammatory, symmetric small-joint	Rheumatoid arthritis (RA); SLE; mixed connective tissue disease; polyarticular juvenile idiopathic arthritis
Seronegative spondyloarthritis (often asymmetric, lower-limb, axial)	Psoriatic arthritis; reactive arthritis; enteropathic (IBD-associated) arthritis; ankylosing spondylitis
Crystal-induced	Chronic tophaceous gout (may evolve into a polyarticular RA-mimic); CPPD (pseudogout)
Infective / post-infective	Polyarticular septic arthritis; gonococcal arthritis; <i>acute viral</i> — Chikungunya, parvovirus B19, hepatitis B, rubella; <i>chronic</i> hepatitis C polyarthritides; acute rheumatic fever
Connective-tissue / vasculitic	Systemic sclerosis, inflammatory myositis (polymyositis/dermatomyositis), Still's disease, sarcoid arthropathy, granulomatosis with polyangiitis (GPA)
Non-inflammatory / degenerative	Generalised (nodal) osteoarthritis
Paraneoplastic	Hypertrophic pulmonary osteoarthropathy (lung/GI carcinoma) — clubbing, periosteal new bone, RF-negative

Pattern recognition — the key to narrowing the differential

- **Temporal evolution:** *chronic/persistent* (OA, RA); *additive* — new joints add while old persist (RA, psoriatic arthritis); *intermittent* — symptom-free intervals (crystal arthritis, Lyme); *migratory* — inflammation moves from joint to joint (acute rheumatic fever, gonococcal and viral arthritis).
- **Symmetry & distribution:** RA is symmetric and additive, affecting **PIP, MCP, intercarpal and carpometacarpal** (wrist) joints with palpable synovial hypertrophy and *swan-neck/boutonnière* deformities, and characteristically **sparcs the DIP joints**. **Spondyloarthritis, reactive arthritis and gout** are typically *asymmetric and oligoarticular*, favouring the **lower limbs**; spine/sacroiliac involvement points away from RA. **Psoriatic arthritis** may involve DIP joints with **dactylitis** (“sausage digit”), nail pitting/onycholysis and *pencil-in-cup* radiographic change.
- **Extra-articular clues:** fever (Still's disease, infection, vasculitis), rash (SLE, psoriatic), nail changes (psoriatic/reactive), oral/genital ulcers and uveitis (Behçet's, spondyloarthritis), sicca (Sjögren's), Raynaud's (scleroderma/MCTD), proximal weakness (myositis). GPA arthritis prefers **larger joints (hips, ankles, wrists)** and **sparcs the small hand joints**, helping separate it from RA.

Pattern	Think of
Symmetric small-joint polyarthritis, DIP-sparing	Rheumatoid arthritis
Asymmetric, lower-limb, axial/sacroiliac	Spondyloarthritis, reactive arthritis
Acute symmetric self-limiting + fever, recent infection	Viral (Chikungunya, parvovirus B19)
Migratory + carditis/erythema marginatum	Acute rheumatic fever
DIP + nail disease + dactylitis	Psoriatic arthritis
Polyarthralgia >50 yr, proximal stiffness, RF-negative	Polymyalgia rheumatica

Clinical evaluation & investigations

- ▶ **History:** age/sex/ethnicity (gout & spondyloarthritis — men; RA, SLE, fibromyalgia — women), onset/chronology, evolution pattern, precipitants (trauma, drugs — Table 382-2, antecedent infection, comorbidities), and a full rheumatic review of systems.
- ▶ **Examination:** count tender/swollen joints (a *28-joint count* — PIPs, MCPs, wrists, elbows, shoulders, knees — is standard), distinguish true synovitis (boggy, grape-like) from bony hypertrophy (firm) and effusion (fluctuant; “bulge sign”/patellar ballottement at the knee), assess range of motion and deformity, and seek extra-articular signs.
- ▶ **Laboratory (targeted, confirmatory — not a screening battery):** FBC; ESR/CRP; uric acid (men 4.0–8.6 mg/dL; women 3.0–5.9; up to 50% normal during an acute attack); RF (positive in ~80% of RA but also in chronic infection, SLE, Sjögren’s) and anti-CCP/ACPA (more specific — high-titre or RF/anti-CCP *double positivity* predicts erosive disease); ANA with reflex profiling when SLE/CTD suspected; ASO/anti-DNase B (rheumatic fever); viral serology and hepatitis screen. Remember low pre-test probability gives poor predictive value (4–5% of healthy people are RF/ANA positive).
- ▶ **Synovial fluid analysis** — *always* indicated when sepsis, crystals or haemarthrosis is suspected, and for a flare in a single joint of a chronic polyarthritis (see table).
- ▶ **Imaging:** plain radiographs for chronicity/erosions/chondrocalcinosis; **ultrasound with power Doppler** detects early synovitis/erosions; **MRI** for early erosive change, osteonecrosis and axial disease; **DECT** localises urate deposition.

Synovial fluid	Appearance	WBC/ μ L	PMN	Examples
Normal	Clear, viscous	<200	<25%	—
Non-inflammatory	Clear, viscous, amber (“string sign”)	<2000	mononuclear	OA, trauma

Synovial fluid	Appearance	WBC/ μ L	PMN	Examples
Inflammatory	Turbid, yellow, low viscosity	2000–50,000	PMN predominant	RA, gout, psoriatic, SLE
Septic	Opaque, purulent	>50,000 (often >100,000)	>75%	Septic arthritis
Haemorrhagic	Bloody	—	—	Trauma, coagulopathy, neuropathic

Crystals: monosodium urate — long, **needle-shaped**, **negatively birefringent** (gout); calcium pyrophosphate — short, **rhomboid**, **positively birefringent** (pseudogout). Gram stain and culture (plus NAAT for gonococcus, AFB/fungal culture for chronic monoarthritis) whenever infection is possible — crystal and septic arthritis can co-exist.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm for musculoskeletal/polyarthritis evaluation** (Harrison Fig. 382-1): boxes/branches labelled — *Is it articular?* → *Acute vs Chronic (>6 wk)* → *Inflammation present? (morning stiffness, soft-tissue swelling, systemic symptoms, ESR/CRP)* → *Number of joints (1–3 vs >3)* → *Symmetric?* → *PIP/MCP/MTP involved?* → *Rheumatoid arthritis / SLE / Scleroderma / Psoriatic / Reactive / Enteropathic.*
- ▶ **Hand joint-distribution map** (Fig. 382-3) labelled: *1st CMC & DIP/PIP = OA (Heberden's & Bouchard's nodes); PIP/MCP/wrist = RA (DIP-sparing, swan-neck/boutonnière); DIP + dactylitis + nail pitting = psoriatic arthritis; 2nd–3rd MCP = haemochromatosis/CPD.*

Clinical / Diagnostic significance

- ▶ **Red-flag polyarthritis**: new-onset febrile polyarthritis demands exclusion of **polyarticular septic arthritis** (mortality ~30%), disseminated gonococcal infection, endocarditis and crystal disease before labelling it autoimmune.
- ▶ **Early RA recognition matters** — disease-modifying therapy (DMARDs) should begin as soon as the diagnosis is certain to prevent erosions and deformity; NSAIDs do not alter progression.
- ▶ **Viral polyarthritis** (Chikungunya, parvovirus B19) mimics early RA but is usually febrile, self-limiting within weeks, and serology-confirmed — avoids unnecessary immunosuppression. **Hepatitis C** causes a chronic, *non-erosive*, RF-positive but anti-CCP-negative polyarthritis.
- ▶ **Don't miss mimics**: PMR (polyarthralgia >50 yr, RF-negative, proximal girdle stiffness, high ESR), GPA (large joints, small-hand-sparing), and paraneoplastic hypertrophic osteoarthropathy (clubbing, periosteal reaction, RF-negative).

High-yield exam pointers

- ▶ Polyarthritis = ≥ 4 joints (Harrison); CMDT defines polyarticular as ≥ 5 joints, oligoarticular 2–4 — quote both.
- ▶ The **four questions**: articular?, inflammatory?, acute/chronic?, how many/which joints — the spine of every answer.
- ▶ Symmetric, DIP-sparing, PIP/MCP/wrist = RA; asymmetric, lower-limb, DIP + dactylitis = psoriatic/spondyloarthritis.
- ▶ Temporal patterns: **migratory** = rheumatic fever, gonococcal, viral; **additive** = RA, psoriatic; **intermittent** = crystal, Lyme.
- ▶ Anti-CCP is more specific than RF; double positivity predicts erosive RA; up to 50% of active RA/SLE have a normal ESR/CRP.
- ▶ Synovial WBC: <2000 non-inflammatory, 2000–50,000 inflammatory, >50,000 (PMN >75%) septic. MSU = negatively birefringent needles; CPPD = positively birefringent rhomboids.
- ▶ ESR, RF and ANA are **confirmatory, not screening** tests — low yield when pre-test probability is low.
- ▶ Febrile polyarthritis = exclude sepsis first.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Approach to Articular and Musculoskeletal Disorders” (J.J. Cush) — diagnostic framework, joint-pattern and temporal classification, synovial fluid analysis (Fig. 382-6), ANA patterns (Table 382-4), drug-induced musculoskeletal conditions, imaging; and “Osteoarthritis” for the degenerative differential.
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic, & Allergic Disorders” (Yazdany et al.) — diagnostic value of the joint pattern (Table 23-1), joint-fluid examination (Tables 23-2/23-3), and the differential diagnosis of polyarthritis/RA-mimics (viral, hepatitis C, gout, spondyloarthritis, PMR, GPA, paraneoplastic).

Coverage note: The corpus covers the *approach to* and *differential of* polyarthritis thoroughly within these two chapters; disease-specific classification criteria (e.g., 2010 ACR/EULAR RA criteria, Jones criteria) are detailed in their dedicated chapters and are summarised here only as far as the cited sources support.



Psoriatic arthritis

Asked in: Paper III Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory arthritis in the spondyloarthritis spectrum, associated with cutaneous and/or nail psoriasis and usually

negative rheumatoid factor. It may involve peripheral joints, sacroiliac joints and spine, entheses, tendon sheaths, and whole digits, producing dactylitis. Untreated disease can cause progressive erosive damage, deformity, disability, reduced quality of life, and increased cardiometabolic morbidity.

Etiopathogenesis and epidemiology

- ▶ **Psoriasis is common:** skin psoriasis affects about 2-3% of the population; PsA develops in a substantial minority of patients with psoriasis, with Harrison giving an approximate prevalence of 30% among psoriasis patients and Bologna reporting 5-30% depending on the series.
- ▶ **Temporal relation:** in nearly 80% of PsA patients, psoriasis precedes musculoskeletal disease; in about 10%, arthritis may precede skin disease, and simultaneous onset also occurs. Hence, hidden psoriasis must be actively sought.
- ▶ **Age:** PsA most often appears in adult life, classically around 30-50 years, while psoriatic disease also has peaks in early and later adulthood.
- ▶ **Genetic and immune basis:** PsA is part of the spondyloarthritis family, with HLA-B27 especially relevant in axial PsA; Harrison reports HLA-B27 in about 20% of all PsA and about 50% of axial PsA.
- ▶ **Cytokine axis:** psoriatic disease is driven predominantly by IL-17 and IL-23 pathways, with contributions from TNF-alpha, IL-1 beta, and IL-6. This explains the efficacy of TNF, IL-17, IL-12/23, and IL-23 inhibitors.
- ▶ **Nail-joint link:** nail disease is a strong predictor of PsA because the nail unit is anatomically linked to the distal interphalangeal (DIP) joint enthesis. Nail involvement is much more frequent in PsA than psoriasis without arthritis.
- ▶ **Comorbid disease burden:** depression, obesity, metabolic syndrome, diabetes mellitus, fatty liver disease, hypertension, and cardiovascular disease are common and must be screened for.

Clinical phenotypes

Phenotype	High-yield clinical features
Asymmetric oligoarthritis	Often early PsA; fewer than 4 joints; commonly lower limb or small joints of hands/feet; may later become polyarticular and more symmetric.
Symmetric polyarthritis	Resembles rheumatoid arthritis but usually seronegative, with psoriasis/nail disease, DIP disease, dactylitis, enthesitis, or axial features.
DIP-predominant arthritis	Classic clue; DIP pain, swelling, stiffness, and deformity with nail pitting, onycholysis, subungual hyperkeratosis, or oil-drop change.
Spondylitis / sacroiliitis	Inflammatory back or neck pain, morning stiffness, improvement with activity; sacroiliitis may be

Phenotype	High-yield clinical features
	unilateral/asymmetric and syndesmophytes are often bulky, asymmetric, and nonmarginal.
Arthritis mutilans	Severe destructive form with osteolysis, telescoping digits, acro-osteolysis, and major deformity; uncommon but exam-important.

- ▶ Phenotypes overlap; do not force a patient into only one group. Modern descriptions add **enthesitis**, **dactylitis**, and **tenosynovitis** as core musculoskeletal domains.
- ▶ **Dactylitis** is diffuse inflammatory swelling of a whole finger or toe, due to involvement of joints, tendons, bone, and soft tissue; persistent dactylitis predicts structural damage.
- ▶ **Enthesitis** commonly affects the Achilles tendon insertion, plantar fascia, quadriceps insertion on the patella, patellar tendon insertion on the tibia, medial/lateral epicondyles, pelvic rim, spinous processes, and intercostal muscle insertions.

Cutaneous, nail and extra-articular disease

- ▶ **Skin psoriasis**: sharply demarcated erythematous plaques with silvery micaceous scale, commonly on scalp, elbows, knees, gluteal cleft, palms/soles, and intertriginous sites. Koebner phenomenon, infection, stress, lithium, beta blockers, antimalarials, and systemic glucocorticoid withdrawal may exacerbate psoriasis.
- ▶ **Hidden psoriasis**: inspect scalp, umbilicus, gluteal/natal cleft, genitals, inframammary areas, palms/soles, and external auditory canal in all seronegative arthritis.
- ▶ **Nail matrix disease**: pitting, leukonychia, crumbling, and red spots in the lunula.
- ▶ **Nail bed disease**: onycholysis, subungual hyperkeratosis, oil-drop/salmon patch change, and splinter hemorrhages.
- ▶ **Eye disease**: uveitis occurs in about 5% of PsA; acute anterior uveitis is typical, but posterior or bilateral disease may occur.
- ▶ **Gut and mucosal disease**: Crohn disease or ulcerative colitis may coexist; painful mouth ulcers and rarely urethritis can occur.
- ▶ **Systemic risk**: patients with psoriasis/PsA have increased cardiovascular risk, endothelial dysfunction, subclinical atherosclerosis, depression, and suicidality; obesity worsens disease activity and treatment response.

Diagnosis and classification

- ▶ The diagnosis is primarily **clinical**: inflammatory musculoskeletal disease plus psoriasis, nail disease, family history, typical pattern, dactylitis, enthesitis, or characteristic imaging.
- ▶ **CASPAR criteria**: inflammatory articular disease involving joint, spine, or enthesitis plus ≥ 3 points:

CASPAR item	Points
Current psoriasis diagnosed by rheumatologist/dermatologist	2
Personal history of psoriasis	1
Family history of psoriasis in first- or second-degree relative	1
Typical psoriatic nail dystrophy: pitting, onycholysis, hyperkeratosis	1
Negative rheumatoid factor	1
Current dactylitis or past dactylitis recorded by a rheumatologist	1
Juxta-articular new bone formation on hand/foot radiograph, excluding osteophytes	1

- ▶ CASPAR is a classification tool with high specificity and sensitivity, useful in exams and studies; bedside diagnosis still rests on pattern recognition and exclusion of mimics.
- ▶ **Laboratory tests are supportive, not diagnostic:** ESR/CRP are elevated in only about 50% despite active disease; high ESR/CRP predicts more severe disease and damage.
- ▶ RF is usually negative; low-titer RF or anti-CCP can occur in fewer than 10%, so seropositivity does not completely exclude overlap or coexisting RA.
- ▶ If PsA presents as monoarthritis, perform **synovial fluid analysis** to exclude septic arthritis, gout, and CPPD. Inflammatory fluid with WBC >2000/mcL, no crystals, and negative Gram stain/culture supports inflammatory arthritis in the right clinical setting.

Investigations and imaging

- ▶ **Baseline assessment:** tender/swollen joint count, dactylitis count, enthesitis examination, nail count, psoriasis body surface area, axial symptoms, function, pain score, ESR/CRP, CBC, renal and liver function, and cardiometabolic risk profile.
- ▶ **Disease activity tools:** DAPSA and Minimal Disease Activity are commonly used; skin burden can be estimated by palms, with one patient palm approximating 1% body surface area.
- ▶ **Plain radiographs:** obtain hands, feet, pelvis, spine, and symptomatic joints. Early disease may show soft-tissue swelling; periarticular osteopenia is usually absent.
- ▶ **Characteristic X-ray signs:** marginal erosions with **fluffy periosteal new bone**, joint-space narrowing, bony ankylosis, **pencil-in-cup deformity**, ray-distribution damage, osteolysis, and **acro-osteolysis** in arthritis mutilans.
- ▶ **Axial imaging:** pelvic radiograph may show asymmetric or unilateral sacroiliitis; spine films may show bulky, asymmetric, nonmarginal “chunky” syndesmophytes, often involving cervical and lumbar spine.

- ▶ **Ultrasound with Doppler:** useful for synovitis, tenosynovitis, erosions, and differentiating inflammatory enthesitis from mechanical pain or fibromyalgia tender points.
- ▶ **MRI:** detects synovitis, erosions, enthesitis, and active axial inflammation with bone marrow edema on STIR before radiographic change. CT is reserved when MRI is unavailable/contraindicated; bone scan is neither sensitive nor specific.

Management

- ▶ **Aim:** treat to target, with remission or low disease activity, prevention of structural damage, restored function, social participation, and improved quality of life.
- ▶ **Team and domains:** manage with rheumatology plus dermatology; add ophthalmology, gastroenterology, psychiatry, cardiology, endocrinology, dietetics, physiotherapy, and occupational therapy according to domains.
- ▶ **NSAIDs:** useful initially for short-term relief of peripheral arthritis, enthesitis, dactylitis, and axial symptoms; rarely sufficient alone and require monitoring for renal, gastrointestinal, hypertensive, and cardiovascular toxicity.
- ▶ **Local glucocorticoid injections:** useful for active arthritis, enthesitis, or dactylitis. Avoid injections around weight-bearing lower-limb entheses because of tendon rupture risk.
- ▶ **Systemic glucocorticoids:** generally avoid; if unavoidable for acute arthritis flare, use the lowest effective dose for the shortest time because tapering may precipitate pustular psoriasis.
- ▶ **Conventional synthetic DMARDs:** methotrexate, sulfasalazine, or leflunomide should be considered early for active peripheral arthritis, enthesitis, or dactylitis. Methotrexate is preferred when clinically relevant psoriasis is present; csDMARDs are not useful for predominant axial disease.
- ▶ **Targeted oral agents:** apremilast may be used for active non-axial musculoskeletal disease or skin disease; JAK inhibitors such as tofacitinib or upadacitinib are options, generally after TNF inhibitor failure and with attention to cardiovascular, malignancy, zoster, and thrombotic risk.
- ▶ **Biologic DMARDs:** TNF inhibitors include etanercept, adalimumab, infliximab, certolizumab, and golimumab; IL-12/23 inhibition includes ustekinumab; IL-17 inhibition includes secukinumab, ixekizumab, and bimekizumab; IL-23 inhibition includes guselkumab and risankizumab.
- ▶ **Domain choice:** for predominant skin disease with musculoskeletal disease, IL-12/23, IL-17, or IL-23 inhibitors are preferred over TNF inhibitors. For axial disease after NSAID failure, use a biologic or JAK inhibitor rather than csDMARD. For active IBD, prefer monoclonal anti-TNF, IL-12/23, IL-23, or JAK inhibitor therapy and avoid IL-17 inhibitors in active IBD. For uveitis, monoclonal anti-TNF therapy is preferred.
- ▶ **Precautions:** screen for latent tuberculosis, hepatitis B, and hepatitis C before biologics or JAK inhibitors. Avoid starting immunosuppression during severe infection. TNF inhibitors may

worsen congestive heart failure or demyelinating disease; IL-17 inhibitors can cause mucocutaneous Candida and worsen active IBD.

- ▶ **Skin/nail therapy:** topical glucocorticoids, vitamin D analogues, topical retinoids, PUVA/UVB, and cyclosporine can help skin and nail disease but have limited musculoskeletal efficacy. Oral glucocorticoids should not be used for psoriasis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hand/foot PsA diagram:** label DIP arthritis, PIP involvement, dactylitis/sausage digit, nail pitting, onycholysis, fluffy periosteal new bone, pencil-in-cup deformity, ankylosis, and acro-osteolysis.
- ▶ **Domain-based management wheel:** label peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis, nail disease, IBD, and uveitis; place NSAIDs, csDMARDs, biologic DMARDs, and targeted synthetic DMARDs around the wheel.

Clinical / Diagnostic significance

- ▶ In any **seronegative inflammatory arthritis**, look for psoriasis in hidden sites and examine nails; a single patch in scalp, umbilicus, or gluteal cleft can clinch the diagnosis.
- ▶ Distinguish PsA from **RA** by DIP disease, nail dystrophy, dactylitis, enthesitis, asymmetric/ray distribution, absence of nodules/RF, and axial disease.
- ▶ Distinguish PsA from **OA** by inflammatory stiffness, soft-tissue swelling, erosions with new bone, nail disease, dactylitis, and absence of pure osteophyte/Heberden-node pattern.
- ▶ Distinguish PsA monoarthritis from **gout, CPPD, and septic arthritis** by synovial fluid microscopy, Gram stain, and culture; psoriasis increases uric acid turnover, so gout can coexist.
- ▶ Distinguish axial PsA from ankylosing spondylitis by asymmetric sacroiliitis, bulky nonmarginal syndesmophytes, cervical involvement, and prominent peripheral/nail disease.
- ▶ Early diagnosis matters because PsA can produce irreversible erosions, joint lysis, ankylosis, deformity, and functional loss within months in aggressive cases.
- ▶ Cardiovascular prevention is part of PsA care: screen and treat hypertension, diabetes, dyslipidemia, obesity, smoking, fatty liver disease, depression, and suicidality.

High-yield exam pointers

- ▶ PsA = psoriasis/nail disease + seronegative inflammatory arthritis + enthesitis/dactylitis/axial disease.
- ▶ Five classical phenotypes: asymmetric oligoarthritis, symmetric polyarthritis, DIP arthritis, spondylitis, arthritis mutilans.
- ▶ Dactylitis is a severity marker; enthesitis commonly affects Achilles insertion and plantar fascia.

- ▶ Nail findings: pitting, onycholysis, subungual hyperkeratosis, oil-drop change, splinter hemorrhages.
- ▶ CASPAR: inflammatory articular disease plus ≥ 3 points; current psoriasis scores 2.
- ▶ X-ray triad for exams: erosions plus fluffy new bone, pencil-in-cup deformity, asymmetric sacroiliitis/chunky syndesmophytes.
- ▶ ESR/CRP may be normal; RF/anti-CCP are usually negative but low-titer positivity can occur.
- ▶ Treatment is domain-based and treat-to-target; csDMARDs help peripheral disease, not axial disease.
- ▶ Avoid systemic steroids when possible; tapering can precipitate pustular psoriasis.

SOURCE & COVERAGE

Harrison 22e — “Spondyloarthritis”; Harrison 22e — “Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders”; Bolognia Dermatology — “Psoriasis”; CMDT 2026 — “Rheumatologic, Immunologic, & Allergic Disorders”; Braunwald — “Rheumatic Diseases and the Cardiovascular System”.



Raynaud's Phenomenon

Asked in: Paper II Nov 2019 · Paper III May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — *Raynaud phenomenon (RP)* is a syndrome of **episodic, reversible digital ischaemia** caused by an exaggerated vasoconstrictor response of digital arteries and cutaneous arterioles to **cold exposure or emotional stress**. It manifests as a sharply-demarcated, often *triphasic* colour change of the digits — **pallor** → **cyanosis** → **rubor**. It is broadly divided into **primary (idiopathic) RP** (no underlying disease) and **secondary RP** (associated with another disorder, most importantly systemic sclerosis). Distinguishing the two is the central clinical task, because secondary RP can progress to ulceration, gangrene and digital loss.

Pathophysiology

- ▶ The final common pathway is **inappropriate vasospasm of digital arteries, precapillary arterioles and cutaneous arteriovenous shunts**, triggered by cold or sympathetic (emotional) stimuli.
- ▶ Three interacting categories of abnormality are recognised:
 - **Neural** — exaggerated sympathetic / **α -adrenergic (α_2) vasoconstrictor** reactivity of digital vessels.
 - **Vascular / endothelial** — endothelial dysfunction with reduced vasodilators (**nitric oxide**, prostacyclin) and excess vasoconstrictors (**endothelin-1**); in secondary RP there is true structural vasculopathy with intimal proliferation.

- **Intravascular** — platelet activation, raised plasma viscosity and impaired fibrinolysis (relevant in blood dyscrasias).
- ▶ In **systemic sclerosis** the digital vessels show a **proliferative obliterative vasculopathy**, so vasospasm is superimposed on fixed structural narrowing — explaining the severity, ischaemic ulcers and autoamputation seen in secondary RP.
- ▶ The therapeutic rationale follows the mechanism: **calcium-channel blockers** / **α-blockers** counter vasoconstriction, **PDE-5 inhibitors and nitrates** augment the NO–cGMP pathway, and **endothelin-receptor antagonists** / **prostacyclins** correct the vasodilator deficit.

Clinical features — the triphasic colour response

- ▶ Classic well-demarcated colour sequence on cold/stress exposure:
 - **Pallor (white)** — *ischaemic phase*; vasospasm of digital arteries.
 - **Cyanosis (blue)** — deoxygenated blood pooling in dilated capillaries and venules; accompanied by cold, numbness or paraesthesia.
 - **Rubor (red)** — on rewarming, *reactive hyperaemia* with throbbing, painful, warm digits.
- ▶ The full triphasic response is typical but **not universal** — some patients have only pallor + cyanosis, others only cyanosis.
- ▶ **Fingers > toes** (toes affected in ~40%); attacks usually begin in one or two fingertips and extend to involve whole/all fingers; the **thumbs are characteristically spared**.
- ▶ Rare sites: **earlobes, tip of nose, tongue, nipple, penis**.
- ▶ Frequent association with **migraine** and **variant (Prinzmetal) angina** from coronary vasospasm — suggesting a shared vasospastic predisposition.
- ▶ Attacks terminate spontaneously or on rewarming; the patient is typically **asymptomatic between attacks**.

Primary versus secondary RP

Feature	Primary RP (Raynaud disease)	Secondary RP
Frequency	>50% of all RP; 2–6% of adults	Less common
Sex / age	Women ≈5×; onset 15–30 / 20–40 yr	Either sex; older onset
Pattern	Symmetric, bilateral, all fingers	May be unilateral / 1–2 digits only
Underlying disease	None (by definition, after exclusion)	Rheumatic/other disease present
Nailfold capillaries	Normal (regular hairpin loops)	Abnormal — dilated/giant loops, dropout

Feature	Primary RP (Raynaud disease)	Secondary RP
ANA / serology	Negative	Often positive
Tissue damage	No pitting, ulcer or gangrene; <1% lose part of a digit	Yes — pitting, ulcers, gangrene, autoamputation
Course	Mild; improves spontaneously in ~15%, progresses in ~30%	Depends on underlying disease

- *LeRoy–Medsger criteria* for **primary RP**: symmetric attacks, **no necrosis/ulceration**, no identifiable secondary cause, **normal nailfold capillaries**, negative ANA and normal ESR.

Causes of secondary RP (Harrison/CMDT classification)

Category	Examples
Connective-tissue / rheumatic	Systemic sclerosis (80–90%; presenting symptom in 30%), SLE (~20%), dermatomyositis/polymyositis (~30%), rheumatoid arthritis, MCTD, Sjögren syndrome
Arterial occlusive	Atherosclerosis (common in men >50 yr), thromboangiitis obliterans/Buerger (young male smokers), acute arterial occlusion/embolism, thoracic outlet syndrome
Pulmonary	Pulmonary (arterial) hypertension
Neurological	Carpal tunnel syndrome, complex regional pain syndrome, intervertebral disc disease, syringomyelia, spinal cord tumour, stroke, poliomyelitis
Blood dyscrasias	Cold agglutinins , cryoglobulinaemia , cryofibrinogenaemia , myeloproliferative disorders, lymphoplasmacytic lymphoma (Waldenström macroglobulinaemia)
Trauma / occupational	Vibration injury (chain-saw, jackhammer), hammer-hand syndrome , electric shock, frostbite, typing, piano playing
Drugs & toxins	Ergot derivatives , methysergide , β-blockers , sympathomimetics, serotonin agonists (sumatriptan), cocaine, nicotine/cafeine; chemotherapy — bleomycin , vinblastine , cisplatin , gemcitabine ; vinyl chloride, epoxy resins
Endocrine / misc.	Hypothyroidism, pheochromocytoma, migraine

Diagnostic approach

- ▶ **Clinical diagnosis** — based on the characteristic colour changes; the key step is to screen for a secondary cause.
- ▶ **Bedside examination** is often normal; radial, ulnar and pedal pulses are normal in primary RP (diminished/absent pulses point to occlusive disease/Buerger). Look for **sclerodactyly**, **digital pitting/ulcers**, **skin tightening**, **telangiectasia**, **calcinosis**, **rash**, **synovitis**.
- ▶ **Nailfold capillaroscopy** — the single most useful office test. Place a drop of **grade-B immersion oil** at the cuticle and view with a **dermatoscope or ophthalmoscope set to 40 dioptres**. *Dropout of capillaries with dilatation of remaining loops (giant capillaries)* indicates **secondary RP**, most often systemic sclerosis. The finding is **highly specific but of low sensitivity**.
- ▶ **Serology** — ANA, anti-centromere (limited SSc/CREST), anti-Scl-70 (topoisomerase I, diffuse SSc), anti-RNA polymerase III, ENA panel; complement, cryoglobulins, cold agglutinins as indicated.
- ▶ **Other** — ESR/CRP, FBC (myeloproliferative/hyperviscosity), TFTs; nerve-conduction studies for carpal tunnel; vascular imaging only if fixed occlusive disease is suspected. **Digital angiography is not indicated** for diagnosis of primary RP.

Management

- ▶ **General / non-pharmacological (first-line, often sufficient in primary RP):**
 - **Keep the whole body warm** — gloves/mittens *plus* warm clothing for trunk, head and feet to prevent cold-induced reflex vasoconstriction.
 - **Stop smoking**; protect hands from trauma; treat fissures with emollients; **avoid precipitating drugs** (β -blockers, ergot, sympathomimetic decongestants/amphetamines).
- ▶ **Pharmacological (reserve for severe symptoms or tissue injury):**
 - **Dihydropyridine calcium-channel blockers = first-line** — slow-release **nifedipine 30–120 mg/day**, **amlodipine 5–20 mg/day** (also felodipine, isradipine, nisoldipine); more effective than verapamil, nicardipine and **diltiazem** (less effective). CCBs work better in **primary** than secondary RP.
 - **α 1-adrenergic antagonists** — prazosin (also doxazosin, terazosin).
 - **PDE-5 inhibitors** — **sildenafil, tadalafil, vardenafil** — useful in **secondary RP** (e.g. systemic sclerosis), added to or substituted for CCBs.
 - **Topical nitrates** (nitroglycerin); ARBs; SSRIs (**fluoxetine**) as add-ons.
 - **Endothelin-receptor antagonist bosentan** — prevents/heals **digital ulcers** in systemic sclerosis.
 - **IV prostacyclin / analogues** — **epoprostenol, iloprost, treprostinil** — for critical digital ischaemia / threatened digital loss.

- ▶ **Procedural** — **digital (peripheral) sympathectomy** for progressive ischaemia refractory to medical therapy. **Botulinum toxin** injection has shown inconsistent/negative results in controlled trials.
- ▶ **Admit** patients with **critical digital ischaemia** (severe pain, demarcation) for intensive therapy; refer secondary RP to a rheumatologist.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Triphasic colour change of a digit** — three finger panels in sequence with labels: *Phase 1 — Pallor (white): digital artery vasospasm / ischaemia; Phase 2 — Cyanosis (blue): deoxygenated blood in dilated capillaries-venules, numbness; Phase 3 — Rubor (red): reactive hyperaemia on rewarming, throbbing pain.* Add trigger arrow “Cold / emotional stress”.
- ▶ **Nailfold capillaroscopy comparison** — two boxes: *Primary RP — regular, evenly-spaced hairpin capillary loops (normal) vs Secondary RP (scleroderma pattern) — dilated/giant loops, haemorrhages and capillary dropout (avascular areas).*

Clinical / Diagnostic significance

- ▶ RP is the **commonest and earliest manifestation of systemic sclerosis** (presenting symptom in 30%, may precede skin disease by years) and is a core feature of the **CREST syndrome** (*Calcinosis, Raynaud, oEsophageal dysmotility, Sclerodactyly, Telangiectasia*) of limited cutaneous SSc.
- ▶ The triad of **RP + abnormal nailfold capillaroscopy + a specific autoantibody** (anti-centromere or anti-Scl-70) strongly predicts evolution to a definite connective-tissue disease and warrants surveillance for **interstitial lung disease and pulmonary hypertension**.
- ▶ **Red flags for secondary RP**: onset >40 yr or in a male, **asymmetric/unilateral** attacks, digital pitting/ulcers/gangrene, abnormal nailfolds, positive ANA, systemic features.
- ▶ Recognising RP as a marker of **vasospasm** also flags associations with **migraine** and **coronary (variant) angina**.

High-yield exam pointers

- ▶ **Triphasic colour change** = white → blue → red (pallor–cyanosis–rubor); thumbs typically **spared**.
- ▶ **Primary RP**: >50% of cases, young women, **bilateral/symmetric, normal nailfolds, negative ANA, no tissue loss** (<1% lose a digit).
- ▶ **Secondary RP**: **systemic sclerosis (80–90%)** is the prototype; also SLE (~20%), DM/PM (~30%), RA, MCTD.
- ▶ **Nailfold capillaroscopy** (immersion oil + ophthalmoscope at 40 D): **dilated loops + dropout = secondary RP**; highly specific, low sensitivity.

- ▶ **First-line drug** = dihydropyridine CCB (nifedipine/amlodipine); CCBs work better in primary RP.
- ▶ **PDE-5 inhibitors, bosentan and IV prostacyclins (iloprost)** are reserved for **secondary RP with digital ulcers / critical ischaemia**.
- ▶ **LeRoy–Medsgers criteria** define primary RP (symmetric, no necrosis, normal capillaries, ANA negative, normal ESR).
- ▶ **Buerger disease and acrocyanosis** are key differentials — Buerger: male smokers, absent pulses, 1–2 digits; acrocyanosis: **persistent (not episodic)**, diffuse cyanosis, no pallor phase.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “*Arterial Diseases of the Extremities*” (Raynaud phenomenon: classification, primary vs secondary, clinical features, treatment) and “*Systemic Sclerosis (Scleroderma) and Related Disorders*” (secondary RP, scleroderma vasculopathy, nailfold/acro-osteolysis).
- ▶ **CMDT 2026** — “*Raynaud Phenomenon*” and “*Systemic Sclerosis*” (Rheumatologic, Immunologic & Allergic Disorders) — essentials of diagnosis, Table 23–9 causes of secondary RP, nailfold capillaroscopy technique, drug regimens and doses.
- ▶ **Coverage note:** The named **LeRoy–Medsgers criteria** for primary RP and the explicit **neural/vascular/intravascular** mechanistic triad are universally-accepted standard internal medicine but are not stated verbatim in the cited corpus; all disease associations, percentages, drugs and doses given here are taken directly from Harrison 22e and CMDT 2026.



Reactive arthritis

Asked in: Paper III 09/2025 · Paper III Jul 2021 · Paper III Nov 2019 (3×) — RGUHS MD General Medicine

Definition / Introduction

Reactive arthritis (ReA) is a sterile, immune-mediated inflammatory arthritis that develops *after* a urogenital or gastrointestinal infection with well-defined triggering microorganisms that are **not cultivable from the affected joints**. It belongs to the **peripheral spondyloarthritis (pSpA)** family, is strongly linked to **HLA-B27**, and classically presents as an asymmetric lower-limb oligoarthritis accompanied by extra-articular (ocular, mucocutaneous, genitourinary) features. The historical triad of arthritis, conjunctivitis and urethritis was formerly termed *Reiter syndrome*, an eponym now largely abandoned.

Place within spondyloarthritis & classification

- ▶ **Spondyloarthritis (SpA)** is a family of immune-mediated arthritides sharing axial/peripheral joint disease, enthesitis, dactylitis, uveitis, psoriasis, IBD, absence of rheumatoid factor/nodules, familial clustering and **HLA-B27** association (Moll & Wright, 1974).
- ▶ The **2009 ASAS** classification splits SpA into **axial SpA** (radiographic = ankylosing spondylitis, and non-radiographic) and **peripheral SpA**.
- ▶ **ReA is a peripheral SpA**, alongside **psoriatic arthritis**, **IBD-associated arthritis** and **undifferentiated pSpA**. Its hallmark features per the SpA spectrum table are: *urethritis, history of preceding Salmonella/Shigella/Yersinia/Campylobacter/Chlamydia infection, mucosal ulcers, conjunctivitis and keratoderma blennorrhagica*.
- ▶ **Nomenclature discipline (Harrison)**: the term ReA is *restricted* to acute SpA triggered by a genitourinary or GI infection and related to HLA-B27. Arthritides following acute rheumatic fever, meningococcus, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Chlamydia pneumoniae*, beta-haemolytic streptococci, some live vaccines and COVID do **not** fit the SpA construct and are termed “**post-infectious arthritides**”, not ReA.

Aetiopathogenesis

Component	Detail
GI (dysenteric) triggers	<i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia enterocolitica</i> , <i>Campylobacter</i> — develops 1–4 weeks after enteritis
Urogenital (venereal) trigger	<i>Chlamydia trachomatis</i> ($\pm$ <i>Ureaplasma urealyticum</i>)
Genetic	HLA-B27 present in 50–80% of patients (Harrison); CMDT: ~80% in White, 50–60% in Black patients
Latent interval	1 day to 4 weeks between infecting episode and arthritis
Joint fluid	Culture-negative (sterile) — distinguishes from septic arthritis

- ▶ **Mechanism**: an antecedent mucosal infection at the gut or urogenital tract, in a genetically predisposed (HLA-B27⁺) host, drives a **barrier-integrity loss** allowing translocation of bacteria/microbial peptides that incite immune activation at joints and entheses. Proposed HLA-B27 mechanisms include the “**arthritogenic peptide**” theory (HLA-B27 presents microbial peptides to CD8⁺ T cells $\rightarrow$ molecular mimicry), **HLA-B27 homodimer** interaction with KIR3DL2 driving IL-17, and unfolded-protein-response-linked IL-23 release. The downstream effector axis is **TNF- α** and the **IL-23/IL-17 pathway**.
- ▶ **HLA-B27 may promote intracellular survival/persistence** of the triggering organism (e.g., *Chlamydia*) in macrophages, providing a route to chronicity.
- ▶ **Epidemiology**: young adults, male predominance for venereal-triggered disease; overall incidence $\approx$ **3.4 cases per 100,000 person-years**; about **2.6%** of patients develop ReA after an

enteric infection (Campylobacter/Salmonella/Shigella/Yersinia). Prevalence parallels the **North–South gradient of HLA-B27** (classic Scandinavian post-dysentery outbreaks, now declining with improved hygiene).

Clinical features

- ▶ **Inflammatory musculoskeletal disease is essential for diagnosis.** Typical pattern: **asymmetric, oligoarticular** (≤ 4 joints) inflammatory arthritis of **large weight-bearing lower-limb joints** (knee, ankle).
- ▶ **Enthesitis** (Achilles tendinitis, plantar fasciitis — heel pain), **tendonitis, bursitis, dactylitis** (“sausage digit”), **inflammatory back pain** and **sacroiliitis**.

System	Manifestation
Joints	Asymmetric LL oligoarthritis; enthesitis; dactylitis; sacroiliitis/spondylitis ($\geq 20\%$, esp. after recurrences)
Ocular	Conjunctivitis (mild, early); acute anterior uveitis (later, more significant, HLA-B27 ⁺)
Genitourinary	Urethritis (sterile); circinate balanitis
Mucocutaneous	Keratoderma blennorrhagica (palms/soles, indistinguishable from pustular psoriasis); painless oral ulcers/stomatitis ; nail changes mimicking psoriasis; <i>erythema nodosum</i>
Cardiac	Carditis and aortic regurgitation (uncommon)
Systemic	Fever, weight loss common at onset

- ▶ **Classic triad** (“can’t see, can’t pee, can’t bend the knee”): **arthritis + conjunctivitis + urethritis** — the full triad is present in a minority.

Investigations / Diagnosis

- ▶ **Clinical diagnosis** — recognition of the pattern plus identification of an **antecedent infection**, and **exclusion** of other causes (notably septic/gonococcal arthritis and other post-infectious arthritides).
- ▶ **Identify the trigger: stool cultures** (Salmonella, Shigella, Campylobacter, Yersinia) — often negative by the time arthritis appears, as GI symptoms have resolved; **molecular testing / NAAT for Chlamydia trachomatis*** — all patients should be offered Chlamydia screening*.
- ▶ **HLA-B27** — supports diagnosis and predicts chronicity/uveitis; not diagnostic alone.
- ▶ **Inflammatory markers:** ESR/CRP raised (non-specific). **RF and anti-CCP negative** (seronegative).
- ▶ **Synovial fluid:** inflammatory but **sterile (culture-negative)** — crucial to exclude septic arthritis.

- ▶ **Imaging:** plain films may show enthesophytes, “fluffy” periostitis, sacroiliitis in chronic/recurrent disease; MRI for early sacroiliitis/enthesitis.
- ▶ Serology for enteric pathogens is used mainly in **epidemiological studies** (low yield in routine practice).

Differential diagnosis

Mimic	Discriminating feature
Gonococcal (disseminated GC) arthritis	Marked improvement within 24–48 h of antibiotics; positive cultures/NAAT; tenosynovitis, pustular skin lesions
Septic (non-gonococcal) arthritis	Monoarticular, synovial WBC often >50,000/μL, positive Gram stain/culture
Psoriatic arthritis	Pre-existing psoriasis; keratoderma is histologically identical to pustular psoriasis
Ankylosing spondylitis / axSpA	Predominant axial disease, no antecedent infection
Rheumatoid arthritis	Symmetric small-joint polyarthritis, RF/anti-CCP positive
Behçet disease	Painful oral/genital ulcers (ReA ulcers are painless), ocular & joint overlap
Acute rheumatic fever / crystal arthritis	Migratory; ASO/streptococcal evidence; crystals on polarised microscopy

Management / Treatment

- ▶ **No formal ReA treatment guidelines exist;** management mirrors that of **peripheral SpA**.
- ▶ **Acute arthritis (first line):** NSAIDs at the highest tolerable dose are the mainstay. **Intra-articular glucocorticoids** for mono-/oligoarthritis; **short-term low-dose systemic glucocorticoids** for polyarticular involvement.
- ▶ **Antibiotics: not used routinely.** Treating an active non-gonococcal STI reduces the chance of ReA developing. For **chronic Chlamydia-induced ReA, one RCT showed a 6-month course of rifampin (300 mg BD) plus either doxycycline (100 mg BD) or azithromycin outperformed placebo* — not replicated, so *long-term antibiotics are not** recommended generally.
- ▶ **Chronic ReA (>6 months / NSAID-refractory):** conventional DMARDs — **sulfasalazine (1 g BD, up to 3 g/day) or methotrexate (up to 25 mg/week)**; if refractory, **TNF inhibitors** (or anti-IL-17 biologics), as used across the other spondyloarthropathies.
- ▶ **Course/prognosis:** often **self-limiting**, resolving over weeks to months; recurrences are common. **HLA-B27 positivity predicts evolution to chronicity**, recurrent disease and sacroiliitis/AS, sometimes with permanent articular destruction.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ “Clinical features of reactive arthritis” – stick-figure schematic with labels: *Acute anterior uveitis / conjunctivitis* (eye), *painless oral ulcers* (mouth), *urethritis + circinate balanitis* (genitalia), *keratoderma blennorrhagica* (soles), *asymmetric oligoarthritis of knee & ankle* (lower limbs), *dactylitis* (“sausage digit”), *enthesitis – Achilles/plantar fascia* (heel), *sacroiliitis* (pelvis).
- ▶ **Pathogenesis flow diagram:** *Triggering infection (GI: Salmonella/Shigella/Yersinia/Campylobacter OR GU: Chlamydia) → Barrier-integrity loss / antigen translocation → HLA-B27⁺ host (arthritogenic peptide → CD8⁺ T cell; TNF-α & IL-23/IL-17 axis) → Sterile reactive synovitis + enthesitis (1 day–4 weeks later).*

Clinical / Diagnostic significance

- ▶ Always exclude septic and gonococcal arthritis first by synovial fluid analysis and culture — the single most important practical step in any acute mono-/oligoarthritis.
- ▶ A sterile arthritis + recent diarrhoea or urethritis in a young adult should trigger HLA-B27 testing and *Chlamydia* screening of the patient (and partner).
- ▶ Anterior uveitis in an HLA-B27⁺ patient is an ophthalmic emergency requiring urgent slit-lamp review; it may recur and threaten vision.
- ▶ ReA can be the **presenting illness of underlying HIV** and may run a more severe, treatment-resistant course in that setting — screen when clinically appropriate.

High-yield exam pointers

- ▶ **Triggers:** GI — *Salmonella, Shigella, Yersinia, Campylobacter*; GU — *Chlamydia trachomatis*. Latent interval 1 day–4 weeks.
- ▶ HLA-B27 positive in 50–80%; predicts chronicity, sacroiliitis and uveitis.
- ▶ Joint fluid is **STERILE (culture-negative)** — defining feature vs septic arthritis.
- ▶ **Classic triad** = arthritis + conjunctivitis + urethritis (“can’t see, can’t pee, can’t bend the knee”); old eponym *Reiter syndrome*.
- ▶ Skin/mucosa: **keratoderma blennorrhagica** (≈ pustular psoriasis), **circinate balanitis**, **painless oral ulcers**.
- ▶ **RF/anti-CCP negative** (seronegative spondyloarthritis); part of **peripheral SpA**.
- ▶ **Treatment:** NSAIDs first → intra-articular/short systemic steroids → **sulfasalazine/methotrexate** → TNFi; antibiotics *not* routine.
- ▶ ≥20% develop **sacroiliitis/AS** with recurrence; mostly self-limiting but may become chronic.
- ▶ **DDx pearl:** gonococcal arthritis improves dramatically within 24–48 h of antibiotics; Behçet ulcers are **painful** whereas ReA ulcers are **painless**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Spondyloarthritis” (Reactive Arthritis section: clinical features, triggers, HLA-B27 association/pathogenesis, diagnosis and treatment; SpA spectrum/ASAS classification).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic, & Allergic Disorders” (Reactive Arthritis: Essentials of Diagnosis, clinical findings, differential diagnosis, current treatment including the rifampin-plus-doxycycline/azithromycin regimen and biologics).

Coverage note: The corpus does not use the eponym *Reiter syndrome* or the “can’t see, can’t pee, can’t bend the knee” mnemonic — these are included as universally accepted standard internal-medicine teaching for completeness; all organism lists, doses, percentages and criteria above are taken verbatim from Harrison 22e and CMDT 2026.



Seronegative spondylarthritis: Define, causes and tabulate the differences between the different types

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Seronegative spondylarthritis* (*spondyloarthritis*, *SpA*) is a family of immune-mediated inflammatory arthritides that share overlapping clinical, genetic and pathological features and are united by the **absence of rheumatoid factor (RF) and anti-CCP antibodies** (“seronegative”) and by a striking association with **HLA-B27**. First delineated by *Moll and Wright (1974)* as distinct from rheumatoid arthritis (RA), the group is characterised by **sacroiliitis/inflammatory spinal lesions, asymmetric large-joint lower-limb oligoarthritis, enthesitis, dactylitis (“sausage digit”)**, and extra-articular features (acute anterior uveitis, psoriasis, inflammatory bowel disease [IBD]) with a familial tendency. Cumulative prevalence is ~2–3% — commoner than RA.

Concept of “seronegative” and the SpA spectrum

- ▶ “**Seronegative**” historically distinguished these arthritides from “seropositive” RA: RF and anti-CCP are *negative*, and rheumatoid nodules are absent.
- ▶ The 2009 ASAS (Assessment of SpondyloArthritis international Society) framework divides SpA by *dominant* clinical pattern into **axial SpA (axSpA)** and **peripheral SpA (pSpA)** — “axial” involvement is implied by the name but is *not* mandatory.
- ▶ Distinguishing musculoskeletal signature: **asymmetric, mono-/oligoarticular (≤4 joints) inflammatory arthritis of large lower-limb joints (esp. knee) with enthesitis, tendonitis and dactylitis** — contrasting with the symmetric polyarticular MCP/PIP involvement of RA.

Spondyloarthritis (SpA)	Conditions included
Axial SpA (axSpA)	Radiographic axSpA = Ankylosing spondylitis (AS); Non-radiographic axSpA (nr-axSpA)
Peripheral SpA (pSpA)	Psoriatic arthritis (PsA); Reactive arthritis (ReA); IBD-associated arthritis; Undifferentiated pSpA
Sometimes included under pSpA	SAPHO syndrome; acne-associated arthritis; hidradenitis suppurativa-associated arthritis

Causes — aetiology and pathogenesis

SpA is a prototypic immune-mediated disease that uniquely **couple inflammation to structural damage** — inflammatory bone loss coexists with *pathological new bone formation* (syndesmophytes, ankylosis → “bamboo spine”).

► Genetic susceptibility (strongest):

- **HLA-B27** — an MHC class I allele, *the* major genetic risk factor; present in 85–90% of AS but only ~5–8% of healthy Caucasians. Risk of axSpA is ~5% in B27-positive subjects, rising to ~20% in B27-positive first-degree relatives of patients.
- Pathogenic allotypes (e.g. *HLA-B2704, B2705) *confer risk*, whereas HLA-B2706 and B2709* do not — implicating specific peptide presentation.
- Non-MHC genes: ERAP1 (peptide-trimming enzyme; epistasis with HLA-B27), IL-23R polymorphisms (shared across SpA), and HLA-Cw6 in PsA.

► Proposed HLA-B27 mechanisms: (1) *arthritogenic peptide* theory — B27 presents microbial peptides to CD8+ T cells with molecular mimicry; (2) **HLA-B27 homodimer** formation engaging KIR3DL2 on T/NK cells → IL-17; (3) misfolding → **unfolded protein response / autophagy** → IL-23.

► Environmental / triggering factors in genetically predisposed hosts:

- **Gut barrier loss and intestinal dysbiosis** — germ-free HLA-B27 transgenic rats fail to develop disease; subclinical gut inflammation is seen in up to 50% of new-onset SpA.
- **Antecedent infection (ReA)**: enteric *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter* or urogenital *Chlamydia trachomatis*.
- **Mechanical stress** at entheses → microdamage, immune activation and aberrant repair (new bone formation).
- **Effector cytokine hubs**: TNF- α (common to all domains) and the IL-23/IL-17 axis ($\gamma\delta$ T cells, Tc17/Th17, ILC3 at entheses) drive osteoproliferation via prostaglandin E2, IL-17A/F, IL-22, BMP and Wnt pathways — the rationale for biologic therapy.

Tabulated differences between the types

Feature	Ankylosing spondylitis (r-axSpA)	Psoriatic arthritis (PsA)	Reactive arthritis (ReA)	IBD-associated arthritis
Peak onset / sex	2nd–3rd decade, <45 y; M:F 2:1	Any age; $\approx$ M = F	Young men predominate	Any age
HLA-B27	85–90%	~20% overall ($\approx$ 50% if axial/spondylitic)	50–80%	~50% <i>when sacroiliitis present</i> (B27 not a risk factor for IBD itself)
Trigger / association	None; familial, B27	Cutaneous & nail psoriasis	GI (<i>Salmonella/Shigella/Yersinia/Campylobacter</i>) or GU (<i>Chlamydia</i>) infection, 1 day–4 weeks earlier	Crohn's disease / ulcerative colitis
Sacroiliitis	Bilateral, symmetric	Often asymmetric / unilateral , may have spondylitis without sacroiliitis	Asymmetric / unilateral	Bilateral, symmetric (indistinguishable from AS)
Syndesmophytes	Thin, marginal, vertical, symmetric	Chunky, non-marginal , asymmetric	Coarse, non-marginal, asymmetric	As in AS
Peripheral arthritis	~30–40%; asymmetric oligoarthritis, lower limb; hips (root joint)	Oligoarticular $\rightarrow$ polyarticular; DIP disease; arthritis mutilans	Asymmetric oligoarthritis, lower limbs	Asymmetric oligoarthritis of large joints; may parallel or run independent of bowel activity
Enthesitis / dactylitis	Enthesitis common; dactylitis rare	Both common; dactylitis a <i>severity marker</i>	Both common	Variable
Skin / mucosa	Psoriasis in ~10%	Psoriasis (definitional); nail disease ~90%	Keratoderma blennorrhagica, circinate balanitis, oral ulcers	Mucosal/IBD activity ($\pm$ erythema nodosum)

Feature	Ankylosing spondylitis (r-axSpA)	Psoriatic arthritis (PsA)	Reactive arthritis (ReA)	IBD-associated arthritis
Eye	Acute anterior uveitis ~40% (unilateral, episodic)	Uveitis ~5% (may be posterior/bilateral)	Conjunctivitis (early) + anterior uveitis	Anterior uveitis
Hallmark / eponym	“Bamboo spine”; Romanus (shiny-corner) & Andersson lesions	“Pencil-in-cup” deformity; “fluffy” periosteal new bone	<i>Reiter triad</i> = arthritis + urethritis + conjunctivitis	Gut-joint axis; arthritis may pre-date IBD

Classification criteria worth knowing

- **Modified New York criteria for AS** — *definite AS* = ≥ 1 clinical + 1 radiographic criterion:

Clinical criteria	Radiographic criterion
Low back pain >3 months, improved by exercise, not by rest	Bilateral grade ≥ 2 sacroiliitis, OR
Limited lumbar motion (frontal & lateral planes)	Unilateral/bilateral grade 3–4 sacroiliitis
Reduced chest expansion	(Sacroiliitis graded 0–4: 0 normal $\rightarrow$ 4 total ankylosis)

- **CASPAR criteria (PsA)**: inflammatory articular disease *plus* ≥ 3 points from — current psoriasis (2) / personal/family history (1); psoriatic nail dystrophy; RF negative; dactylitis; juxta-articular new bone on radiograph (each 1). Specificity 98.7%, sensitivity 91.4%.
- **ASAS criteria for peripheral SpA**: arthritis or enthesitis or dactylitis *plus* ≥ 1 of (psoriasis, IBD, preceding infection, HLA-B27, uveitis, sacroiliitis on imaging) *or* ≥ 2 of the remaining SpA features.
- **Inflammatory back pain** (vs mechanical): insidious onset <45 y, >3 months, morning stiffness >30 min, night pain (second half), improves with exercise/not rest, good NSAID response.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Spectrum of SpA tree** — *Root box*: “Seronegative Spondyloarthritis (RF/anti-CCP negative, HLA-B27 linked)”. *Branch 1* — **Axial SpA**: radiographic axSpA (= Ankylosing spondylitis) and non-radiographic axSpA. *Branch 2* — **Peripheral SpA**: Psoriatic arthritis,

Reactive arthritis, IBD-associated arthritis, Undifferentiated pSpA. Side note: “sometimes included — SAPHO, acne-associated, hidradenitis suppurativa”.

- ▶ **Pelvic/spine radiograph schematic** — label: **bilateral symmetric sacroiliitis, squaring of vertebral bodies, shiny corner (Romanus) sign, marginal vertical syndesmophytes, “bamboo spine”, and (for PsA) “pencil-in-cup” deformity with fluffy periosteal new bone.**

Clinical / Diagnostic significance

- ▶ **Investigations:** RF and anti-CCP *negative*; ESR/CRP raised in only ~30–50% (neither sensitive nor specific). **HLA-B27** supports diagnosis but is not confirmatory (occurs in healthy people). **X-ray pelvis (AP/Ferguson view)** for sacroiliitis; **MRI sacroiliac joints (STIR)** detects early osteitis/bone-marrow oedema before radiographic change; low-dose CT is an emerging alternative.
- ▶ **Differential diagnosis of “sacroiliitis”:** DISH (flowing right-sided thoracic osteophytes, normal SI joints), osteitis condensans ilii (multiparous women), septic sacroiliitis (TB, brucellosis), insufficiency fracture.
- ▶ **Management (treat-to-target → low disease activity/remission):** NSAIDs at full dose first-line for axial disease + physiotherapy and smoking cessation; **csDMARDs (sulfasalazine, methotrexate)** help *peripheral* disease only (ineffective for axial). Escalate to **TNF inhibitors** (etanercept, adalimumab, infliximab, golimumab, certolizumab) or **IL-17 inhibitors** (secukinumab, ixekizumab; bimekizumab), then **JAK inhibitors** (tofacitinib, upadacitinib). Screen for **latent TB, HBV, HCV** before biologics. PsA adds IL-12/23 (ustekinumab), IL-23 (guselkumab, risankizumab), PDE-4 (apremilast), TYK2 (deucravacitinib). **Systemic steroids are ineffective/avoided in axSpA.**
- ▶ **Domain-/comorbidity-tailored choice:** TNF *monoclonal antibodies* preferred for coexistent uveitis or IBD; **IL-17 inhibitors are contraindicated in active IBD**; JAKi reserved post-TNF failure (CV/malignancy black-box warning).

High-yield exam pointers

- ▶ “Seronegative” = RF and anti-CCP **negative, no nodules**; unifying link is **HLA-B27** (strongest in AS, 85–90%).
- ▶ **Moll & Wright (1974)** separated SpA from RA and described **5 PsA patterns**: asymmetric oligoarticular, symmetric polyarticular, DIP-predominant, spondylitis, arthritis mutilans.
- ▶ **Modified New York criteria** define AS; sacroiliitis graded 0–4; **CASPAR** for PsA; **ASAS** criteria for axial & peripheral SpA.

- ▶ **ReA** = *sterile* arthritis 1–4 weeks after enteric/urogenital infection; **Reiter triad** = arthritis + urethritis + conjunctivitis (“can’t see, can’t pee, can’t climb a tree”); keratoderma blennorrhagica + circinate balanitis.
- ▶ **AS sacroiliitis** = **bilateral/symmetric** with **marginal vertical syndesmophytes**; **PsA** = **asymmetric** with **chunky non-marginal syndesmophytes** and “pencil-in-cup”.
- ▶ **Acute anterior uveitis** (unilateral, episodic) is the commonest extra-articular feature of axSpA (~40%).
- ▶ Late complications of AS: vertebral fracture (lower cervical), cauda equina syndrome, aortic regurgitation, AV block, apical pulmonary fibrosis, **IgA nephropathy / AA amyloidosis**.
- ▶ **IL-17 inhibitors are contraindicated in active IBD**; TNF monoclonals preferred when uveitis/IBD coexist.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Spondyloarthritis” (Deodhar & Elewaut): definition, SpA spectrum, HLA-B27/pathogenesis, modified New York & sacroiliitis grading, CASPAR & ASAS criteria, and individual disease descriptions (AS, PsA, ReA, IBD-associated, undifferentiated pSpA).
- ▶ **CMDT 2026** — “Rheumatologic, Immunologic, & Allergic Disorders” (Axial spondyloarthritis, Psoriatic arthritis, Reactive arthritis, IBD-associated spondyloarthritis): current diagnostic essentials and treatment (NSAIDs, TNFi, IL-17i, JAKi; domain-based PsA therapy).



Sjögren’s syndrome

Asked in: Paper III Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Sjögren’s syndrome (Sjögren’s disease) is a prototype systemic autoimmune disorder characterised by **lymphocytic infiltration of the exocrine glands** (chiefly lacrimal and salivary) producing **keratoconjunctivitis sicca** (dry eyes) and **xerostomia** (dry mouth), together with profound **B-cell hyperactivity**. It exists as a *primary* disorder or *secondary* to another rheumatic disease (most often rheumatoid arthritis, SLE, limited scleroderma, primary biliary cholangitis, Hashimoto thyroiditis). It is the autoimmune disease with the **highest risk of lymphoma**, making it an ideal model of both autoimmunity and lymphoid malignancy.

Epidemiology and Pathogenesis

- ▶ **Demographics**: middle-aged women predominate — female-to-male ratio **10–20:1** (CMDT quotes ~9:1); peak onset 40–60 years but any age including childhood. Prevalence ~0.5–1%; 5–

20% of patients with other autoimmune diseases express sicca features. *Earlier-onset* disease is more aggressive (more systemic features and autoantibodies).

- ▶ **Core lesion:** activated T lymphocytes dominate early periductal infiltrates; in heavy lesions B-cell populations prevail with formation of **ectopic germinal centres**. Follicular, myeloid and plasmacytoid dendritic cells and macrophages are also present; inflammasome activation correlates with lymphoma risk.
- ▶ **Autoimmune epithelitis** (term coined by *Moutsopoulos*): ductal/acinar epithelial cells are active participants — they (1) express costimulatory molecules and surface **Ro/La autoantigens**, (2) secrete proinflammatory cytokines and lymphocyte-attracting chemokines, (3) express **Toll-like receptors** (TLR) 3, 7, 9 linking innate immunity to autoreactivity, and (4) display ICAM/CD40. Epithelial cells show *increased apoptosis*, whereas infiltrating lymphocytes resist it.
- ▶ **BAFF axis:** epithelial **B-cell-activating factor** (BAFF), induced by type I/II interferons, is elevated in serum (especially with hypergammaglobulinaemia/autoantibodies) and exerts an antiapoptotic effect on B cells — the central driver of B-cell hyperactivity.
- ▶ **Genetics:** **HLA-DQA1\0501*; **interferon/BAFF-axis genes** (IRF5, STAT4, BAFF); **B-cell genes** (EBF1, BLK**); and combined deficiencies of the classical complement pathway. Triggers include viruses, hormonal factors and stressful life events on a genetically primed background.

Clinical Manifestations

Glandular (sicca) features

- ▶ **Xerostomia:** difficulty swallowing dry food, burning mouth, increased **dental caries** (caries at the gum line strongly suggests Sjögren's), dry erythematous sticky mucosa, atrophic filiform papillae and a **deeply fissured tongue**; saliva is scanty or cloudy.
- ▶ **Keratoconjunctivitis sicca:** gritty/sandy foreign-body sensation, burning, redness, photophobia (photophobia may herald corneal ulceration); due to destruction of corneal and bulbar conjunctival epithelium.
- ▶ **Parotid/major salivary gland enlargement** (intermittent or persistent) in about two-thirds; other glands → dry nose/throat/**xerotrachea**, oesophageal dysmotility, atrophic gastritis, vaginal dryness with dyspareunia, dry skin.

Extraglandular (systemic) manifestations — in ~one-third; classified as nonspecific, periepithelial, immune-complex-mediated, and lymphoma (Harrison Table 373-1):

Manifestation	~Prevalence	Remarks
Fatigue / myalgias	25%	Overlapping fibromyalgia
Arthralgias / arthritis	60%	Nonerosive ; may give <i>Jaccoud's arthropathy</i>
Raynaud's phenomenon	37%	Precedes sicca in one-third

Manifestation	~Prevalence	Remarks
Lung involvement	14%	Small-airway disease, lymphocytic interstitial pneumonitis (bronchitis sicca)
Kidney involvement	9%	Interstitial nephritis → distal (type I) RTA, hyposthenuria; nephrocalcinosis if untreated; <i>distal RTA in ~20% (CMDT)</i>
Liver involvement	6%	Primary biliary cholangitis (autoimmune cholangitis)
Small-vessel vasculitis	9%	Palpable purpura , urticaria, ulcers (immune-complex, cryoglobulin-associated)
Peripheral neuropathy	2%	Sensory/sensorimotor; mononeuritis multiplex
Glomerulonephritis	2%	Membranoproliferative with type II/III cryoglobulinaemia
Lymphoma	6%	Glandular MALT (marginal-zone) lymphoma most common

- ▶ **Neurological:** broad spectrum — peripheral neuropathy, dysautonomia, rarely CNS disease; *myelitis with anti-aquaporin-4 antibodies (NMO-spectrum)* is described.
- ▶ **Cardiovascular:** increased risk, as in RA and SLE.

Investigations and Autoantibody Profile

- ▶ **Ocular tests:** Schirmer's I test (≤ 5 mm wetting in 5 min is abnormal); tear break-up time / tear lysozyme; slit-lamp staining with **Rose Bengal** or **lissamine green** → punctate corneal/conjunctival erosions and filaments; **ocular staining score** ≥ 5 (or *van Bijsterveld score* ≥ 4).
- ▶ **Salivary tests:** **sialometry** — unstimulated whole salivary flow ≤ 0.1 mL/min; **salivary gland ultrasound** (hyperechoic bands, hypoechoic foci) of diagnostic and prognostic value; MRI/sialography.
- ▶ **Labial minor salivary gland biopsy:** the histopathologic standard — **focal lymphocytic sialadenitis with focus score** ≥ 1 (≥ 1 focus of ≥ 50 lymphocytes per 4 mm^2).
- ▶ **Serology:** elevated ESR, polyclonal **hypergammaglobulinaemia**, ANA ($\sim 95\%$), **rheumatoid factor** ($\sim 70\%$), and antibodies to **Ro52/Ro60 (SS-A)** and **La (SS-B)**; leukopenia common. Low **C4**, **cryoglobulins**, and **monoclonal gammopathy** flag higher risk of vasculitis/lymphoma. Anti-Ro52 may associate with interstitial lung disease.

- ▶ **Niche antibodies:** anticentromere (limited-scleroderma picture), antimitochondrial (autoimmune cholangitis/PBC), anti-21-hydroxylase (blunted adrenal response), anti-CCP (erosive arthritis subset), anti-calponin-3 (peripheral neuropathy), anti-AQP4 (myelitis).

Classification Criteria and Differential Diagnosis

- ▶ **2016 ACR/EULAR classification criteria** (applied to patients with at least one symptom of ocular/oral dryness or suspicion from systemic disease, after exclusions) — weighted score, classify if total ≥ 4 :

Item	Weight
Labial salivary gland with focal lymphocytic sialadenitis, focus score ≥ 1	3
Anti-SSA/Ro positive	3
Ocular staining score ≥ 5 (or van Bijsterveld ≥ 4) in ≥ 1 eye	1
Schirmer's ≤ 5 mm/5 min in ≥ 1 eye	1
Unstimulated whole salivary flow ≤ 0.1 mL/min	1

- ▶ **Mandatory exclusions:** prior head-and-neck radiation, active **hepatitis C**, **AIDS**, **sarcoidosis**, **amyloidosis**, graft-versus-host disease, **IgG4-related disease**.
- ▶ **Differential of sicca / bilateral parotid enlargement:** drugs (anticholinergic, antihypertensive, antidepressant), viral infection (HCV, HIV, mumps, EBV, CMV), sarcoidosis, **IgG4-related disease**, diabetes, amyloidosis, lymphoma. Key discriminators: HIV sicca = young males, parotid CD8 infiltrate, anti-Ro/La negative, HIV serology positive; sarcoidosis = noncaseating granulomas; HCV = lymphocytic infiltrate but milder, anti-SS-A/B negative.

Lymphoma Risk (high-yield)

- ▶ Highest lymphoma risk of any autoimmune disease (~5–10% lifetime); usually **extranodal, low-grade marginal-zone (MALT) B-cell lymphoma**, often found incidentally on labial biopsy.
- ▶ **Predictive risk factors** (Harrison Fig 373-2): persistent **parotid enlargement**, severe tongue atrophy, **palpable purpura**, **low C4**, **monoclonal gammopathy**, **cryoglobulins**, leukopenia, RF and anti-Ro/La positivity, and on histology **germinal-centre formation** with heavy focal lymphocytic infiltrates. CMDT adds splenomegaly, vasculitis, peripheral neuropathy and anaemia.
- ▶ **Worse survival** with B-symptoms, nodal mass > 7 cm, and intermediate/high histological grade. FDG-PET/CT helps exclude lymphoma when suspected.

Treatment

- ▶ **Symptomatic/local (cornerstone):** artificial tears (hydroxypropyl methylcellulose, polyvinyl alcohol, 0.5% methylcellulose), **topical ciclosporin 0.05%** or **lifitegrast 5%** eye drops; boric-acid ointment/eye-patching for corneal ulcers. Frequent sips of water, sugar-free gum/candies; meticulous oral hygiene with **fluoride** to preserve dentition. **Avoid** drugs that worsen dryness (diuretics, antihypertensives, anticholinergics, antidepressants, decongestants).
- ▶ **Secretagogues:** muscarinic agonists **pilocarpine 5 mg** (TID–QID) and **cevimeline 30 mg** TID.
- ▶ **Musculoskeletal disease:** **hydroxychloroquine 200–400 mg/day** and/or **methotrexate 0.2–0.3 mg/kg/week** for arthralgia/mild arthritis.
- ▶ **Distal RTA:** oral **sodium bicarbonate 0.5–2 mmol/kg/day** in four divided doses.
- ▶ **Systemic/severe disease (vasculitis, purpura, persistent arthritis):** glucocorticoids and **rituximab (anti-CD20)**. Emerging B-cell-directed strategies: sequential **belimumab** → **rituximab**, **ianalumab** (anti-BAFF-receptor), CD40L/CD40-targeting agents; **nipocalimab** (FcRn blocker; FDA Breakthrough Therapy designation 2024). Lymphoma is treated per standard oncological guidelines.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis of autoimmune epithelitis (flow diagram):** Genetic background (HLA-DQA1\0501, *IRF5*, *STAT4*, *BLK*) + triggers (*viruses, hormones, stress*) → *activated glandular epithelial cell (surface Ro/La, TLR 3/7/9, BAFF, chemokines)* → *recruitment of T cells then B cells* → *ectopic germinal centre* → *hypergammaglobulinaemia, anti-Ro/La, cryoglobulins* → *glandular destruction (sicca) and risk of MALT lymphoma*. Labels: epithelial cell, T cell, B cell, BAFF, germinal centre, anti-Ro/anti-La, lymphoma*.
- ▶ **Sicca complex face/eye schematic:** dry fissured tongue, dental caries at gum line, parotid enlargement; eye with Schirmer's strip (≤ 5 mm/5 min) and Rose Bengal-stained punctate keratitis. Labels: *xerostomia, parotid enlargement, keratoconjunctivitis sicca, Schirmer's test, Rose Bengal staining*.

Clinical / Diagnostic significance

- ▶ Suspect Sjögren's in any patient with persistent dry eyes/mouth, **bilateral parotid swelling**, Raynaud's, palpable purpura, or features of **distal RTA**; always take a drug history and exclude HCV/HIV, sarcoidosis and IgG4-related disease.
- ▶ The triad of **anti-Ro/La + focus score ≥ 1 labial biopsy + objective sicca tests** secures classification; biopsy and ultrasound carry prognostic weight.
- ▶ New or persistent parotid enlargement, purpura, low C4 or cryoglobulins mandates **active lymphoma surveillance**.
- ▶ **Checkpoint inhibitors (anti-PD-1/PD-L1)** can trigger de-novo Sjögren's — relevant in oncology patients.

- ▶ Anti-Ro/La are transplacental → risk of **neonatal lupus and congenital heart block** in offspring.

High-yield exam pointers

- ▶ **Autoimmune epithelitis** — the unifying concept; periepithelial lymphocytic infiltration of lung/kidney/liver.
- ▶ F:M **10–20:1**; prevalence ~0.5–1%; primary vs secondary (RA > SLE > scleroderma > PBC).
- ▶ **Anti-SSA/Ro and anti-SSB/La** are the hallmark antibodies; RF positive in ~70%, ANA ~95%.
- ▶ **Schirmer's** ≤5 mm/5 min; **focus score** ≥1 on labial biopsy; unstimulated salivary flow ≤0.1 mL/min.
- ▶ **2016 ACR/EULAR** weighted criteria — anti-Ro and biopsy weighted 3 each; classify at ≥4.
- ▶ **Distal (type I) RTA** in ~20%; interstitial nephritis, hyposthenuria, nephrocalcinosis.
- ▶ **Highest lymphoma risk** of all autoimmune diseases → **extranodal marginal-zone (MALT) lymphoma**.
- ▶ First-line therapy is **substitutive/secretagogue** (artificial tears, pilocarpine/cevimeline); **rituximab/Hcq/MTX** for systemic disease.
- ▶ **Jaccoud's arthropathy** (reversible nonerosive deformity) and **NMO/anti-AQP4 myelitis** are classic associations.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Sjögren's Disease" (pathogenesis, autoimmune epithelitis, extraglandular-manifestation table, lymphoma risk factors, 2016 ACR/EULAR diagnostic algorithm, treatment).
- ▶ CMDT 2026 — "Rheumatologic, Immunologic, & Allergic Disorders: Sjögren Disease" (essentials, clinical findings, distal RTA frequency, ocular/oral therapy, lifitegrast, belimumab→rituximab, ivalumab, nipocalimab, prognosis/lymphoma predictors).
- ▶ Coverage note: The dedicated 2016 ACR/EULAR criterion **weights** (3/3/1/1/1, threshold ≥4) are universally accepted rheumatology; Harrison lists the same component items and exclusions in its diagnostic algorithm but does not tabulate the numeric weights.



Clinical Presentations and Extraglandular Manifestations of Sjögren's Syndrome

Asked in: Paper III May 2025 — RGUHS MD General Medicine

Definition / Introduction — *Sjögren's disease (syndrome)* is a prototype systemic autoimmune disorder characterised by **chronic lymphocytic (CD4⁺ T-cell) infiltration of the exocrine glands** — chiefly salivary and lacrimal — producing **xerostomia** and **keratoconjunctivitis sicca (KCS)**, on a background of intense **B-cell hyperactivity** (hypergammaglobulinaemia, anti-Ro/anti-La). It may occur **alone**

(primary) or with another rheumatic disease (secondary/associated) — most often rheumatoid arthritis, limited scleroderma, SLE, primary biliary cholangitis, or Hashimoto thyroiditis. Middle-aged women dominate (F:M $\approx$ 9–20:1; prevalence $\sim$ 0.5–1%), and the disease carries the **highest lymphoma risk of any autoimmune disease**.

Glandular (sicca) manifestations — the clinical core

Most patients present with symptoms of impaired exocrine function; the course is slow and usually benign.

- ▶ **Oral (xerostomia):** difficulty swallowing dry food, *burning mouth*, **rampant dental caries** (caries at the gum line strongly suggests the disease), poor denture tolerance, “cotton mouth”, difficulty speaking. Examination shows a dry, erythematous, sticky mucosa; in severe cases the tongue dorsum loses filiform papillae and becomes **deeply fissured**; saliva is unexpressible or cloudy.
- ▶ **Ocular (keratoconjunctivitis sicca):** sensation of *sand/gravel* under the lids, burning, itching, redness, photosensitivity, eye fatigue, stringy secretions at inner canthi, intolerance of contact lenses; **corneal ulceration** is a painful complication of severe dryness. Due to destruction of corneal/bulbar conjunctival epithelium.
- ▶ **Salivary gland enlargement:** intermittent or persistent **parotid (or other major gland) enlargement in ~one-third (two-thirds in some series)** — relapsing; firm, non-tender. *A hard, nodular, or rapidly enlarging gland must raise suspicion of lymphoma.*
- ▶ **Other exocrine surfaces:** dry nose/throat/trachea (**xerotrachea**, dry cough), oesophageal mucosal dysmotility, atrophic gastritis, vaginal dryness with **dyspareunia**, and dry skin.

Extraglandular (systemic) manifestations

Systemic features occur in **~one-third** of patients and are classified by mechanism into **non-specific, periepithelial** (“autoimmune epithelitis”), **immune-complex-mediated**, and **lymphoma** (Moutsopoulos). Prevalences below are from Harrison Table 373-1 (primary disease).

Category	Manifestation	~Prevalence	Remarks
Non-specific	Fatigability / myalgias	25%	Fibromyalgia overlap
	Arthralgias / arthritis	60%	Usually non-erosive ; can give <i>Jaccoud’s arthropathy</i>
	Raynaud’s phenomenon	37%	In one-third, <i>precedes</i> sicca symptoms
Periepithelial	Lung involvement	14%	Small-airway disease / <i>lymphocytic interstitial pneumonitis</i> , bronchitis sicca, ILD

Category	Manifestation	~Prevalence	Remarks
	Kidney (interstitial)	9%	Interstitial nephritis → distal (type I) RTA, hyposthenuria; usually asymptomatic; untreated acidosis → nephrocalcinosis
	Liver	6%	Primary biliary cholangitis (stage I); antimitochondrial Ab
Immune-complex	Small-vessel vasculitis	9%	Palpable purpura, urticarial lesions, skin ulcers, mononeuritis multiplex; with cryoglobulinaemia
	Peripheral neuropathy	2%	Sensory or sensorimotor polyneuropathy
	Glomerulonephritis	2%	Membranoproliferative, with mixed type II/III cryoglobulinaemia
Malignant	Lymphoma	6%	Glandular MALT lymphoma most common

- ▶ **Renal tubular acidosis (distal type I)** is the classic renal lesion — CMDT cites it in ~20% of patients; treat with oral sodium bicarbonate. Glomerulonephritis (immune-complex/cryoglobulinaemic) is rarer.
- ▶ **Neurological spectrum is broad and can be devastating:** peripheral/sensory ataxic neuropathy, *autonomic dysfunction (dysautonomia)*, cranial (especially trigeminal) neuropathy, and CNS disease. Myelitis with anti-aquaporin-4 antibodies (**neuromyelitis optica spectrum disorder**) and MS-like lesions are recognised. *Anticalponin-3* antibodies are associated with peripheral neuropathy.
- ▶ **Cutaneous:** beyond vasculitic purpura, annular erythema and xerosis occur.
- ▶ **Cardiovascular:** like RA and SLE, an **increased cardiovascular risk** is reported. *Neonatal lupus / congenital heart block* is the offspring risk in anti-Ro/La-positive mothers.

Lymphoma — the defining late complication

- ▶ Sjögren's carries the **highest lymphoma risk among autoimmune diseases** (driven by sustained B-cell activation, BAFF, and germinal-centre formation).
- ▶ Most are **extranodal, low-grade, marginal-zone B-cell (MALT) lymphomas**, often arising in salivary glands and found incidentally on labial biopsy; affected nodes are usually peripheral.

- ▶ **Risk factors (Fig. 373-2):** *clinical* — persistent **parotid enlargement**, palpable purpura, severe tongue atrophy, splenomegaly, peripheral neuropathy; *haematologic/serologic* — leukopenia, **low C4**, **monoclonal gammopathy**, **mixed monoclonal cryoglobulins**, persistent RF/anti-Ro-La; *histologic* — heavy focal lymphocytic infiltrates and **germinal-centre formation** on minor salivary gland biopsy.
- ▶ Worse survival with **B symptoms**, **nodal mass >7 cm**, and **intermediate/high histologic grade**; FDG-PET/CT helps exclude transformation.

Laboratory and autoantibody profile

- ▶ **Cytopenias:** mild anaemia, leukopenia, infrequent lymphopenia, eosinophilia.
- ▶ **B-cell hyperactivity:** **polyclonal hypergammaglobulinaemia**, raised ESR, positive ANA (~95%) and **rheumatoid factor** (~70%).
- ▶ **Specific autoantibodies:** anti-Ro/SSA (Ro52, Ro60) and anti-La/SSB — correlate with earlier onset, systemic/extraglandular disease; Ro52 links to interstitial lung disease.
- ▶ **Markers of severity:** **cryoglobulins** and **low C4** (vasculitis, lymphoma risk); anticentromere Ab (limited-scleroderma-like picture); antimitochondrial Ab (autoimmune cholangitis); anti-citrullinated peptide Ab (associated arthritis); anti-21-hydroxylase Ab (blunted adrenal response).

Diagnosis, classification criteria & differential diagnosis

- ▶ **Objective tests:** Schirmer I test ≤ 5 mm/5 min, tear break-up time, **ocular staining score** (lissamine green/Rose Bengal; score ≥ 5 , or *van Bijsterveld* ≥ 4); **unstimulated whole salivary flow** ≤ 0.1 mL/min (sialometry); salivary gland **ultrasound** (hypoechoic areas — diagnostic/prognostic); and **labial minor salivary gland biopsy** showing **focal lymphocytic sialadenitis**, **focus score ≥ 1 focus/4 mm²**.
- ▶ **2016 ACR/EULAR classification criteria** (weighted; **total ≥ 4** classifies, with at least one sicca symptom and after exclusions): labial gland focal lymphocytic sialadenitis with focus score ≥ 1 = 3; anti-SSA/Ro positive = 3; ocular staining score ≥ 5 (or *van Bijsterveld* ≥ 4) = 1; Schirmer ≤ 5 mm/5 min = 1; salivary flow ≤ 0.1 mL/min = 1.
- ▶ **Exclusions:** prior head/neck irradiation, active **hepatitis C**, **AIDS**, **sarcoidosis**, amyloidosis, graft-versus-host disease, **IgG4-related disease**.
- ▶ **Differential of sicca / bilateral parotid swelling:** HCV and HIV (diffuse CD8⁺ infiltration), **sarcoidosis** (non-caseating granulomas), IgG4-related disease, mumps/EBV/CMV, amyloidosis, drugs (anticholinergics, antihypertensives, antidepressants), diabetes, and previously checkpoint-inhibitor (PD-1/PD-L1)–triggered sicca.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Classification of extraglandular manifestations (radial/spoke diagram):** centre box “Sjögren’s disease — B-cell hyperactivity”; four spokes labelled **Non-specific** (fatigue, arthralgia, Raynaud’s), **Periepithelial / autoimmune epithelitis** (lung, kidney–RTA, liver–PBC), **Immune-complex-mediated** (purpura/vasculitis, MPGN, peripheral neuropathy, cryoglobulinaemia, low C4), **Lymphoma** (MALT).
- ▶ **Labial minor salivary gland biopsy histology:** label acinus, duct, focal lymphocytic infiltrate (≥ 50 lymphocytes = one focus), germinal centre, and “focus score $\geq 1 / 4 \text{ mm}^2$ ”.

Clinical / Diagnostic significance

- ▶ Caries at the gum line + parotid swelling + dry eyes in a middle-aged woman is the bedside triad prompting work-up.
- ▶ A hard/rapidly enlarging parotid, palpable purpura, low C4, cryoglobulins, or monoclonal band mandates evaluation for MALT lymphoma.
- ▶ Anti-Ro/La positivity carries **obstetric implications** — neonatal lupus and **congenital complete heart block**; screen and monitor pregnancies.
- ▶ Unexplained distal RTA, nephrocalcinosis, hypokalaemic paralysis, or NMOSD/transverse myelitis should trigger sicca screening.
- ▶ Exclude HCV, HIV, sarcoidosis, IgG4-RD before labelling primary disease.

High-yield exam pointers

- ▶ Two cardinal symptoms = xerostomia + keratoconjunctivitis sicca (sicca complex).
- ▶ Pathology = autoimmune epithelitis; major infiltrating cell = activated CD4^+ T lymphocyte; driver = BAFF-mediated B-cell hyperactivity.
- ▶ Anti-Ro/SSA + anti-La/SSB are the hallmark antibodies; RF ~70%, ANA ~95%.
- ▶ Arthritis is non-erosive (Jaccoud’s); Raynaud’s precedes sicca in one-third.
- ▶ Distal (type I) RTA is the classic renal lesion (~20%); **interstitial nephritis** > glomerulonephritis.
- ▶ Highest lymphoma risk of any autoimmune disease — usually MALT type; red flags = persistent parotid swelling, purpura, low C4, cryoglobulins, monoclonal gammopathy.
- ▶ **Diagnosis:** Schirmer $\leq 5 \text{ mm}/5 \text{ min}$, focus score ≥ 1 on lip biopsy, salivary flow $\leq 0.1 \text{ mL/min}$ → 2016 ACR/EULAR score ≥ 4 .
- ▶ **Treatment:** secretagogues pilocarpine 5 mg / cevimeline 30 mg, artificial tears, topical ciclosporin/lifitegrast; hydroxychloroquine/methotrexate for arthritis; rituximab/glucocorticoids and sequential belimumab→rituximab for systemic/vasculitic disease; oral bicarbonate for RTA.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Sjögren's Disease” (Moutsopoulos & Mavragani): definition, pathogenesis, glandular/extraglandular manifestations and Table 373-1, lymphoma risk factors (Fig. 373-2), autoantibodies, 2016 ACR/EULAR diagnostic algorithm and differentials.
- ▶ **CMDT 2026** — “Sjögren Disease,” Rheumatologic, Immunologic, & Allergic Disorders: essentials, distal RTA frequency, neurologic spectrum (dysautonomia, NMO), Schirmer/lip-biopsy/sialometry/ultrasound, current B-cell therapy (belimumab→rituximab, ianalumab, nipocalimab).
- ▶ Coverage note: corpus is robust for this topic; the 2016 ACR/EULAR **weighted score** (3/3/1/1/1, **cut-off** ≥4) is stated as the universally accepted criteria — Harrison lists the same component items/thresholds (Fig. 373-3) but does not print the numeric weights.



Extra-articular Manifestations of Rheumatoid Arthritis and Their Management

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Rheumatoid arthritis (RA) is a chronic, systemic, immune-mediated inflammatory disease characterised by a symmetric, erosive polyarthritis of the small joints. Although predominantly articular, RA is fundamentally a **systemic disease**, and clinically significant *extra-articular manifestations* (EAMs) develop during its course in **up to 40% of patients**, sometimes even before the onset of arthritis. EAMs cluster in patients with a history of cigarette smoking, early significant disability, and seropositivity for **rheumatoid factor (RF)** or **anti-citrullinated protein antibodies (ACPA)**; their presence signifies severe disease and shortens survival. Their management rests on **aggressive control of the underlying RA** plus organ-specific therapy.

Determinants and overview of extra-articular disease

- ▶ **Risk factors for EAMs:** long-standing disease, high disease activity, smoking, high-titre RF/ACPA seropositivity, the HLA-DRB1 *shared epitope*, and hypocomplementemia (for vasculitis).
- ▶ EAMs contribute disproportionately to **morbidity and mortality** — patients with systemic involvement have shortened survival (overall RA mortality ~2× general population; median life expectancy reduced ~7 years in men, ~3 years in women).
- ▶ The incidence/severity of some EAMs (notably **Felty's syndrome** and **vasculitis**) has **declined** in the era of early, aggressive DMARD therapy.
- ▶ Most frequent EAMs: subcutaneous nodules, secondary Sjögren's, interstitial lung disease, pulmonary nodules, and anaemia.

Systemic and organ-specific extra-articular manifestations

System	Manifestations (key points)
Constitutional	Fatigue, malaise, low-grade fever, weight loss, depression, cachexia; reflect inflammatory burden, may precede arthritis. Fever $>38.3^{\circ}\text{C}$ (101°F) should raise suspicion of vasculitis or infection .
Cutaneous / Nodules	<i>Rheumatoid nodules</i> in 20–40% — firm, non-tender, adherent to periosteum/tendon/bursa over pressure points (forearm, olecranon, sacrum, Achilles tendon); correlate with seropositivity. Also purpura, pyoderma gangrenosum , digital infarcts. <i>Accelerated nodulosis</i> in up to 10% on long-term methotrexate.
Ocular	Keratoconjunctivitis sicca (secondary Sjögren's, ~10%), episcleritis , scleritis , scleromalacia perforans (from scleral nodules), peripheral ulcerative keratitis.
Oral	Xerostomia, periodontitis.
Pulmonary	Pleuritis is the commonest pulmonary feature — exudative effusion (monocytes/neutrophils, characteristically low glucose, low pH). Interstitial lung disease (ILD) in ~10–12% — patterns are UIP (honeycombing) and NSIP (ground-glass + reticulation); restrictive PFTs with reduced DLCO ; diagnosed on HRCT . Pulmonary nodules ; <i>Caplan's syndrome</i> = rheumatoid pneumoconiosis (nodules + silica/coal exposure). Also organising pneumonia, bronchiolitis, bronchiectasis, pulmonary vasculitis.
Cardiac	Pericardium is the commonest cardiac site — clinical pericarditis $<10\%$ but detectable on echo/autopsy in ~50%; asymptomatic effusions up to 20%. Also myocarditis (necrotizing/granulomatous), cardiomyopathy, arrhythmia, mitral regurgitation; accelerated ischaemic heart disease .
Vasculitis	<i>Rheumatoid vasculitis</i> (now $<1\%$) — long-standing, RF/ACPA-positive, hypocomplementemic disease. Nail-fold/digital pulp infarcts, petechiae, purpura, livedo reticularis, gangrene, painful leg ulcers; mononeuritis multiplex / sensorimotor polyneuropathy.
Haematologic	Normochromic normocytic anaemia of chronic disease (commonest; tracks CRP/ESR); reactive thrombocytosis. Felty's syndrome = triad of

System	Manifestations (key points)
	neutropenia + splenomegaly + nodular RA (<1%, late severe disease). T-cell large granular lymphocyte (T-LGL) leukaemia mimics Felty's. Lymphoma risk increased 2–4× (commonest = diffuse large B-cell lymphoma).
Neurologic	Cervical (atlantoaxial C1–C2) subluxation → compressive myelopathy (<10%); peripheral entrapment (carpal tunnel/median nerve); vasculitic neuropathy.
Renal	Membranous nephropathy; secondary (AA) amyloidosis from chronic inflammation.
Skeletal / Endocrine	Generalised osteoporosis (~2× risk; ~1/3 of postmenopausal women with RA) and fragility/hip fractures; hypoandrogenism.

Associated systemic comorbidities (high-yield)

- ▶ **Cardiovascular disease** is the single most common cause of death in RA — coronary and carotid atherosclerosis and heart failure are increased ~2-fold, *independent* of traditional risk factors, driven by systemic inflammation. Aggressive control of hypertension, diabetes, obesity, smoking, and RA inflammation improves outcomes.
- ▶ **Osteoporosis** — promoted by the inflammatory milieu (osteoclast activation via RANKL), chronic glucocorticoids, and immobility.
- ▶ **Infection** — both disease- and immunosuppression-related; a single joint inflamed out of proportion must be aspirated to exclude **septic arthritis**.

General principles of management

- ▶ **Treat-to-target (T2T)**: early, aggressive therapy started *as soon as the diagnosis is certain*, with frequent escalation/modification of DMARDs to reach **low disease activity or remission** (monitored by DAS-28, CDAI, SDAI); ACR/EULAR provisional remission = tender joints ≤1, swollen joints ≤1, CRP ≤1 mg/dL, patient global ≤1, **or** SDAI ≤3.3.
- ▶ **Minimise long-term glucocorticoids**; individualise to maximise efficacy and minimise toxicity.
- ▶ Multidisciplinary care: smoking cessation, exercise (~150 min/week moderate-vigorous), physiotherapy, foot orthotics/wrist splints, cardiovascular risk reduction, osteoporosis screening/prophylaxis, and vaccination.

Pharmacological management (drug classes)

Class	Agents & key dosing	Major cautions
NSAIDs	Non-selective COX-1/COX-2 inhibition	Adjunctive/symptomatic only — do <i>not</i> prevent erosions; never monotherapy. Gastritis, PUD, renal injury.
Glucocorticoids	Low-dose prednisone 5–10 mg/d (bridging/flare); intra-articular triamcinolone 10–40 mg ($\leq 4 \times / \text{yr}$); high-dose for serious EAMs	Osteoporosis (give bisphosphonate prophylaxis), infection, hyperglycaemia; use shortest duration (< 3 months).
Conventional synthetic DMARDs (csDMARDs)	Methotrexate = anchor drug, 7.5–25 mg weekly PO/SC + folic acid 1 mg/d ; Sulfasalazine 500 mg BD $\rightarrow$ up to 3 g/d; Leflunomide 20 mg/d; Hydroxychloroquine 200–400 mg/d (≤ 5 mg/kg)	MTX: hepatotoxicity, myelosuppression, pneumonitis, teratogenic (avoid in pregnancy/significant renal impairment). SSZ: check G6PD, cytopenias. LEF: teratogenic, long half-life. HCQ: retinal toxicity — baseline + annual eye exam.
Biologic DMARDs (bDMARDs)	TNF inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab); Abatacept (CTLA-4 Ig, blocks T-cell co-stimulation); Rituximab (anti-CD20 B-cell depletion); IL-6R inhibitors (tocilizumab, sarilumab); Anakinra (IL-1RA)	All $\uparrow$ infection. TNFi: screen/treat latent TB before starting; avoid in chronic HBV and NYHA class III/IV heart failure; rare demyelination/drug-induced lupus. Rituximab: HBV reactivation , rare PML ($\sim 1:25,000$). IL-6R: dyslipidaemia, neutropenia, GI perforation.
Targeted synthetic DMARDs (tsDMARDs)	JAK inhibitors — tofacitinib 5 mg BD, baricitinib 2 mg OD, upadacitinib 15 mg OD (oral)	FDA black-box warning: $\uparrow$ serious infection (herpes zoster), thrombosis/VTE , MACE , malignancy , death ; screen for TB.

- **Stepwise (treat-to-target) approach:** start **methotrexate** monotherapy; if inadequate response at 3–6 months, escalate to **oral triple therapy** (MTX + **sulfasalazine** + **hydroxychloroquine**) or add an **anti-TNF / non-TNF biologic** $\pm$ MTX. Switching to an agent with a *different mechanism* (e.g., abatacept, rituximab, IL-6R or JAK inhibitor) is appropriate after biologic failure; **biologic DMARDs are not combined** with each other.

Specific management of extra-articular disease

- **General rule:** effective control of underlying RA favourably modifies most EAMs, and early aggressive treatment may *prevent* their occurrence.

- ▶ **RA-ILD:** challenging because MTX and leflunomide are themselves pulmonary toxins — treat with **high-dose corticosteroids plus azathioprine, mycophenolate mofetil, or rituximab.**
- ▶ **Severe EAMs** (necrotizing scleritis, pericarditis, vasculitis): **high-dose glucocorticoids** ± cytotoxic/immunosuppressive therapy; vasculitic ulcers may need immunosuppression and skin grafting.
- ▶ **Felty's syndrome:** treat with DMARDs (methotrexate); distinguish from T-LGL leukaemia.
- ▶ **Cervical myelopathy from atlantoaxial subluxation:** neurosurgical stabilisation when neurologic compromise occurs.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — “Extra-articular manifestations of RA” body chart (a labelled human figure):** label organ pointers — *Ocular:* keratoconjunctivitis sicca, episcleritis, scleritis; *Oral:* xerostomia, periodontitis; *Pulmonary:* pleural effusion, pulmonary nodules, interstitial lung disease, organising pneumonia; *Cardiac:* pericarditis, myocarditis, ischaemic heart disease; *Haematologic:* anaemia of chronic disease, neutropenia, splenomegaly, **Felty's syndrome**, lymphoma; *Neurologic:* cervical myelopathy; *Renal:* membranous nephropathy, secondary amyloidosis; *Skin:* rheumatoid nodules, purpura, pyoderma gangrenosum; *Skeletal:* osteoporosis.
- ▶ **Diagram 2 — Treat-to-target escalation ladder:** boxes from bottom to top — *MTX monotherapy* → *MTX + triple therapy OR add anti-TNF/non-TNF biologic ± MTX* → *switch mechanism (abatacept / rituximab / IL-6R / JAK inhibitor)*; side arrow labelled “**Target = low disease activity / remission (DAS-28, CDAI, SDAI)**”; bracket labelled “glucocorticoid bridge, NSAID adjunct”.

Clinical / Diagnostic significance

- ▶ Presence of EAMs marks **severe, seropositive disease** and mandates aggressive systemic therapy and vigilant monitoring.
- ▶ **Workup pearls:** HRCT + PFTs (DLCO) for suspected ILD; echocardiography for pericardial disease; nerve conduction studies for mononeuritis multiplex; CBC + splenic imaging and peripheral-blood flow cytometry (to exclude T-LGL) in cytopenic patients; flexion–extension cervical radiographs/MRI for atlantoaxial subluxation (important **pre-operative/pre-intubation** assessment).
- ▶ A new fever or a single disproportionately inflamed joint demands exclusion of **infection / septic arthritis** before attributing it to a flare.

High-yield exam pointers

- ▶ EAMs occur in **up to 40%** of RA; predicted by smoking + RF/ACPA seropositivity + high disease activity.

- ▶ **Pleuritis** = commonest pulmonary EAM; pleural fluid characteristically **low glucose, low pH** (exudate).
- ▶ **Felty's syndrome** = **neutropenia + splenomegaly + nodular RA**; mimicked by T-LGL leukaemia.
- ▶ **Caplan's syndrome** = RA pulmonary nodules + pneumoconiosis (silica/coal).
- ▶ **Cardiovascular disease** = **leading cause of death** in RA; secondary **AA amyloidosis** and membranous nephropathy are the renal EAMs.
- ▶ **Methotrexate** = anchor DMARD (+ folic acid); **hydroxychloroquine** needs **annual retinal screening**.
- ▶ **Screen for latent TB before any TNF inhibitor**; avoid TNFi in chronic HBV and NYHA III/IV heart failure.
- ▶ **RA-ILD** treated with steroids + azathioprine/mycophenolate/rituximab (avoid MTX/leflunomide-related lung toxicity).
- ▶ **Treat-to-target**: aim for low disease activity/remission (DAS-28/SDAI/CDAI).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Rheumatoid Arthritis" (extra-articular manifestations Fig. 370-2; DMARD table; treatment of extra-articular manifestations and treat-to-target approach).
- ▶ **CMDT 2026** — "Rheumatologic, Immunologic, & Allergic Disorders: Rheumatoid Arthritis" (current drug dosing, corticosteroid and DMARD management, ocular and Felty's detail).

♦ ♦ ♦

Endocrinology

♦ ♦ ♦

Pharmacotherapy of Obesity in a Young Adult with Type 2 Diabetes and Hypertension (BMI 46 kg/m²)

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — This 25-year-old man weighs 118 kg at a height of 1.60 m, giving a BMI of 46.1 kg/m² — *class III (extreme) obesity* (WHO/NIH: class I 30–34.9, class II 35–39.9, class III ≥40). He already carries two adiposity-driven complications — **type 2 diabetes mellitus (T2DM)** and **hypertension** — and has failed structured lifestyle measures. He therefore meets criteria for **adjunct anti-obesity pharmacotherapy** (BMI ≥30, or ≥27 with comorbidity) and, given BMI ≥40, is simultaneously a candidate for **metabolic/bariatric surgery**. The strategic principle is to choose agents

that deliver weight loss *and* concurrently improve glycaemia, blood pressure and cardiovascular risk, while deliberately avoiding weight-promoting drugs.

Clinical assessment and rationale for drug therapy

- **Eligibility:** Adjuvant pharmacotherapy is indicated for BMI ≥ 30 kg/m², or ≥ 27 kg/m² with obesity-related disease, when diet and physical activity have failed — this patient qualifies on both counts.
- **Goal of therapy:** Improve obesity-related complications and quality of life; a realistic initial target is **8–10% weight loss over 6 months**; even **5–10% total-body-weight (TBW) loss** produces clinically meaningful, dose-related improvements in blood glucose, blood pressure, triglycerides and HDL.
- **“Treat-to-multiple-target” logic:** Because he has T2DM + hypertension + extreme obesity, the ideal agent is a “threefer” — a glucose-lowering drug that also causes weight loss and lowers BP. The **incretin (nutrient-stimulated hormone) class — GLP-1 receptor agonists and the GLP-1/GIP dual agonist tirzepatide** — fits all three, and is favoured by the diabetes algorithm whenever the management goal is “HbA1c + weight reduction” or there is ASCVD/ASCVD risk.
- **Drug must accompany an active lifestyle programme** — pharmacotherapy works best as an adjunct, not a replacement, for diet, exercise and behaviour modification.

Preferred therapy — incretin-based (nutrient-stimulated hormone) agents

These directly serve all of this patient’s problems and are the cornerstone of his treatment.

Drug	Mechanism of action	Dose / route	Placebo-subtracted weight loss	Key adverse effects	Contraindications
Semaglutide 2.4 mg	GLP-1 receptor agonist — ↑glucose-dependent insulin secretion, ↓glucagon, slows gastric emptying, acts on arcuate nucleus/NTS to ↓appetite	SC once weekly; titrate 0.25→0.5→1→1.7→2.4 mg q4-weekly	~12.5% (STEP 1–4: 6.2–14.8% at 68 wk)	Nausea, diarrhoea, constipation, vomiting; pancreatitis, cholelithiasis	Personal/family history of medullary thyroid carcinoma (MTC), MEN-2; caution if pancreatitis

Drug	Mechanism of action	Dose / route	Placebo-subtracted weight loss	Key adverse effects	Contraindications
Tirzepatide	Dual GIP + GLP-1 receptor agonist — GIP acts synergistically with GLP-1 in the brain for greater appetite suppression	SC once weekly; titrate 2.5 mg → max 15 mg	~17.8% (SURMOUNT-1: 20.9% vs 3.1% placebo at 15 mg)	Nausea, diarrhoea, constipation, abdominal pain	As above (MTC, MEN-2); caution pancreatitis
Liraglutide 3.0 mg	GLP-1 receptor agonist (97% homology to human GLP-1)	SC once daily; 0.6 mg/wk increments to 3.0 mg	~5.4% (SCALE: 3.4–6.1%)	Nausea, diarrhoea, constipation, vomiting	As above

- **Indications:** chronic weight management (all three) *and* T2DM (semaglutide, liraglutide, tirzepatide are independently approved glucose-lowering drugs) — making them uniquely suited to this patient.
- **Expected efficacy:** dual benefit — tirzepatide/semaglutide give the largest weight loss of any licensed medical therapy, **lower HbA1c by ~1–2%**, do **not** cause hypoglycaemia (glucose-dependent action) and reduce systolic BP through weight loss.
- **Cardiovascular value:** the SELECT trial showed semaglutide 2.4 mg reduced **major adverse cardiovascular events (MACE)** by ~20% in overweight/obese patients with established CVD; LEADER-type data show GLP-1 RAs reduce CV events and diabetic kidney disease in T2DM — directly relevant to a young diabetic-hypertensive patient with decades of risk ahead.

Anti-diabetic drugs that also assist weight loss and comorbidity control

- **Metformin (first-line for T2DM):** reduces hepatic glucose production and modestly improves peripheral glucose uptake; **promotes mild weight loss**, lowers insulin levels and improves lipids; start low, titrate to **max 2000 mg/day**. Adverse effects: GI upset (diarrhoea, nausea, metallic taste), ↓vitamin B12, rare lactic acidosis. Avoid if **eGFR <30 mL/min**, acidosis, unstable CHF, hepatic disease.
- **SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin):** block proximal-tubule glucose reabsorption → glucosuria, insulin-independent glucose lowering, **modest weight loss**, and a **diuretic-mediated 3–6 mmHg fall in systolic BP** — directly helping his hypertension. They reduce ASCVD events/CV mortality, reduce heart-failure hospitalisation and slow diabetic

kidney disease. Adverse effects: genital/urinary mycotic infection, volume depletion, euglycaemic DKA; do not initiate at eGFR <45 and avoid in stage 4 CKD.

- ▶ **Drugs to deliberately AVOID** (cause weight gain and worsen the index problem): **insulin, sulfonylureas, and thiazolidinediones** (TZDs add 2–3 kg, fluid retention/CHF risk). Sulfonylureas and insulin also carry hypoglycaemia risk. These run counter to the weight-loss goal and should be later/last-line here.

Other (non-incretin) anti-obesity medications

- ▶ **Phentermine / topiramate ER (PHEN/TPM)**: catecholamine releaser + anticonvulsant (GABA modulation, carbonic-anhydrase inhibition, glutamate antagonism); oral once daily, max 15/92 mg; placebo-subtracted weight loss ~8% (EQUIP/CONQUER 6.6–9.3%). AE: paraesthesia, dry mouth, dysgeusia, insomnia, cognitive impairment; **teratogenic (oral clefts)** — needs contraception/pregnancy testing. *Caution in this patient: uncontrolled hypertension is a contraindication* to phentermine-containing agents (they raise BP/HR).
- ▶ **Naltrexone SR / bupropion SR**: opioid antagonist + dopamine/noradrenaline reuptake inhibitor — disinhibits hypothalamic POMC/α-MSH to reduce intake; oral 2 tabs BID; weight loss ~5% (COR trials 4.2–5.1%). AE: nausea, constipation, headache, **small rise in BP/pulse**; contraindicated in uncontrolled hypertension, seizure disorder, chronic opioid use, MAOI within 14 days.
- ▶ **Orlistat**: GI/pancreatic lipase inhibitor — blocks absorption of ~30% of dietary fat at 120 mg tid; minimally absorbed, so no systemic toxicity; weight loss ~4.1%. AE: steatorrhea, oily spotting, faecal urgency, fat-soluble vitamin (A, D, E, K, β-carotene) depletion — supplement vitamins.
- ▶ **Setmelanotide**: MC4-receptor agonist for **monogenic/syndromic obesity only** (POMC, PCSK1, LEPR deficiency, Bardet–Biedl syndrome) — not for common polygenic obesity, but worth knowing in a *young-onset, extreme* obesity case where a secondary cause should be excluded.

Concurrent control of hypertension and escalation to surgery

- ▶ **Treat the comorbidities in parallel**: much of his hypertension and dysglycaemia will improve as weight falls. For pharmacological BP control in a diabetic, an **ACE inhibitor or ARB** is preferred (renoprotection/albuminuria reduction); weight-neutral add-ons (CCB, thiazide) as needed. SGLT2 inhibitors and GLP-1 RAs provide additional BP lowering.
- ▶ **Exclude secondary causes** in a young, extremely obese diabetic-hypertensive: drug-induced weight gain, hypothyroidism, Cushing's syndrome, hypothalamic disease, and (for resistant hypertension) endocrine hypertension.
- ▶ **Metabolic / bariatric surgery** is indicated and appropriate here — **BMI ≥40**, or ≥35 with a comorbidity, after failure of lifestyle ± medication. **Sleeve gastrectomy** and **Roux-en-Y gastric bypass** are commonest; restrictive-malabsorptive bypass yields ~28–33% TBW loss at 12–18 months, marked T2DM improvement (Swedish Obese Subjects: 78% lower incidence of T2DM;

~68% achieve initial diabetes remission within 5 years) and reduced all-cause/CV mortality. Requires lifelong vitamin B12, iron, folate, calcium and vitamin D supplementation after malabsorptive procedures.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **CNS appetite-regulation circuit with drug action sites:** Label — *Arcuate nucleus (ARC)* with POMC/CART (anorexigenic) and AgRP/NPY (orexigenic) neurons; α -MSH $\rightarrow$ MC4R in the *paraventricular nucleus (PVN)*; *nucleus tractus solitarius (NTS)* and *brainstem*; *mesolimbic reward (VTA $\rightarrow$ NAc, dopamine)*. Map drugs onto targets: GLP-1R $\rightarrow$ liraglutide/semaglutide/tirzepatide, GIP-R $\rightarrow$ tirzepatide, MC4R $\rightarrow$ setmelanotide, μ -opioid receptor $\rightarrow$ naltrexone, POMC/dopamine $\rightarrow$ bupropion, NE release/GABA $\rightarrow$ phentermine/topiramate, gut peptides (PYY, CCK, ghrelin, leptin, amylin) as afferent inputs.
- ▶ **Obesity-treatment pyramid / algorithm:** base = *Lifestyle (diet 500–750 kcal deficit, ≥ 150 min/wk activity, behaviour therapy)* $\rightarrow$ *Pharmacotherapy (BMI ≥ 30 or ≥ 27 + comorbidity)* $\rightarrow$ *Bariatric/metabolic surgery (BMI ≥ 40 , or ≥ 35 + comorbidity)*. Side branch: T2DM algorithm — “goal = HbA1c + weight reduction $\rightarrow$ GLP-1 RA / structured medical weight programme / metabolic surgery.”

Clinical / Diagnostic significance

- ▶ **Investigations before/with therapy:** fasting lipid profile, chemistry panel, HbA1c, blood pressure, waist circumference (South-Asian cut-off >90 cm in men), TSH and overnight dexamethasone/Cushing screen if clinically suggested, ECG; baseline renal function (guides metformin/SGLT2i dosing).
- ▶ **Monitoring on therapy:** weight/BMI trajectory and “stopping rules” (review benefit at 12–16 weeks for phentermine, PHEN/TPM and NB), HbA1c, BP, renal function; watch for GLP-1 RA GI intolerance, gallstones/pancreatitis, and euglycaemic DKA with SGLT2i; vitamin B12 on metformin.
- ▶ **Management pearl:** in this *young* patient the choice of weight-losing glucose-lowering drugs (incretins $\pm$ SGLT2i + metformin) over weight-gaining ones (insulin/sulfonylurea/TZD) sets the trajectory of his diabetes, BP and lifelong cardiovascular risk.

High-yield exam pointers

- ▶ BMI = $118 \div (1.60)^2 = 46.1$ kg/m² $\rightarrow$ class III (extreme) obesity (≥ 40); qualifies for *both* pharmacotherapy and bariatric surgery.
- ▶ Drug eligibility: BMI ≥ 30 , or ≥ 27 with comorbidity, after failed lifestyle. Realistic goal 8–10% in 6 months; 5–10% TBW loss already gives clinical benefit.

- ▶ **First choice here = GLP-1 RA (semaglutide) or dual GLP-1/GIP agonist (tirzepatide)** — they treat obesity *and* T2DM, lower BP, cut CV events (SELECT –20% MACE), and don't cause hypoglycaemia.
- ▶ Approximate placebo-subtracted weight loss: **tirzepatide ~17–21% > semaglutide ~12–15% > PHEN/TPM ~8% > liraglutide/NB ~5% > orlistat ~4%.**
- ▶ **SGLT2 inhibitors** add weight loss + **3–6 mmHg systolic BP fall** + CV/renal protection; **metformin** is first-line, weight-neutral/mild loss.
- ▶ **Avoid weight-gaining agents:** insulin, sulfonylureas, thiazolidinediones. **Phentermine/PHEN-TPM and naltrexone-bupropion are contraindicated in uncontrolled hypertension.**
- ▶ GLP-1 RAs/tirzepatide contraindicated in **medullary thyroid carcinoma / MEN-2**; orlistat causes steatorrhea + fat-soluble vitamin deficiency.
- ▶ **Bariatric surgery** (sleeve gastrectomy / Roux-en-Y): **28–33% TBW loss**, T2DM remission, reduced mortality — definitive option at BMI ≥40.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Evaluation and Management of Obesity” (anti-obesity pharmacotherapy: mechanisms, doses, EQUIP/CONQUER, COR, SCALE, STEP, SURMOUNT, SELECT trial data, antiobesity-medication table, bariatric surgery) and “Diabetes Mellitus: Management and Therapies” (glucose-lowering agent classes, T2DM management algorithm, metformin/SGLT2i/GLP-1 RA/tirzepatide).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Obesity and Neuroendocrine Control of Energy Stores” (drug action-site circuitry, phentermine/orlistat/naltrexone-bupropion detail, tirzepatide SURPASS/SURMOUNT efficacy).
- ▶ **CMDT 2026** — “Nutrition, Nutritional Disorders, & Obesity” (BMI classes, obesity-medication selection and stopping rules, liraglutide/semaglutide/tirzepatide efficacy meta-analyses, bariatric-surgery criteria).



Acquired Hypopituitarism

Asked in: Paper IV Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — *Hypopituitarism* is deficient secretion of one or more anterior pituitary trophic hormones, arising from disease of the pituitary, pituitary stalk, or hypothalamus. **Acquired hypopituitarism** is the far commoner adult form and reflects the compressive mass effect of tumours, or local pituitary/hypothalamic traumatic, vascular, autoimmune, inflammatory, infiltrative, or irradiation damage (as opposed to inherited/developmental causes). Loss of all anterior hormones is

termed **panhypopituitarism**. It carries a documented two- to three-fold excess of cardiovascular and cerebrovascular mortality, so prompt recognition and physiological hormone replacement are essential.

Etiology of acquired hypopituitarism

Causes are best grouped by mechanism (the “vascular–traumatic–neoplastic–inflammatory/infiltrative–infective–iatrogenic” framework):

Category	Representative causes
Neoplastic / compressive	Pituitary adenoma (esp. non-functioning macroadenoma ≥ 1 cm), craniopharyngioma, Rathke’s cleft cyst, meningioma, germinoma/glioma, hypothalamic hamartoma; metastases (breast 45%, lung); lymphoma, leukaemia
Vascular	Pituitary apoplexy; Sheehan’s syndrome (postpartum necrosis); subarachnoid haemorrhage; sickle-cell disease; snake (viper) bite venom; arteritis
Traumatic / iatrogenic	Traumatic brain injury (incl. contact sports, blast); neurosurgical resection; cranial/head-&-neck radiotherapy ; cardiopulmonary bypass
Inflammatory / autoimmune	Lymphocytic hypophysitis ; immune-checkpoint-inhibitor hypophysitis; granulomatous and IgG4-related hypophysitis
Infiltrative	Sarcoidosis, haemochromatosis , Langerhans-cell histiocytosis (histiocytosis X), amyloidosis
Infective	Tuberculosis, fungal (histoplasmosis), tertiary syphilis, opportunistic AIDS-related infection, toxoplasmosis, <i>Pneumocystis</i>
Functional / drug-induced	High-dose/exogenous glucocorticoids (HPA suppression), opioids, megestrol, GnRH agonists (e.g. leuprolide), bexarotene, mitotane; starvation, anorexia nervosa, critical illness, COVID-19

- Mass lesions cause failure by compressing the gland, stalk (“stalk-section” effect → early hyperprolactinaemia from loss of dopamine inhibition, with later loss of other hormones), or hypothalamus.
- **Cranial irradiation:** up to two-thirds develop hormone insufficiency after a median dose of ~50 Gy (5000 rad) to the skull base, evolving over 5–15 years, usually from hypothalamic rather than pituitary damage.

Pattern and sequence of hormone loss

- ▶ With progressive compression/destruction, trophic hormones are typically lost in a **predictable sequence**:

GH → FSH → LH → TSH → ACTH (mnemonic “Go Look For The Adenoma”). PRL is usually preserved or *elevated* (stalk effect); PRL deficiency (failed lactation) implies severe destruction, as in Sheehan’s.

- ▶ In children the presenting feature is **growth retardation**; in adults **hypogonadism is the earliest symptom**.

Axis lost	Clinical consequence
GH	Child: short stature, hypoglycaemia. Adult (AGHD): ↑central/visceral fat, ↓lean mass, ↓exercise capacity, dyslipidaemia, ↓bone density, poor quality of life
FSH/LH (gonadotrophin)	Women: oligo-/amenorrhoea, infertility, ↓libido, breast atrophy. Men: ↓libido, erectile dysfunction, ↓muscle/beard, soft testes; osteoporosis in both
TSH	Secondary (central) hypothyroidism: low free T4 with <i>low/inappropriately normal</i> TSH
ACTH	Secondary adrenal insufficiency: fatigue, anorexia, nausea, hypotension, hypoglycaemia, hyponatraemia — no hyperpigmentation, no hyperkalaemia (mineralocorticoid axis preserved)
PRL	Failure of postpartum lactation
AVP (posterior)	Polyuria/polydipsia (AVP deficiency / cranial diabetes insipidus) — points to stalk/hypothalamic involvement

Special acquired entities (high-yield)

- ▶ **Sheehan’s syndrome** — hypopituitarism from **postpartum pituitary necrosis** after severe peripartum haemorrhage/hypotension; the gland is enlarged and vulnerable in pregnancy. Classic clues: **failure to lactate** and **postpartum amenorrhoea**; onset is usually insidious over **10–20 years** (mean diagnostic delay ~9 years), presenting with hyponatraemia, hypoglycaemia, or anaemia. Acute Sheehan MRI: enlarged pituitary with a thin peripheral rim of gadolinium enhancement.
- ▶ **Pituitary apoplexy** — acute intrapituitary haemorrhage/infarction, usually into a pre-existing adenoma. **Endocrine emergency**: sudden severe headache, visual loss, ophthalmoplegia (cranial nerves III/IV/VI), meningism, and acute hypocortisolism → hypoglycaemia, hypotension, shock. Manage with **high-dose glucocorticoids**; **urgent transsphenoidal decompression** for progressive visual loss, cranial-nerve palsy, or deteriorating consciousness.
- ▶ **Lymphocytic hypophysitis** — autoimmune; most often in **late pregnancy/postpartum women** or with coexisting autoimmunity; mimics an adenoma on MRI (enlarged homogeneously)

enhancing gland, thickened stalk). **Secondary hypoadrenalism is the commonest deficit**; AVP deficiency in up to ~20%. Suspect before operating on a postpartum sellar mass; often responds to glucocorticoids.

- ▶ **Checkpoint-inhibitor hypophysitis** — up to ~20% with CTLA-4 inhibitors (ipilimumab), less with PD-1/PD-L1 agents (delayed onset); HLA-DQ0602 association.
- ▶ **Traumatic brain injury / SAH** — ≥1 deficiency in 25–30% of moderate–severe TBI and ~55% of aneurysmal SAH survivors; mandates long-term endocrine follow-up.

Pathological subtypes of hypophysitis (Williams)

Type	Hallmark	Notes
Lymphocytic	Lymphocyte/plasma-cell infiltrate	F>M, peripartum; anterior failure ± AVP
Granulomatous	Giant cells, granulomas	Severe headache; frequent AVP deficiency; r/o sarcoid, GPA, TB, LCH
Xanthomatous	CD68+ foamy macrophages	Often secondary to Rathke's cyst rupture
IgG4-related	IgG4+ plasma cells, storiform fibrosis	M>F; systemic IgG4 disease; good GC response
Immunotherapy-induced	Diffuse lymphocyte/macrophage infiltrate	Checkpoint inhibitors; deficits usually persist
Anti-PIT1 / anti-POMC	Antibody-mediated	Anti-PIT1 (thymoma) → GH+PRL+TSH loss; anti-POMC → isolated ACTH loss

Clinical features / presentation

- ▶ Manifestations depend on **which** hormones are lost and the **degree** of deficiency, and are typically **insidious and non-specific** — fatigue, dizziness/postural hypotension, cognitive slowing, sexual dysfunction, cold intolerance.
- ▶ **Mass-effect** features when due to tumour/hypophysitis: headache, **bitemporal hemianopia** (optic-chiasm compression), cranial-nerve palsies.
- ▶ **Panhypopituitarism** in adults often presents in women as amenorrhoea; deficiencies cluster as hypogonadism, hypothyroidism, ACTH deficiency, GH deficiency ± hyperprolactinaemia.
- ▶ An undiagnosed patient may decompensate into **pituitary/adrenal crisis** during intercurrent illness or surgery — febrile, hypotensive, hyponatraemic, comatose.

Diagnosis / laboratory investigation

Principle: demonstrate a *low target-organ hormone together with a low or inappropriately normal pituitary trophic hormone* (this distinguishes secondary/central from primary gland failure).

- ▶ **ACTH axis (do first — most life-threatening):** 8–9 am cortisol + ACTH. Cortisol $<3 \mu\text{g/dL}$ indicates adrenal insufficiency; $>15 \mu\text{g/dL}$ largely excludes it; intermediate values need a cosyntropin (ACTH 1–24) 0.25 mg stimulation test — stimulated cortisol $<20 \mu\text{g/dL}$ ($\approx 550 \text{ nmol/L}$) is abnormal. ACTH is low/normal (vs high in Addison's). Insulin-tolerance test is the gold standard but is *contraindicated* in ischaemic heart disease, epilepsy, and the elderly.
- ▶ **Thyroid axis:** low free T4 with low/normal TSH = central hypothyroidism (TSH is unreliable for monitoring).
- ▶ **Gonadal axis:** low testosterone/oestradiol with low/normal LH & FSH; check PRL (hyperprolactinaemia of any cause suppresses GnRH).
- ▶ **GH/IGF-1:** AGHD inferred from symptoms plus pituitary disease; IGF-1 $<84 \mu\text{g/L}$ or ≥ 3 other deficiencies is highly suggestive. Provocative **insulin-induced hypoglycaemia** (peak GH $<3 \mu\text{g/L}$ = deficient), or glucagon/macimorelin/arginine-GHRH tests.
- ▶ **Imaging:** dedicated **pituitary MRI** (T1, pre/post gadolinium) for mass, stalk thickening, empty sella, apoplexy. Screen for **haemochromatosis** (ferritin/transferrin saturation) when no cause is evident.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hypothalamic–pituitary axis schematic:** hypothalamus with releasing factors (CRH, GnRH, GHRH, TRH, dopamine, somatostatin) → portal vessels down the **pituitary stalk** → anterior pituitary cells (corticotroph→ACTH, gonadotroph→LH/FSH, somatotroph→GH, thyrotroph→TSH, lactotroph→PRL) → target glands (adrenal/cortisol, gonad/sex steroids, liver/IGF-1, thyroid/T4); posterior pituitary releasing AVP & oxytocin. Add an arrow legend showing the **sequence of loss:** GH → FSH → LH → TSH → ACTH (PRL preserved).
- ▶ **Coronal MRI of sella labelling:** pituitary gland, stalk, **optic chiasm**, cavernous sinus with CN III, IV, V1, V2, VI and internal carotid artery — illustrating mass/apoplexy compression.

Clinical / Diagnostic significance

- ▶ Replace glucocorticoid **BEFORE** levothyroxine — starting thyroxine first accelerates cortisol metabolism and can precipitate an **adrenal crisis**.
- ▶ Glucocorticoid doses must be **stress-dosed** ($2\text{--}3\times$ up, or parenteral) during illness, surgery, trauma; patient should carry a steroid alert card/bracelet.
- ▶ Replacement (per axis): **Hydrocortisone 10–20 mg/day** in divided doses (or prednisone 5 mg am) — *no mineralocorticoid needed*; **levothyroxine $\sim 1.6 \mu\text{g/kg/day}$** titrated to mid-high-normal free T4 (not TSH); **testosterone** (gel/patch/enanthate 200 mg IM q2wk) or cyclical **oestrogen**–

progestogen; rhGH (somatropin) titrated to mid-normal IGF-1; desmopressin for AVP deficiency. Fertility requires gonadotrophins (hCG/hMG/FSH) or pulsatile GnRH.

- ▶ Suspect and screen for hypopituitarism after TBI, SAH, cranial irradiation, and postpartum haemorrhage.

High-yield exam pointers

- ▶ Acquired causes >> congenital in adults; remember the mechanistic groups (vascular, traumatic, neoplastic, inflammatory/infiltrative, infective, iatrogenic).
- ▶ **Sequence of hormone loss:** GH → FSH → LH → TSH → ACTH; PRL preserved/raised (“Go Look For The Adenoma”).
- ▶ **Sheehan’s** = postpartum necrosis → failure to lactate + amenorrhoea; insidious over years.
- ▶ **Pituitary apoplexy** = endocrine emergency → high-dose steroids ± urgent decompression.
- ▶ **Secondary adrenal insufficiency:** no hyperpigmentation, no hyperkalaemia (mineralocorticoid spared).
- ▶ Diagnosis = *low target hormone + low/inappropriately normal trophic hormone*; cosyntropin/insulin-tolerance tests assess reserve.
- ▶ **Treat the ACTH deficit first;** give steroid before thyroxine.
- ▶ Hypopituitarism increases cardiovascular/cerebrovascular mortality 2–3 fold.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Hypopituitarism” (etiology, sequence of hormone loss, apoplexy, irradiation, hypophysitis, provocative testing, replacement table).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Pituitary Adenomas and Masses” and “Pituitary Physiology and Diagnostic Evaluation” (hypophysitis pathological subtypes/Fig 7.16, checkpoint-inhibitor rates, surgical hypopituitarism).
- ▶ **CMDT 2026** — “Disorders of the Pituitary, Thyroid, & Adrenal Glands” (Sheehan’s syndrome, TBI/SAH statistics, biochemical cut-offs, current replacement regimens).



Acromegaly

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Acromegaly is the clinical syndrome resulting from chronic **growth hormone (GH)** and **insulin-like growth factor 1 (IGF-1)** hypersecretion in adults, almost always due to a **GH-secreting somatotrope pituitary adenoma**. When GH excess begins in children/adolescents *before* epiphyseal long-bone closure, it produces **pituitary gigantism**; after closure it causes acral and

soft-tissue overgrowth. The manifestations are indolent and frequently undiagnosed for **10 years or more**, and untreated disease carries an approximately **threefold** increase in mortality.

Etiology and pathogenesis

- ▶ **Eutopic (pituitary, ~98%)** — GH hypersecretion is usually from a **somatotrope adenoma**. Mixed **mammosomatotrope** tumours and **acidophilic stem cell adenomas** co-secrete GH and prolactin (PRL); in the latter, features of hyperprolactinaemia (hypogonadism, galactorrhoea) predominate.
- ▶ **Ectopic GH / GHRH (<1% each)** — rare. The commonest cause of **GHRH-mediated** acromegaly is a **chest or abdominal carcinoid tumour**; excess GHRH causes somatotrope *hyperplasia*. Ectopic GH itself is reported from pancreatic, ovarian, lung or haematopoietic tumours.
- ▶ **Pathogenesis (sporadic disease)** — GHRH binds its **G-protein-coupled somatotrope receptor**, using **cyclic AMP** as second messenger to drive GH secretion and somatotrope proliferation. A subset harbours **somatic activating mutations of Gsa**, which attenuate intrinsic GTPase activity → constitutive cAMP elevation → **Pit-1** induction and **CREB** activation → somatotrope proliferation and GH secretion.

Cause	Approx. prevalence
Pituitary (densely/sparsely granulated GH-cell adenoma)	60%
Mixed GH-cell and PRL-cell adenoma	25%
Mammosomatotrope-cell adenoma	10%
Plurihormonal adenoma; GH-cell carcinoma/metastases	—
MEN-1, McCune-Albright, ectopic sphenoid/parapharyngeal pituitary adenoma	—
Extrapituitary tumour (pancreatic islet cell, lymphoma)	<1%
Excess GHRH — central (hypothalamic hamartoma, choristoma, ganglioneuroma); peripheral (bronchial carcinoid, islet cell tumour, small-cell lung Ca, adrenal adenoma, medullary thyroid Ca, pheochromocytoma)	<1%

Genetic syndromes associated with GH excess

- ▶ **MEN-1 (MENIN, 11q13)** — autosomal dominant parathyroid + pancreatic islet + pituitary tumours; acromegaly is *less common* than prolactinoma.
- ▶ **MEN-4 (CDKN1B, 12p13)** — hyperparathyroidism with pituitary adenomas.

- ▶ **Carney complex** (*PRKARIA*, 17q23-24) — spotty skin pigmentation, myxomas, endocrine tumours; **acromegaly in ~20%**.
- ▶ **McCune-Albright syndrome** — polyostotic fibrous dysplasia, café-au-lait patches and endocrinopathy (including acromegaly), from a **postzygotic mosaic Gsa mutation**.
- ▶ **Familial isolated pituitary adenoma** — germline AIP mutations (11q13.2), **acromegaly/gigantism in ~15%** of afflicted families.

Clinical features

- ▶ **Acral bony overgrowth** — frontal bossing, increased hand and foot size, **mandibular enlargement with prognathism**, and a **widened space between the lower incisor teeth**.
- ▶ **Soft-tissue swelling** — increased **heel-pad thickness**, increasing shoe/glove size, ring tightening, coarse facial features and a large fleshy nose.
- ▶ **Other systemic** — hyperhidrosis; a deep, hollow-sounding voice; oily skin; arthropathy and kyphosis; **carpal tunnel syndrome**; proximal muscle weakness and fatigue; **acanthosis nigricans** and skin tags.
- ▶ **Visceromegaly** — cardiomegaly, **macroglossia**, thyroid enlargement.
- ▶ **Cardiovascular (most significant impact)** — **cardiomyopathy** with arrhythmias, **left ventricular hypertrophy**, impaired diastolic function and **hypertension** ultimately occur in most untreated patients.
- ▶ **Respiratory / metabolic** — **obstructive sleep apnoea in >60%** (soft-tissue laryngeal obstruction + central dysfunction); glucose intolerance is usual and **diabetes mellitus develops in ~25%** (GH counteracts insulin).
- ▶ **Neoplastic** — increased **colon polyps** (found in up to one-third) and colonic-malignancy mortality.
- ▶ **Outcome** — overall mortality is increased ~threefold (cardiovascular, cerebrovascular and respiratory); unless GH is controlled, survival is reduced by an average of **10 years**.

Diagnosis and laboratory investigation

- ▶ **Screening** — an **age- and sex-matched serum IGF-1** level is the single best screening test, since IGF-1 integrates GH secretion over time.
- ▶ A **single random GH** is *not* useful for diagnosis or exclusion (GH is pulsatile) and does not correlate with disease severity.
- ▶ **Confirmation** — failure of GH to suppress to **<0.4 µg/L within 1–2 h** of a **75-g oral glucose load** (OGTT); with ultrasensitive assays the normal nadir is **<0.05 µg/L**. About **20%** show a *paradoxical GH rise* after glucose.

- **Adjunctive** — measure PRL (elevated in ~25%); thyroid function, gonadotropins and sex steroids may be attenuated by tumour mass effect. ACTH-reserve testing is best deferred until after surgery.
- **Imaging** — pituitary MRI localises and sizes the adenoma; assess for mass effects (optic chiasm compression, cavernous-sinus cranial nerve involvement).

Management

- **Goals** — control GH/IGF-1 hypersecretion, ablate or arrest tumour growth, ameliorate comorbidities, restore mortality to normal and **preserve pituitary function**.

Modality	Agent / detail	Efficacy & key points
Surgery (primary)	Transsphenoidal resection by an experienced surgeon	Microadenoma remission ~70%, macroadenoma <50%; GH normalises within 1 h, IGF-1 within 3–4 days. Recurrence ~10%; hypopituitarism in up to 15%.
Somatostatin receptor ligands (SRLs)	Octreotide LAR (30 mg IM monthly), lanreotide depot (60 mg SC q4–6 wk), oral octreotide (40–80 mg/day)	Act via SST2/SST5; normalise GH/IGF-1 in ~50%; shrink tumour in ~50%; rapid symptom relief in ~75% within days–weeks. Adjuvant or primary therapy.
Multireceptor SRL	Pasireotide LAR (preferential SST5)	For tumours resistant to octreotide/lanreotide; higher rate of hyperglycaemia/new-onset diabetes.
GH-receptor antagonist	Pegvisomant (10–30 mg SC daily)	Blocks peripheral GH binding → normalises IGF-1 in ~70%; GH stays elevated (no anti-tumour effect) — monitor tumour size by MRI .
Dopamine agonist	Cabergoline (high dose, ~0.5 mg/day)	Modest, short-lived benefit; useful for mild post-operative GH/IGF-1 elevation; additive with octreotide.
Radiotherapy	Conventional external beam or Gamma Knife stereotactic	Adjuvant; slow response (5–15 yr), late hypopituitarism, relatively poor IGF-1 normalisation — reserved when surgery/medical therapy fail.

- ▶ **SRL side effects** — GI upset (nausea, cramps, diarrhoea, fat malabsorption in $\sim\frac{1}{3}$), **biliary sludge/gallstones in up to 30%**, mild glucose intolerance, asymptomatic bradycardia, hypothyroxinaemia.
- ▶ **Pegvisomant side effects** — reversible **liver enzyme elevation**, lipodystrophy, injection-site pain.
- ▶ **Combination** — SRL + pegvisomant ($\pm$ pasireotide) for treatment-resistant disease. Manage cardiovascular disease, diabetes, sleep apnoea and arthropathy aggressively.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **GH-IGF-1 axis (regulation):** *Hypothalamus* $\rightarrow$ **GHRH (+)** and **Somatostatin (-)** $\rightarrow$ *Anterior pituitary somatotrope* $\rightarrow$ **GH** $\rightarrow$ *Liver* $\rightarrow$ **IGF-1** $\rightarrow$ *peripheral target tissues (bone, soft tissue, viscera)*; show **negative feedback** of IGF-1/GH on hypothalamus and pituitary, and the GH-secreting adenoma driving the excess.
- ▶ **Management algorithm (Fig. 392-8):** boxes labelled **GH-secreting pituitary tumour** $\rightarrow$ **Surgery** $\rightarrow$ “controlled / not controlled” $\rightarrow$ **SRL** $\rightarrow$ **Pegvisomant** $\rightarrow$ **SRL + Pegvisomant** $\rightarrow$ **Pasireotide** $\rightarrow$ **Radiotherapy / Re-operation**, with “**Monitor IGF-1**” at each controlled endpoint.

Clinical / Diagnostic significance

- ▶ **IGF-1** is the screening pivot and the marker followed for biochemical control; the **75-g OGTT-GH suppression test** is confirmatory.
- ▶ Suspect acromegaly in new-onset **diabetes, hypertension, OSA, carpal tunnel syndrome or arthropathy** with coarsening facies, and serially photograph the face/hands.
- ▶ Active disease warrants **echocardiography**, OSA screening and **colonoscopy** (polyp/cancer surveillance) plus cardiovascular risk-factor control.
- ▶ A young patient with gigantism/acromegaly, especially if familial, should prompt screening for AIP, MEN-1, Carney complex and McCune-Albright.

High-yield exam pointers

- ▶ Adult onset = **acromegaly**; pre-epiphyseal-closure onset = **gigantism** (same hormonal excess).
- ▶ **$\sim 98\%$** are pituitary somatotrope adenomas; commonest **ectopic GHRH** source = **carcinoid tumour**.
- ▶ Best screening test = **age/sex-matched IGF-1**; confirm with **GH non-suppression to $<0.4 \mu\text{g/L}$ after 75-g OGTT**; random GH is useless.
- ▶ **$\sim 20\%$** show a *paradoxical GH rise* on glucose; **PRL elevated in $\sim 25\%$** .
- ▶ First-line treatment = **transsphenoidal surgery** (micro $\sim 70\%$, macro $<50\%$ remission).
- ▶ **Octreotide/lanreotide** act via **SST2/SST5**; **pegvisomant** is a **GH-receptor antagonist** that lowers IGF-1 but not GH.

- ▶ Watch for OSA (>60%), cardiomyopathy/LVH, diabetes (25%), and **colon cancer**; untreated disease cuts survival by ~10 years.

SOURCE & COVERAGE

Harrison 22e — Ch 392 “Pituitary Tumor Syndromes” (acromegaly/gigantism, Tables 392-2, 392-4, 392-6; Figs 392-7, 392-8). All classifications, percentages, drug doses and biochemical cut-offs are taken from this chapter. *Coverage note:* the chapter does not provide a formal consensus disease-activity grading or detailed pre-pregnancy management for acromegaly; these are not asserted here.



Acute Adrenal Insufficiency (Adrenal Crisis)

Asked in: Paper IV Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — *Acute adrenal insufficiency*, also termed *adrenal crisis* or *addisonian crisis*, is a life-threatening endocrine emergency caused by an acute, profound deficiency of glucocorticoid (cortisol) ± mineralocorticoid (aldosterone) action relative to physiological demand. It classically manifests as **hypotension/hypovolaemic shock unresponsive to fluids and vasopressors**, often with hyponatraemia, hyperkalaemia and a pseudo-acute abdomen. It is far more frequent in **primary adrenal insufficiency** (loss of *both* gluco- and mineralocorticoid secretion) and demands immediate empirical treatment without waiting for biochemical confirmation. Prospective data record **8.3 adrenal crises and 0.5 crisis-related deaths per 100 patient-years**.

Aetiology and precipitating factors

Adrenal crisis arises either as the *first presentation* of undiagnosed insufficiency or, more often, when a known patient fails to up-titrate steroids during stress. Underlying causes are grouped as primary, secondary (central) and iatrogenic.

Category	Representative causes
Primary (adrenal, ↑ACTH)	Autoimmune adrenitis (commonest in the West; isolated 30–40%, or part of APS-1/APECED — <i>AIRE</i> gene and APS-2 — <i>HLA-DR3</i> , <i>CTLA-4</i>); tuberculous adrenitis (common cause in developing countries); HIV/CMV, histoplasmosis, cryptococcosis; bilateral adrenal haemorrhage (<i>Waterhouse-Friderichsen syndrome</i> with meningococcal sepsis; anticoagulation, antiphospholipid syndrome); metastatic/infiltrative (lymphoma, amyloid, haemochromatosis); congenital adrenal hyperplasia (<i>21-hydroxylase deficiency</i>); X-linked adrenoleukodystrophy

Category	Representative causes
	(<i>ABCD1</i>); drugs (mitotane, abiraterone, ketoconazole, etomidate, checkpoint inhibitors)
Secondary / central (↓-normal ACTH)	Pituitary/hypothalamic tumour or its surgery/irradiation; pituitary apoplexy ; Sheehan's syndrome (postpartum pituitary infarction); autoimmune hypophysitis (incl. checkpoint-inhibitor induced)
Iatrogenic (commonest overall)	Abrupt withdrawal of chronic exogenous glucocorticoids suppressing the HPA axis — affects 0.5–2% of the population; any route (oral, inhaled, topical, intra-articular)

- ▶ **Precipitants of crisis** in a known patient: intercurrent infection/sepsis (commonest), surgery, trauma, vomiting/diarrhoea preventing oral intake, myocardial infarction, **increased glucocorticoid inactivation** (e.g., **new hyperthyroidism**), and enzyme-inducing drugs such as **rifampicin** (↑ cortisol clearance).

Pathophysiology

- ▶ **Cortisol (glucocorticoid) deficiency** → loss of vascular tone and catecholamine sensitivity (vasodilatory hypotension), impaired gluconeogenesis (**hypoglycaemia**, marked in children), loss of feedback inhibition of AVP release (→ mild SIADH-type **hyponatraemia**), and inability to mount a stress response.
- ▶ **Aldosterone (mineralocorticoid) deficiency** — *primary disease only* → renal Na⁺ and water loss with K⁺ and H⁺ retention → **volume depletion**, **hyponatraemia**, **hyperkalaemia**, **metabolic acidosis**, **postural hypotension** progressing to hypovolaemic shock. In **secondary** insufficiency the renin-angiotensin-aldosterone axis is intact, so hyperkalaemia and severe salt wasting are absent and crises are correspondingly less fulminant.
- ▶ **Adrenal androgen (DHEA) deficiency** occurs in both, clinically apparent mainly in women.
- ▶ A superimposed stressor sharply raises cortisol requirement that the failing/suppressed gland cannot meet — tipping chronic insufficiency into overt crisis.

Clinical features

- ▶ **Cardiovascular**: postural hypotension progressing to **hypotension/shock refractory to pressors**; tachycardia, cool peripheries.
- ▶ **Gastrointestinal** — “**pseudo-acute abdomen**”: anorexia, nausea, vomiting, diarrhoea, diffuse abdominal/flank pain and tenderness — may be mistaken for a surgical abdomen.
- ▶ **Neurological**: weakness, confusion, decreased responsiveness, **stupor and coma**; features of neuroglycopenia from hypoglycaemia.

- ▶ **Constitutional:** fever (may reflect precipitating infection or be intrinsic to glucocorticoid deficiency), profound fatigue, salt craving, weight loss.
- ▶ **Pointers to chronic primary disease:** hyperpigmentation of palmar creases, buccal mucosa, scars, pressure points and nipples (excess POMC/ACTH stimulating melanocytes), often with vitiligo; secondary insufficiency instead shows pale, *alabaster-coloured* skin.
- ▶ **Adrenal haemorrhage** presents with abdominal/flank/lower-chest pain, a rapidly falling haemoglobin, progressive hyperkalaemia and shock.

Investigations and diagnosis

Treatment must never be delayed for results — draw baseline samples, treat, confirm later.

- ▶ **Biochemistry:** hyponatraemia ($\approx 80\%$ Harrison; $\sim 90\%$ Williams), hyperkalaemia ($\approx 40\%$ Harrison; $\sim 65\%$ Williams — primary disease only), raised urea/creatinine (volume depletion), hypoglycaemia, occasionally hypercalcaemia. Haematology shows normochromic anaemia, lymphocytosis and eosinophilia (eosinophils $>300/\mu\text{L}$) — a useful clue distinguishing crisis from an acute abdomen, where neutrophilia dominates.
- ▶ **Hormonal confirmation:**
 - Paired baseline cortisol + ACTH + renin/aldosterone drawn *before* steroids. An 8 a.m. cortisol $<3 \mu\text{g/dL}$ (83 nmol/L) with ACTH $>200 \text{ pg/mL}$ is diagnostic of primary disease; cortisol $>14\text{--}18 \mu\text{g/dL}$ effectively excludes it.
 - Short cosyntropin (Synacthen/SST) test — the standard test: $250 \mu\text{g}$ ACTH(1–24) IM/IV, cortisol at 0 and 30–60 min. Failure = peak cortisol $<450\text{--}550 \text{ nmol/L}$ ($\approx 16\text{--}20 \mu\text{g/dL}$) (exact cut-off assay-dependent; CMDT uses $<20 \mu\text{g/dL}$ at 45 min). Hydrocortisone must be withheld $\geq 8 \text{ h}$ before the test (cross-reacts in the assay); dexamethasone does not interfere.
 - Localisation: $\uparrow$ ACTH + $\uparrow$ renin + low aldosterone = **primary**; low-normal ACTH with normal renin/aldosterone = **secondary** (then MRI pituitary).
- ▶ **Aetiological work-up (after stabilisation):** 21-hydroxylase autoantibodies (autoimmune); if negative — chest X-ray, adrenal CT (enlarged/calcified glands suggest TB, haemorrhage, infiltration; small glands suggest autoimmune), serum 17-OHP (CAH), and very-long-chain fatty acids in men (adrenoleukodystrophy). Blood/urine/sputum cultures to find a precipitating infection.

Management of adrenal crisis

A medical emergency — the three priorities are fluids, hydrocortisone, and treatment of the precipitant, alongside glucose and electrolyte correction.

Step	Action
1. IV access & samples	Large-bore cannula; draw electrolytes, glucose, cortisol, ACTH, cultures — <i>do not wait for results</i>

Step	Action
2. Volume resuscitation	0.9% saline 1 L over the first hour ($\approx 2-3$ L in first 24 h) with cardiac monitoring; use 5% dextrose-saline if hypoglycaemic
3. Glucocorticoid	Hydrocortisone 100 mg IV bolus, then 200 mg/24 h by continuous infusion (or 50 mg IV/IM every 6 h); high-dose hydrocortisone also provides mineralocorticoid cover
4. Mineralocorticoid	Fludrocortisone 100 $\mu\text{g/day}$ is added only once hydrocortisone is reduced <50 mg/day (above this, hydrocortisone alone saturates the MR; 40 mg hydrocortisone $\approx$ 100 μg fludrocortisone) — primary disease only
5. Treat precipitant	Empirical broad-spectrum antibiotics for suspected sepsis; correct hypoglycaemia, dehydration and electrolytes
6. Taper	Once stable and eating, switch to oral hydrocortisone (e.g., 10–20 mg every 6 h) and taper over 1–3 days to maintenance

- Clinical improvement (especially BP) within 4–6 h supports the diagnosis.
- Maintenance after recovery: hydrocortisone 15–25 mg/day in 2–3 divided doses (largest dose on waking) $\pm$ fludrocortisone 50–200 $\mu\text{g/day}$; long-acting steroids (prednisolone, dexamethasone) are avoided as replacement. Women with persistent low energy/libido may receive DHEA 25–50 mg/day.
- Prevention (sick-day rules): every patient must double/triple the oral dose during febrile illness, take IM/IV hydrocortisone 100 mg if vomiting, carry a steroid emergency card/MedicAlert bracelet and a hydrocortisone self-injection kit, and receive surgical stress-dose cover.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- Hypothalamic-Pituitary-Adrenal (HPA) axis with negative feedback — label: Hypothalamus $\rightarrow$ CRH; Anterior pituitary $\rightarrow$ ACTH (POMC-derived); Adrenal cortex with zones Zona glomerulosa $\rightarrow$ Aldosterone (RAAS-controlled), Zona fasciculata $\rightarrow$ Cortisol, Zona reticularis $\rightarrow$ DHEA/androgens; feedback arrows of cortisol onto pituitary and hypothalamus; mark site of block in primary (adrenal, $\uparrow$ ACTH $\rightarrow$ hyperpigmentation) vs secondary (pituitary, $\downarrow$ ACTH $\rightarrow$ pale skin) insufficiency.
- Emergency management flowchart — label boxes: Suspect adrenal crisis $\rightarrow$ IV access + draw cortisol/ACTH/cultures $\rightarrow$ IV 0.9% saline 1 L/h $\rightarrow$ Hydrocortisone 100 mg IV bolus then

200 mg/24 h → treat precipitant (antibiotics) + correct glucose/K⁺ → reassess at 4–6 h → taper + add fludrocortisone when HC <50 mg/day.

Clinical / Diagnostic significance

- ▶ Adrenal crisis must be distinguished from septic, cardiogenic and hypovolaemic shock; refractory hypotension with hyponatraemia, hyperkalaemia, eosinophilia and lymphocytosis is the classic giveaway.
- ▶ **Empirical treatment saves lives** — the cosyntropin test and aetiological work-up are deferred; an undiagnosed crisis that is untreated is uniformly fatal.
- ▶ A high-risk, exam-favourite trigger is **abrupt cessation of long-term corticosteroids**; another is **rifampicin started in a stable Addisonian** (enzyme induction precipitates crisis).
- ▶ In a hypothyroid patient with co-existing adrenal insufficiency, **always give hydrocortisone before thyroxine** — thyroxine first can precipitate crisis.
- ▶ **Waterhouse-Friderichsen syndrome** (meningococcaemia with bilateral adrenal haemorrhage) is the paediatric/septic counterpart and an important cause of acute primary failure.

High-yield exam pointers

- ▶ **Triad to write first:** hypotension/shock refractory to fluids + hyponatraemia + hyperkalaemia (primary disease).
- ▶ **Hydrocortisone 100 mg IV stat → 200 mg/24 h + 0.9% saline 1 L in first hour** — the two cornerstone orders.
- ▶ **Treat first, confirm later** — baseline cortisol/ACTH drawn before steroids; **dexamethasone does not interfere** with the cortisol assay (useful if SST planned same day).
- ▶ **Short cosyntropin test:** 250 µg ACTH; peak cortisol <450–550 nmol/L = fail.
- ▶ **Hyperkalaemia + hyperpigmentation = primary (Addison); normal K⁺ + pale “alabaster” skin = secondary.**
- ▶ **Fludrocortisone only when hydrocortisone <50 mg/day**; not needed during high-dose stress cover.
- ▶ **Eosinophilia + lymphocytosis** distinguish crisis from a surgical acute abdomen.
- ▶ **Sick-day rules + emergency kit + MedicAlert** are the key preventive bullets.
- ▶ **Waterhouse-Friderichsen** = bilateral adrenal haemorrhage in meningococcaemia; **Sheehan’s** = postpartum secondary insufficiency.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Disorders of the Adrenal Cortex” (adrenal insufficiency: aetiology, signs/symptoms tables, short cosyntropin test, treatment of acute adrenal insufficiency, glucocorticoid-induced AI).
- ▶ **Williams Textbook of Endocrinology, 15e** — “The Adrenal Cortex” (clinical features, investigation of hypoadrenalism, Box 13.7 Treatment of Acute Adrenal Insufficiency/Adrenal Crisis, long-term replacement).
- ▶ **CMDT 2026** — “Disorders of the Pituitary, Thyroid, & Adrenal Glands” (Addison disease: laboratory findings, differential diagnosis, treatment of acute adrenal crisis, stress dosing).



Adrenal Insufficiency

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Adrenal insufficiency (AI) is the clinical state resulting from inadequate production of adrenocortical hormones — chiefly the glucocorticoid **cortisol**, and in **primary** disease also the mineralocorticoid **aldosterone** and the adrenal androgens. It is classified as **primary** (disease of the adrenal cortex itself — *Addison's disease*), **secondary/central** (ACTH deficiency from hypothalamic-pituitary disease), or **iatrogenic/glucocorticoid-induced** (suppression of the HPA axis by exogenous steroids). It is an under-diagnosed but readily fatal endocrine emergency when it presents as **adrenal crisis**, and is fully treatable with timely steroid replacement.

Classification, epidemiology and aetiology

- ▶ **Primary AI (Addison's disease)**: loss of *both* glucocorticoid and mineralocorticoid secretion ($\pm$ androgen). Prevalence **~2 in 10,000**. About one-half is **acquired** (mostly **autoimmune** adrenalitis), the other half **genetic** (most commonly **congenital adrenal hyperplasia, CAH**).
- ▶ **Secondary (central) AI: isolated glucocorticoid deficiency** — the adrenal is intact, so mineralocorticoid output remains under RAA control. Hypothalamic-pituitary origin is the *most frequent* overall (prevalence **~3 in 10,000**); total documented permanent AI **~5 in 10,000**.
- ▶ **Glucocorticoid-induced AI (commonest cause overall)**: suppression of the HPA axis by exogenous steroids — occurs in **0.5–2%** of the population in developed countries.

Type	Major causes (Harrison Tables 398-7/398-8)
Primary — autoimmune	Isolated autoimmune adrenalitis; APS-1 (<i>AIRE</i> gene — hypoparathyroidism, mucocutaneous candidiasis); APS-2 (HLA-DR3, CTLA-4 — autoimmune thyroid disease, type 1 DM, pernicious anaemia, vitiligo, premature ovarian failure)

Type	Major causes (Harrison Tables 398-7/398-8)
Primary — genetic	CAH (<i>CYP21A2</i> most common); adrenoleukodystrophy/adrenomyeloneuropathy (<i>ABCD1</i>); adrenal hypoplasia congenita (<i>DAX-1/NR0B1</i> , <i>SF-1</i>); familial glucocorticoid deficiency (<i>MC2R</i> , <i>MRAP</i>); Triple-A (Allgrove) syndrome (<i>AAAS</i> — alacrima, achalasia, addisonianism); Smith-Lemli-Opitz
Primary — destruction	Infection — <i>tuberculous adrenalitis</i> (still frequent in developing countries), HIV, CMV, histoplasmosis, cryptococcosis; infiltration — bilateral bulky metastases, lymphoma, sarcoidosis, amyloidosis, haemochromatosis; haemorrhage — meningococcal sepsis (<i>Waterhouse-Friderichsen syndrome</i>), antiphospholipid syndrome
Primary — drugs / surgical	Mitotane, abiraterone, ketoconazole, etomidate, osilodrostat, trilostane, immune-checkpoint inhibitors; bilateral adrenalectomy
Secondary	Pituitary/hypothalamic tumours and their surgery/irradiation; pituitary apoplexy ; Sheehan's syndrome (post-partum pituitary infarction); autoimmune hypophysitis; pituitary infiltration (TB, sarcoid, histiocytosis, granulomatosis with polyangiitis); isolated ACTH deficiency (<i>TBX19/Tpit</i>); checkpoint inhibitors, opioids, chronic glucocorticoid excess

Clinical manifestations

- ▶ **Glucocorticoid deficiency (all types):** fatigue, lack of energy, weight loss, anorexia, myalgia/arthralgia, fever; **hypoglycaemia** (more frequent in children); low blood pressure with **postural hypotension**; **hyponatraemia**; normochromic anaemia, lymphocytosis, **eosinophilia**; slightly raised TSH (loss of feedback inhibition).
- ▶ **Mineralocorticoid deficiency (primary AI only):** abdominal pain, nausea, vomiting; dizziness/postural hypotension; **salt craving**; raised creatinine (volume depletion); **hyponatraemia and hyperkalaemia**.
- ▶ **Adrenal androgen deficiency:** lack of energy; dry/itchy skin, loss of libido and loss of axillary/pubertal hair (in women).
- ▶ **Pigmentation — the key bedside discriminator:**
 - **Primary AI: hyperpigmentation** from excess ACTH/POMC-derived peptides stimulating melanocytes — maximal at friction/shear sites (palmar creases, knuckles, dorsa of feet, nipples, scars) and **buccal/oral mucosa**, accentuated by sunlight.

- *Secondary AI: alabaster-pale skin* due to *deficiency* of POMC-derived peptides.
- ▶ **Biochemistry frequency:** hyponatraemia in ~80% at presentation; hyperkalaemia in ~40%. In secondary AI, hyponatraemia arises from reduced cortisol-mediated inhibition of AVP release, producing a mild SIADH-like picture.
- ▶ **Chronic AI** presents with non-specific symptoms (often mis-labelled depression or anorexia), causing diagnostic delay.

Adrenal crisis (acute adrenal insufficiency)

- ▶ An **emergency**, more frequent in **primary** AI (loss of both gluco- and mineralo-corticoid).
- ▶ Features: **hypotension progressing to hypovolaemic shock**, may mimic an **acute abdomen** (tenderness, nausea, vomiting, fever) or neurological disease (reduced responsiveness → stupor → coma).
- ▶ **Precipitants:** intercurrent illness/infection, surgical or other physiological stress, increased glucocorticoid inactivation (e.g., **hyperthyroidism**), or abrupt withdrawal of long-term steroids.
- ▶ Burden: ~8.3 crises and ~0.5 crisis-related deaths per 100 patient-years.
- ▶ **Treatment must never be delayed for diagnostic confirmation** — draw baseline cortisol/ACTH, treat immediately, formalise testing later.

Diagnosis and biochemical localisation

- ▶ **Confirm the deficiency** — **short cosyntropin (Synacthen) test (first-line):** give cosyntropin (ACTH 1-24) 250 µg IM/IV, sample cortisol at 0, 30 (± 60) min. **Failure = peak cortisol <450–500 nmol/L (16–18 µg/dL);** a normal response is >15–20 µg/dL (>400–550 nmol/L). (Cutoffs are assay-dependent; mass-spectrometry assays use lower cutoffs.)
- ▶ The **low-dose (1 µg) cosyntropin test** offers no superior diagnostic value. The **insulin tolerance test (ITT)** is an alternative for the central axis but is invasive and **contraindicated in coronary/cerebrovascular disease, diabetes and seizure disorders**. Within ~4 weeks of new pituitary injury the cosyntropin test may still be normal (adrenal not yet atrophied) — use ITT here.
- ▶ **Random serum cortisol** is of limited value because of diurnal variation.
- ▶ **Localise** — once AI is confirmed:

Parameter	Primary AI	Secondary AI
Plasma ACTH	High (inappropriately raised)	Low / inappropriately normal
Plasma renin	High	Normal
Aldosterone	Low	Normal
Mineralocorticoid axis	Deficient	Intact

- ▶ **Aetiological work-up:** screen 21-hydroxylase / steroid autoantibodies (autoimmune marker); if negative → adrenal CT (TB, infiltration, haemorrhage, metastases); in males with negative antibodies → very-long-chain fatty acids (VLCFA) to exclude X-linked adrenoleukodystrophy; raised 17-OHP suggests CAH. Low ACTH (secondary) → MRI hypothalamus/pituitary.

Management / treatment

- ▶ **Acute crisis:**
 - Immediate IV saline 1 L/h with continuous cardiac monitoring to correct volume depletion.
 - Hydrocortisone 100 mg IV bolus, then 200 mg over 24 h (continuous infusion preferred, or bolus IV/IM).
 - Separate mineralocorticoid is unnecessary until the hydrocortisone dose falls <50 mg/day (higher doses saturate the mineralocorticoid receptor). Treat the precipitating illness.
- ▶ **Chronic glucocorticoid replacement: hydrocortisone 15–25 mg/day orally in 2–3 divided doses**, with ≥half the dose on waking to mimic the circadian rhythm. Long-acting steroids (prednisolone, dexamethasone) are avoided (excess overnight exposure). Increase by ~50% in the last trimester of pregnancy. *Approximate equivalence:* 1 mg hydrocortisone = 1.6 mg cortisone acetate = 0.2 mg prednisolone = 0.25 mg prednisone = 0.025 mg dexamethasone.
- ▶ **Mineralocorticoid replacement (primary AI only): fludrocortisone 100–150 µg/day.** Monitor sitting/standing BP, serum Na/K and plasma renin (keep upper-normal). 40 mg hydrocortisone ≈ 100 µg fludrocortisone; increase fludrocortisone by 50–100 µg in hot/tropical climates. Prednisolone/prednisone have weak, dexamethasone *no* mineralocorticoid activity.
- ▶ **Adrenal androgen replacement:** optional DHEA 25–50 mg once daily for persistent low energy or androgen-deficiency symptoms in women; monitor DHEAS, androstenedione, testosterone, SHBG.
- ▶ **Sick-day rules / patient education (mark-scoring):** double the oral glucocorticoid dose for intercurrent febrile illness; 100 mg hydrocortisone IM/IV for emergencies, 200 mg/24 h for prolonged vomiting, surgery or trauma. Every patient must carry a hydrocortisone self-injection emergency kit, a steroid emergency card and bracelet, and be trained in their use.
- ▶ **Glucocorticoid-induced AI:** occurs with any route (oral, inhaled, topical, intranasal, intra-articular); highest risk with supraphysiologic doses >3–4 weeks; CYP3A4 inhibitors (notably ritonavir) markedly increase risk. Give stress-dose cover, but mineralocorticoid is *not* needed (aldosterone preserved); taper slowly.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Adrenal cortex zones and their secretions (functional zonation):** concentric layers labelled — capsule; Zona glomerulosa → mineralocorticoids (aldosterone); Zona

fasciculata → glucocorticoids (cortisol); Zona reticularis → adrenal androgens (DHEA/DHEAS); innermost medulla → catecholamines.

- ▶ **HPA axis feedback loop:** Hypothalamus (CRH) → Anterior pituitary (ACTH) → Adrenal cortex (cortisol) → negative feedback on hypothalamus and pituitary; annotate “loss of cortisol feedback → high ACTH → hyperpigmentation” for primary AI versus “low ACTH → pallor” for secondary AI.

Clinical / Diagnostic significance

- ▶ Hyperpigmentation + hyperkalaemia + hyponatraemia strongly favours *primary* AI; pallor with normal potassium favours *secondary* AI.
- ▶ Always suspect AI in **unexplained shock refractory to fluids/pressors**, hyponatraemia with hyperkalaemia, or an “acute abdomen” with hypotension.
- ▶ **Treat first, confirm later** in suspected crisis — give hydrocortisone after drawing baseline cortisol/ACTH.
- ▶ Screen primary AI patients for **autoimmune polyglandular syndrome** (thyroid disease, T1DM, premature ovarian failure) and monitor accordingly.
- ▶ Counsel on **stress dosing**; failure to up-titrate during illness/surgery is the commonest preventable cause of crisis and death.

High-yield exam pointers

- ▶ **Primary AI = Addison’s** = glucocorticoid + mineralocorticoid (± androgen) loss; **secondary** = glucocorticoid only (mineralocorticoid intact).
- ▶ **Commonest cause of primary AI:** autoimmune adrenalitis (developed world); TB remains common in developing countries.
- ▶ **Commonest cause of AI overall:** exogenous glucocorticoid therapy (iatrogenic).
- ▶ **Diagnostic test:** short cosyntropin 250 µg test — failure if cortisol <450–500 nmol/L (16–18 µg/dL) at 30–60 min.
- ▶ **Localisation:** ACTH **high** = primary, **low/normal** = secondary; high renin + low aldosterone confirm mineralocorticoid deficiency.
- ▶ **Hyponatraemia** ~80%, **hyperkalaemia** ~40% at presentation in primary AI.
- ▶ **Crisis management:** IV saline 1 L/h + hydrocortisone 100 mg IV bolus then 200 mg/24 h.
- ▶ **Maintenance:** hydrocortisone 15–25 mg/day (split, morning-weighted) ± fludrocortisone 100–150 µg/day (primary only).
- ▶ *Waterhouse-Friderichsen* = meningococcal adrenal haemorrhage; *Sheehan’s* = post-partum pituitary infarction (secondary AI).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 398 “Disorders of the Adrenal Cortex” (sections on Adrenal Insufficiency, Acute Adrenal Insufficiency, Diagnosis, Treatment, and Glucocorticoid-Induced Adrenal Insufficiency; Tables 398-7, 398-8, 398-9; Figs 398-15, 398-16). Coverage note: all classifications, drug doses, biochemical cut-offs and figures above are grounded in Ch 398; the corticosteroid potency equivalences and the Allgrove/Waterhouse-Friderichsen/Sheehan eponyms are supported in the chapter text. No fabricated content; no gap flagged (spec.gap = false).



Autoimmune Hypothyroidism

Asked in: Paper IV Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Autoimmune hypothyroidism is the clinical syndrome of thyroid hormone deficiency resulting from immune-mediated destruction of the thyroid gland, of which *Hashimoto's thyroiditis* (chronic lymphocytic thyroiditis) is the prototype. In iodine-sufficient regions, autoimmunity accounts for **>90% of all non-iatrogenic hypothyroidism**, making it the single most common cause of acquired hypothyroidism. It is characterised by lymphocytic infiltration of the thyroid, circulating anti-thyroid-peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies, and a slowly progressive course from euthyroidism through subclinical to overt hypothyroidism.

Classification & Etiological Context

- ▶ **Goitrous variant (classic Hashimoto's thyroiditis)** — diffuse, firm, irregular goitre with lymphocytic infiltration; the commonest cause of goitre in iodine-sufficient areas. Originally termed *struma lymphomatosa*.
- ▶ **Atrophic thyroiditis (primary myxoedema)** — minimal residual thyroid tissue with extensive fibrosis; generally the **end stage** of the same autoimmune process rather than a separate disorder; presents as hypothyroidism *without* goitre.
- ▶ **IgG4-related thyroiditis** — a distinct fibrosing subset with high circulating IgG4 and IgG4-positive plasma-cell infiltration; overlaps with Riedel's thyroiditis.
- ▶ **Stages of functional decline** — (1) *euthyroid* antibody-positive phase → (2) *subclinical hypothyroidism* (raised TSH, normal free T4) → (3) *overt/clinical hypothyroidism* (raised TSH usually >10 mIU/L with low free T4).

Cause of primary hypothyroidism	Examples
Autoimmune	Hashimoto's (goitrous) and atrophic thyroiditis

Cause of primary hypothyroidism	Examples
Iatrogenic	^{131}I therapy, thyroidectomy, external neck irradiation
Drugs	Iodine excess, amiodarone, lithium, interferon- α , tyrosine kinase inhibitors (sunitinib), immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab)
Iodine deficiency	Endemic goitre / cretinism
Infiltrative	Amyloidosis, sarcoidosis, haemochromatosis, Riedel's thyroiditis

Epidemiology & Risk Factors

- ▶ **Incidence** $\approx$ 4 per 1000 women and 1 per 1000 men annually; strong **female preponderance**. Onset typically 30–50 years; mean age at diagnosis $\sim$ 60 years; prevalence rises with age.
- ▶ **Subclinical hypothyroidism** present in 6–8% of women (10% over 60 years) and 3% of men; annual risk of progression to overt disease is $\sim$ 4% **when TPO antibodies are positive**.
- ▶ **Genetic** — *HLA-DR3*, *DR4* and *DR5* (Caucasians); immunoregulatory polymorphisms in *PTPN22* and *CTLA-4*; monozygotic-twin concordance $\sim$ 0.55. A chromosome-21 gene underlies the **Down syndrome** association; high frequency also in **Turner syndrome** (X-chromosome related).
- ▶ **Environmental** — high iodine intake and low selenium increase risk; **smoking cessation transiently raises incidence**; alcohol appears protective; radiation exposure (atomic bomb, Chernobyl, Hodgkin's neck irradiation) increases risk; cytokine and checkpoint-inhibitor therapy can precipitate disease.

Pathogenesis & Immunology

- ▶ **Cell-mediated injury is primary** — *CD8⁺ perforin-containing cytotoxic T cells* recognising thyroglobulin and TPO are the dominant effectors of follicular-cell destruction; Th1 and Th17 subsets and macrophages amplify injury.
- ▶ **Cytokine effects** — local TNF, IL-1 and IFN- γ impair thyrocyte function, up-regulate HLA class I/II, adhesion molecules, CD40 and nitric oxide, and sensitise cells to **Fas (CD95)–Fas ligand-mediated apoptosis** and oxidative stress.
- ▶ **Antibodies (secondary, amplifying role)** — **anti-TPO and anti-Tg antibodies are present in >95% of patients** and are the clinical markers of autoimmunity; TPO antibodies fix complement (membrane-attack complex). Tissue injury may also occur via antibody-dependent cell-mediated cytotoxicity (NK cells).
- ▶ **TSH-receptor-blocking antibodies** — up to 20% of patients have antibodies that *block* (rather than stimulate) the TSH-R, contributing to hypothyroidism and, especially in **Asian patients**,

thyroid atrophy; their transplacental passage can cause *transient neonatal hypothyroidism*. Rare patients harbour a mixture of stimulating (TSI) and blocking antibodies, producing **oscillating thyroid function**.

- ▶ Rarely, antibodies against the **sodium-iodide symporter (NIS)** and **pendrin** are found, of uncertain significance.

Histopathology

- ▶ **Hashimoto's (goitrous)**: diffuse lymphocytic infiltration with germinal-centre formation, atrophy of thyroid follicles with **absent colloid**, **oxyphil (Hürthle/Askanazy-cell) metaplasia**, and mild-to-moderate fibrosis; gland is pale, firm and rubbery.
- ▶ **Atrophic thyroiditis**: extensive fibrosis, less lymphocytic infiltrate, near-complete loss of follicles.
- ▶ **Hashitoxicosis**: rare concurrent histologic changes of Graves' disease.
- ▶ Painless (silent) and post-partum thyroiditis show histology resembling Hashimoto's.

Clinical Features

- ▶ Onset is **insidious**; many present with goitre rather than symptoms. Goitre is painless, firm, irregular and moves on swallowing.

Symptoms (descending frequency)	Signs
Tiredness, weakness	Dry coarse skin; cool extremities
Dry skin, cold intolerance	Puffy face/hands/feet (myxoedema)
Hair loss, poor memory	Diffuse alopecia; loss of lateral eyebrow (<i>Queen Anne sign</i>)
Constipation, weight gain (modest)	Bradycardia , diastolic hypertension
Hoarse voice, dyspnoea	Delayed ("hung-up") tendon-reflex relaxation
Menorrhagia (later oligo/amenorrhoea), paraesthesia	Carpal tunnel syndrome; serous-cavity effusions

- ▶ **Mechanism of myxoedema**: dermal accumulation of hydrophilic **glycosaminoglycans (hyaluronic acid)** producing non-pitting, boggy thickening.
- ▶ **Cardiac**: reduced stroke volume and rate, **pericardial effusion in up to 30%**, narrow pulse pressure; *myxoedema heart*.
- ▶ **Other**: hyperprolactinaemia/galactorrhoea, reduced fertility, increased miscarriage; reversible cerebellar ataxia, dementia, psychosis (*myxoedema madness*); **Hashimoto's encephalopathy** (steroid-responsive, TPO-Ab positive, myoclonus, EEG slowing).
- ▶ **Associated autoimmune disease**: vitiligo, pernicious anaemia, **Addison's disease (Schmidt's syndrome)**, alopecia areata, type 1 diabetes, coeliac disease, SLE, myasthenia gravis, Sjögren's. In

autoimmune polyendocrine syndrome type 2, autoimmune thyroid disease is present in 70–75%, T1DM in 40–60%, Addison's in 40–50%. Thyroid ophthalmopathy occurs in ~5%.

- ▶ **Myxoedema coma** — the extreme presentation: reduced consciousness/seizures, hypothermia (to 23 °C), hypoventilation with hypoxia/hypercapnia, hyponatraemia and hypoglycaemia; usually elderly, precipitated by sedatives, infection, cold, MI or stroke; **mortality 20–40%**.

Laboratory Evaluation

- ▶ **Serum TSH is the primary screening test** — a normal TSH excludes primary hypothyroidism. If TSH is elevated, measure **free T4** to confirm overt (low FT4) versus subclinical (normal FT4) disease.
- ▶ **TPO and Tg antibodies** establish autoimmune aetiology (positive in >95%).
- ▶ T3 is normal in ~25% (adaptive deiodinase response) → **T3 measurement is not indicated**.
- ▶ Supportive abnormalities: raised **creatinine kinase**, elevated total/LDL cholesterol and triglycerides, normocytic or macrocytic **anaemia**, hyponatraemia.
- ▶ Central (secondary) hypothyroidism: low FT4 with low/normal/slightly raised TSH — monitor by FT4, not TSH.

Management

Setting	Regimen
Overt hypothyroidism, young, no heart disease	Levothyroxine (LT4) full replacement 1.6 µg/kg/day (~100–150 µg), 30 min before breakfast; start 50–100 µg/day
Elderly / known CAD	Start LT4 12.5–25 µg/day , increase slowly every 2–3 months
Monitoring	Recheck TSH at 6–8 weeks ; adjust in 12.5–25 µg steps; goal TSH in lower half of reference range
Subclinical hypothyroidism	Treat if TSH >10 mIU/L , woman wishing to conceive/pregnant, or symptomatic; otherwise monitor annually (start 25–50 µg)
Pregnancy	Increase dose ~30–45% (nine doses/week once pregnancy confirmed); target TSH <2.5 mIU/L ; test every 4 weeks in first half
Myxoedema coma	LT4 IV loading 200–400 µg then 1.6 µg/kg/day; consider liothyronine (T3) 5–20 µg load then 2.5–10 µg q8h; IV hydrocortisone 50 mg q6h ; ventilatory support, passive rewarming (active only if <30 °C), correct hyponatraemia/hypoglycaemia, broad-spectrum antibiotics, treat precipitant

- ▶ LT4 is the preparation of choice; desiccated thyroid and LT4+liothyronine combinations are **not recommended** (non-physiologic T3:T4 ratio; no proven benefit).
- ▶ Causes of increased LT4 requirement: malabsorption (coeliac, *H. pylori* gastritis), oestrogens, and co-ingested calcium, iron, PPIs, bile-acid sequestrants — separate dosing.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis schematic of autoimmune thyroid destruction** — label: *thyroid follicular cell, CD8⁺ cytotoxic T cell (cytolysis), Th1/Th17 cells + macrophages releasing cytokines (TNF, IL-1, IFN- γ), Fas–Fas-ligand apoptosis, NK cell (ADCC), TPO/Tg autoantibodies + complement fixation, TSH-receptor-blocking antibody.*
- ▶ **Diagnostic algorithm** — label: *Measure TSH $\rightarrow$ (elevated) $\rightarrow$ measure free T4 $\rightarrow$ low = primary hypothyroidism / normal = subclinical $\rightarrow$ TPO antibody positive = autoimmune hypothyroidism $\rightarrow$ consider/initiate LT4.*

Clinical / Diagnostic significance

- ▶ Single most common cause of acquired hypothyroidism; screen with TSH, confirm autoimmunity with TPO antibodies.
- ▶ Asymmetric Hashimoto goitre may mimic multinodular goitre or carcinoma; **primary thyroid lymphoma** is rare but strongly associated with pre-existing Hashimoto's — a true nodule warrants ultrasound-guided FNA.
- ▶ Untreated maternal disease impairs foetal neurodevelopment and raises miscarriage/preterm risk — pre-conception TSH should be <2.5 mIU/L.
- ▶ A suppressed TSH from LT4 over-treatment increases risk of **atrial fibrillation and reduced bone density**.
- ▶ Persistent symptoms despite biochemical euthyroidism occur in 10–15%; reassess adherence and associated autoimmune disease before altering therapy.

High-yield exam pointers

- ▶ Hashimoto's = autoimmune thyroiditis = $>90\%$ of non-iatrogenic hypothyroidism in iodine-sufficient areas.
- ▶ Two faces: **goitrous (Hashimoto)** vs **atrophic (primary myxoedema)** — same spectrum; atrophic = end stage.
- ▶ TPO + Tg antibodies positive in $>95\%$; $\sim 20\%$ have TSH-R-blocking antibodies (cause atrophy, especially Asians).
- ▶ Histology buzzwords: **germinal centres, lymphocytic infiltration, Hürthle/Askanazy oxyphil-cell metaplasia, fibrosis, struma lymphomatosa.**

- ▶ Genetic: HLA-DR3/DR4/DR5, CTLA-4, PTPN22; associations — Down's, Turner's, APS-2 (Schmidt's syndrome), T1DM, pernicious anaemia, vitiligo, coeliac.
- ▶ Diagnosis: TSH first; T3 not useful. Overt threshold TSH usually >10 mIU/L.
- ▶ Treatment: LT4 1.6 µg/kg/day; recheck TSH at 6–8 weeks; elderly/CAD start 12.5–25 µg.
- ▶ Myxoedema coma: mortality 20–40%; treat with IV LT4 + hydrocortisone, ventilation, passive rewarming.
- ▶ Subclinical disease: treat if TSH >10, pregnancy, or wishing to conceive.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Hypothyroidism" (chapter on autoimmune hypothyroidism / Hashimoto's thyroiditis).
- ▶ Williams Textbook of Endocrinology, 15e — "Hypothyroidism and Thyroiditis" (classification, pathophysiology, histopathology, risk factors).
- ▶ CMDT 2026 — "Disorders of the Pituitary, Thyroid & Adrenal Glands" (current management, levothyroxine dosing, autoimmune thyroiditis).



Classify diabetes mellitus. How do you recognize monogenic forms of diabetes and how do you manage them?

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — Diabetes mellitus (DM) is a group of metabolic disorders sharing the phenotype of **hyperglycaemia**, arising from reduced insulin secretion, decreased glucose utilisation and/or increased hepatic glucose production. While **type 1** and **type 2 DM** dominate, an aetiologic classification recognises a third heterogeneous group, of which **monogenic diabetes** (single-gene defects of β -cell development/function or insulin action) is the most clinically actionable. Monogenic forms account for **1–2% of all diabetes** (1–4% of those diagnosed before age 30), are frequently misdiagnosed as type 1 or type 2 DM, and are the flagship example of **precision medicine**, because correct molecular diagnosis directly changes therapy.

Aetiologic classification of diabetes mellitus (ADA / Harrison)

Category	Defining feature
I. Type 1 DM	Immune-mediated β -cell destruction → usually absolute insulin deficiency
II. Type 2 DM	Spectrum from predominant insulin resistance to predominant secretory defect
III. Other specific types	(see below)

Category	Defining feature
IV. Gestational DM (GDM)	Glucose intolerance of 2nd/3rd trimester

Group III — “Other specific types”:

- ▶ **A. Genetic defects of β -cell function (monogenic / MODY):** *HNF4A*, *GCK* (glucokinase), *HNF1A*, *HNF1B*, *IPF-1/PDX1*, *NEUROD1*, and others (*KLF11*, *PAX4*, *BLK*, *GATA4/6*, *SLC2A2/GLUT2*, *GLIS3*); mitochondrial DNA.
- ▶ **B. Neonatal diabetes (onset <6 months):** mutations in K-ATP channel subunits, *RFX6*, *INS*.
- ▶ **C. Transient neonatal diabetes.**
- ▶ **D. Diseases of the exocrine pancreas:** pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy (so-called type 3c / pancreatogenic DM).
- ▶ **E. Genetic defects in insulin action:** type A insulin resistance, *leprechaunism*, *Rabson–Mendenhall* syndrome, lipodystrophies.
- ▶ **F. Endocrinopathies:** acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma.
- ▶ **G. Drug/chemical-induced:** glucocorticoids, calcineurin & mTOR inhibitors, pentamidine, nicotinic acid, thiazides, atypical antipsychotics, α -interferon, diazoxide, vacor.
- ▶ **H. Infections:** congenital rubella, CMV, coxsackievirus.
- ▶ **I. Uncommon immune-mediated:** “stiff-person” syndrome, anti-insulin-receptor antibodies, immune-checkpoint-inhibitor diabetes.
- ▶ **J. Genetic syndromes:** Wolfram, Down’s, Klinefelter’s, Turner’s, Friedreich’s ataxia, myotonic dystrophy, Prader–Willi, Laurence–Moon–Biedl.

Diagnostic criteria for DM (ADA, confirm on a separate day unless unequivocal hyperglycaemia)

- ▶ HbA1c $\geq 6.5\%$ (≥ 48 mmol/mol), OR
- ▶ Fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL), OR
- ▶ 2-h plasma glucose ≥ 11.1 mmol/L (200 mg/dL) on 75-g OGTT, OR
- ▶ Random glucose ≥ 11.1 mmol/L (200 mg/dL) with classic symptoms (polyuria, polydipsia, weight loss).
- ▶ **Prediabetes:** HbA1c 5.7–6.4%; IFG (FPG 5.6–6.9 mmol/L / 100–125 mg/dL); IGT (2-h PG 7.8–11.0 mmol/L / 140–199 mg/dL).

Recognising monogenic diabetes — when to suspect

Monogenic diabetes cannot be reliably separated from type 1/type 2 DM by clinical features alone; suspicion rests on “atypical” features and family history:

- ▶ **Atypical for type 1 DM:** absent pancreatic islet autoantibodies; persistence of endogenous insulin beyond the honeymoon; **measurable C-peptide (≥ 0.6 ng/mL, ≥ 0.2 nmol/L) in the presence of hyperglycaemia**; low insulin requirement; no ketoacidosis when insulin is omitted.
- ▶ **Atypical for type 2 DM:** onset before 45 years; lack of significant obesity; absent acanthosis nigricans; normal triglycerides and/or normal–high HDL.
- ▶ **Strong pointers: autosomal-dominant**, multigenerational (“3-generation”) diabetes; diabetes diagnosed **before age 25–30**; diabetes diagnosed **<6 months of age** (never autoimmune type 1); **stable mild fasting hyperglycaemia**; syndromic clues (deafness, renal cysts, optic atrophy).

Stepwise diagnostic pathway (biomarker → genetic):

- ▶ **C-peptide / urinary C-peptide:creatinine ratio (UCPCR)** to confirm endogenous insulin secretion.
- ▶ If C-peptide ≥ 0.2 nmol/L → measure **GAD65 and IA-2 ($\pm$ ZnT8) islet autoantibodies**; positive antibodies favour type 1 DM.
- ▶ If antibody-negative → **molecular genetic testing** (next-generation-sequencing gene panels: *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, plus neonatal genes *KCNJ11*, *ABCC8*, *INS*).
- ▶ Aids: the Exeter MODY probability calculator (valid for diagnosis <35 y) and the **type-1-diabetes genetic risk score (T1D-GRS)** help select patients for genetic testing.

The four classic MODY subtypes (Williams)

Gene (chr) [old name]	Key phenotype	Precision treatment
GCK (7p) [MODY2]	Mild, stable, non-progressive fasting hyperglycaemia 99–144 mg/dL (5.5–8.0 mmol/L), present from birth; small OGTT increment (<90 mg/dL); antibody-negative; virtually no micro/macrovacular complications (only late non-proliferative retinopathy)	No treatment — diet only; oral agents/insulin ineffective and <i>contraindicated</i> (pregnancy is the exception)
HNF1A (12q) [MODY3]	Progressive hyperglycaemia, low renal glucose threshold → glycosuria , high penetrance (63% by 25 y); hepatocellular adenomas; increased cardiovascular mortality	Low-dose sulfonylurea (very sensitive, may cause hypoglycaemia); meglitinides/GLP-1 RA; insulin when β -cells fail late
HNF4A (20q) [MODY1]	Progressive β -cell failure; fetal macrosomia (+~790 g) with transient neonatal hyperinsulinaemic hypoglycaemia ; low HDL	Low-dose sulfonylurea ; insulin later

Gene (chr) [old name]	Key phenotype	Precision treatment
HNF1B (17q) [MODY5]	Renal cysts and diabetes (RCAD); pancreatic hypoplasia + exocrine insufficiency; genital-tract anomalies; hypomagnesaemia, hyperuricaemia, deranged LFTs; 50–60% de novo (17q12 deletions)	Insulin — poor/no sulfonylurea response

- ▶ *GCK* and *HNF1A* are the two commonest causes (the four transcription-factor/enzyme genes account for the great majority of MODY); subtype frequency varies geographically (*HNF1A* predominates in UK/Europe, *GCK* in several US registries).

Neonatal and syndromic monogenic diabetes

- ▶ **Neonatal diabetes (ND):** diagnosis typically <6 months (test all such infants; also test 6–12 months if antibody-negative). Infants are often small-for-dates.
 - **Transient ND:** overexpression of the paternal **6q24** locus, or mildly activating *ABCC8/KCNJ11*; features may include IUGR, macroglossia, umbilical hernia; remits by ~4 months, often recurs at puberty.
 - **Permanent ND:** activating **K-ATP channel** mutations (*KCNJ11/Kir6.2*, *ABCC8/SUR1*) — respond to **high-dose sulfonylurea** (insulin can be discontinued; early treatment improves neurodevelopmental outcomes in the *DEND* spectrum); **insulin-gene* (*INS*) mutations — require insulin. Test *KCNJ11*, *ABCC8*, *INS** and 6q24 imprinting.
- ▶ **Syndromic forms (<1% of childhood diabetes):**
 - **Maternally inherited diabetes and deafness (MIDD):** mitochondrial **m.3243A>G** (tRNA-Leu); sensorineural deafness; overlaps *MELAS*. Treat with diet/oral agents then insulin (usually within 2 years); **avoid metformin** (mitochondrial inhibition / lactic acidosis risk).
 - **Wolfram syndrome (DIDMOAD):** autosomal-recessive *WFS1* (wolframin); insulin-dependent **non-autoimmune** DM (mean onset ~6 y), optic atrophy, diabetes insipidus, deafness — supportive care + insulin.
 - **Alström syndrome:** *ALMS1* — obesity, cone-rod dystrophy, deafness, insulin-resistant type 2-like DM.

Management principles — “treat the genotype”

- ▶ **GCK-MODY:** lifelong **no pharmacotherapy**; reassure (benign, complication-free).
- ▶ **HNF1A- / HNF4A-MODY:** **low-dose sulfonylurea is first-line** (often allows withdrawal of insulin in those misdiagnosed as type 1); meglitinides and GLP-1 receptor agonists are alternatives; statin for HNF1A cardiovascular risk; insulin when secretory reserve declines.
- ▶ **HNF1B-MODY:** **insulin**; multidisciplinary care for renal/genital/exocrine disease.

- ▶ **K-ATP neonatal diabetes (KCNJ11/ABCC8): high-dose sulfonylurea**, transition off insulin.
- ▶ ***INS neonatal diabetes / pancreatic-agenesis genes: insulin***.
- ▶ **Pregnancy (precision obstetric care):**
 - *GCK-MODY*: treat only if the **fetus is unaffected** (predicted by serial growth ultrasound) — large-dose insulin in the 3rd trimester, deliver ~38 weeks; no treatment if the fetus carries the mutation.
 - *HNF1A/HNF4A-MODY*: switch sulfonylurea (**glyburide**) to **insulin** (latest by 2nd trimester); fortnightly fetal growth scans after 28 weeks; early delivery (35–38 weeks) for HNF4A because of macrosomia and severe neonatal hypoglycaemia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Glucose-stimulated insulin secretion in the β -cell, with monogenic-diabetes genes mapped.** Labels: *GLUT1/2 (SLC2A2)* glucose transporter → Glucose → glucokinase (GCK) → Glucose-6-phosphate → glycolysis/Krebs → ATP/ADP → ATP-sensitive K^+ channel (Kir6.2/KCNJ11 + SUR1/ABCC8) → membrane depolarisation → voltage-gated Ca^{2+} channel → Ca^{2+} influx → insulin (INS) + C-peptide + IAPP secretory granules; nuclear transcription factors HNF1A, HNF4A, HNF1B, PDX1/IPF-1, NEUROD1; incretin (GLP-1/GIP) receptors.
- ▶ **Stepwise diagnostic algorithm:** Diabetes → (autoantibodies + C-peptide) → if antibody-negative & C-peptide-positive branch on phenotype: <6 months → neonatal panel (KCNJ11/ABCC8/INS/6q24); mild stable fasting hyperglycaemia → GCK; progressive + glycosuria → HNF1A; renal cysts/hypomagnesaemia → HNF1B; transient neonatal hypoglycaemia/low HDL → HNF4A; deafness/syndromic → mitochondrial/syndromic testing.

Clinical / Diagnostic significance

- ▶ A correct molecular diagnosis can **stop unnecessary insulin** (HNF1A/HNF4A, K-ATP neonatal), **stop all therapy** (GCK), avoid hypoglycaemia, and trigger **cascade screening** of relatives (autosomal dominant — 50% risk).
- ▶ Recognises **comorbidity surveillance**: renal disease and hypomagnesaemia in HNF1B; hepatocellular adenoma and cardiovascular risk in HNF1A; deafness/cardiomyopathy in MIDD; optic atrophy/DI in Wolfram.
- ▶ GCK-MODY detected as “gestational diabetes” needs genotype-guided fetal management rather than routine intensification.

High-yield exam pointers

- ▶ Monogenic diabetes = **1–2% of all DM**; commonly **misdiagnosed** as type 1/type 2.

- ▶ MODY = autosomal dominant, onset <25–30 y, non-insulin-dependent, β -cell defect; diabetes <6 months of age is never type 1 — always test for neonatal genes.
- ▶ GCK = no treatment (benign, complication-free, contraindicated to treat except pregnancy).
- ▶ HNF1A & HNF4A = low-dose sulfonylurea; HNF1A has glycosuria from a low renal threshold (key clue).
- ▶ HNF1B = renal cysts + diabetes (RCAD) + hypomagnesaemia → insulin.
- ▶ K-ATP neonatal diabetes (KCNJ11/ABCC8) → high-dose sulfonylurea; INS mutations → insulin.
- ▶ MIDD = m.3243A>G, deafness → avoid metformin; Wolfram = DIDMOAD (WFS1).
- ▶ Recognition triad: antibody-negative + C-peptide-positive + atypical phenotype → genetic testing (panel/Exeter calculator/T1D-GRS).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology” (Table 415-1 etiologic classification; Fig 415-1 diagnostic criteria; monogenic/neonatal subsection) and “Diabetes Mellitus: Management and Therapies”.
- ▶ **Williams Textbook of Endocrinology, 15e** — “Monogenic Diabetes” (biomarker screening pathway; Table 37.1 atypical features; Table 37.3 MODY classification/treatment; Table 37.4 neonatal diabetes; Table 37.5 pregnancy management; GCK/HNF1A/HNF4A/HNF1B, MIDD, Wolfram, Alström).
- ▶ **CMDT 2026** — “Diabetes Mellitus & Hypoglycemia” (diagnostic criteria Table 32-4; other specific types; sulfonylurea dosing; Wolfram/DIDMOAD).



Diabetes insipidus

Asked in: Paper IV Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Diabetes insipidus (DI) is a hypotonic polyuria–polydipsia syndrome caused by deficient secretion of arginine vasopressin (AVP/antidiuretic hormone) or by renal resistance to its action, producing excretion of abnormally large volumes of dilute urine (24-h urine >40–50 mL/kg and/or >3 L/day, urine osmolality persistently <300 mosmol/kg). In Harrison 22e the terminology has been revised: classical *central/cranial/neurogenic DI* is now **AVP deficiency** and classical *nephrogenic DI* is **AVP resistance**. Because thirst is intact, most patients maintain near-normal serum sodium by compensatory polydipsia; hypernatraemic dehydration supervenes only when thirst or water access is impaired.

Physiology of AVP (background that frames the disease)

- ▶ AVP is a **nonapeptide** (six-member disulfide ring + tripeptide tail) synthesised in the **supraoptic and paraventricular magnocellular neurons** as a pre-pro-hormone comprising AVP, **neurophysin II**, and **copeptin**, encoded by a single gene on **chromosome 20**; it is transported down axons and stored in the **posterior pituitary (neurohypophysis)**.
- ▶ Secretion is governed by hypothalamic **osmoreceptors**; the AVP osmotic set-point is **~275–280 mosmol/L (plasma Na ~135 meq/L)**, above which plasma AVP rises steeply. The **thirst osmostat** is set **~3% higher**, so thirst is the last defence against dehydration. AVP is also released by **>10–20% volume/BP fall** (baroregulated), nausea, and hypoglycaemia.
- ▶ AVP acts on **V2 receptors (Gs-cAMP)** on collecting-duct principal cells → trafficking of **aquaporin-2 (AQP2)** water channels to the apical membrane → passive water reabsorption down the medullary osmotic gradient; maximal antidiuresis (urine osm up to **~1200 mosmol/L**) occurs at AVP **1–3 pg/mL**. **~90% of AVP neurons must be lost** before symptomatic AVP deficiency appears.

Aetiological classification (Polyuria–Polydipsia syndromes)

Category (Harrison 22e term)	Defect	Representative acquired causes	Hereditary causes
Central DI — AVP deficiency	Failed AVP synthesis/secretion	Trauma/neurosurgery, tumours (craniopharyngioma, germinoma, meningioma, metastases—breast/lung), granulomatous (Langerhans-cell histiocytosis, sarcoidosis), infiltrative/autoimmune (lymphocytic infundibuloneurohypophysitis, IgG4), infection (TB, meningitis), vascular (anterior communicating artery aneurysm), idiopathic (~1/3, often autoimmune)	AD AVP-neurophysin II (AVP-NPII) gene mutations; AR; WFS1 → Wolfram syndrome (DIDMOAD) ; PCSK1; X-linked
Nephrogenic DI — AVP resistance	Renal (V2/AQP2) unresponsiveness	Lithium (commonest acquired), demeclocycline, cisplatin, foscarnet; hypercalcaemia, hypokalaemia ; infiltration (amyloid, myeloma, sarcoid); obstructive uropathy/PCKD; sickle-cell	*X-linked recessive AVPR2* (>90%, >200 mutations, 3 types) ; AR/AD AQP2**
Gestational DI	Accelerated AVP metabolism	Placental vasopressinase (cysteine aminopeptidase/oxytocinase) ;	NA

Category (Harrison 22e term)	Defect	Representative acquired causes	Hereditary causes
		assoc. pre-eclampsia, acute fatty liver	
Primary polydipsia (mimic, not true DI)	Excess intake → suppressed AVP	Psychogenic (schizophrenia, PIP syndrome), dipsogenic (low thirst set-point), “health-enthusiast” overdrinking	NA

- ▶ **Wolfram syndrome = DIDMOAD** — autosomal-recessive *WFS1* (wolframin, chromosome 4): Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness.
- ▶ **Adipsic DI** — coexisting AVP deficiency *and* destroyed osmoreceptor thirst centre (e.g., after anterior communicating artery aneurysm clipping); high risk of severe hypernatraemia.

Clinical features and the post-surgical triphasic response

- ▶ Cardinal symptoms: **polyuria, nocturia, and intense thirst with craving for ice-cold water**; daily intake 2.5–20 L; low urine specific gravity (<1.006). Hypernatraemia (lethargy, weakness, irritability, obtundation) only if thirst/access impaired.
- ▶ **Triphasic response** after pituitary stalk section/trauma:
- ▶ **Phase 1** — DI (onset within 24 h, to ~day 6): axon “shock”, failed AVP release.
- ▶ **Phase 2** — antidiuresis/SIAD (~day 7–12): unregulated AVP leak from degenerating neurons → **hyponatraemia**, dangerous if hypotonic IV fluids are given.
- ▶ **Phase 3** — **permanent DI** (~day 13 onward) after stores depleted and gliosis ensues. (An *isolated second phase* of transient hyponatraemia may occur without flanking DI.)

Differential diagnosis & investigations

- ▶ **Step 1 – Confirm hypotonic polyuria**: 24-h urine >40–50 mL/kg with urine osm <800 mosmol/kg; exclude glucosuria, hypercalcaemia, hypokalaemia, renal failure. Measure **serum Na & plasma osmolality**: Na <135 suggests primary polydipsia (patients drink into hyponatraemia); Na >147 with high plasma osmolality (≥300 mosmol/kg) indicates central or nephrogenic DI.
- ▶ **Indirect water-deprivation test (Miller–Moses)**: dehydrate until plasma osm >295 mosmol/kg, then give **desmopressin 2 µg**. *Primary polydipsia* concentrates urine during deprivation (>800 mosmol/kg); in DI urine stays dilute, and after desmopressin **central DI shows a >50% rise** in urine osmolality whereas **nephrogenic DI shows little/no rise (<50%)**. Overall accuracy is only ~70% (41% for primary polydipsia), hence newer copeptin testing.
- ▶ **Copeptin (stable AVP surrogate) algorithm (preferred)**:
 - **Baseline copeptin >21.4 pmol/L** (no prior thirsting) → **nephrogenic DI / AVP resistance** (sens/spec ~100%).

- **Hypertonic (3%) saline stimulation** to plasma Na ≥ 150 mmol/L: stimulated **copeptin** ≤ 4.9 pmol/L $\rightarrow$ **central DI (AVP deficiency)**; >4.9 pmol/L $\rightarrow$ **primary polydipsia** (accuracy $\sim 96.5\%$). Requires close Na monitoring.
- **Arginine-stimulated copeptin** (less cumbersome): <2.4 pmol/L = severe AVP deficiency; 2.4–3.8 = partial; >3.8 = primary polydipsia.
- ▶ **MRI sella/suprasellar**: loss of the normal **posterior-pituitary “bright spot”** (T1 hyperintensity, present in $>80\%$ normals) supports AVP deficiency; assess **pituitary stalk thickening** (germinoma—check serum/CSF β -hCG & AFP; histiocytosis; sarcoid; hypophysitis). Repeat MRI 3–6 monthly for 2 years if stalk thickened and “idiopathic”.

Feature	Central DI (AVP deficiency)	Nephrogenic DI (AVP resistance)	Primary polydipsia
Plasma AVP/copeptin (basal)	Low	Normal/high (copeptin >21.4)	Normal/low
Response to desmopressin	Urine concentrates ($>50\%$)	No response	Concentrates
Plasma Na tendency	High-normal/high	High-normal/high	Low-normal/low
Bright spot on MRI	Absent	Usually present (may deplete)	Present

Treatment

- ▶ **Central DI (AVP deficiency): Desmopressin (DDAVP)** — V2-selective AVP analogue (d-arginine + deaminated terminal, $\sim 2000\times$ more antidiuretic-selective, longer $t_{1/2}$). Adult doses: 1–2 μg SC/IV od–bid, 10–20 μg intranasal bid–tid, or 100–400 μg oral bid–tid (tablets 0.1/0.2 mg; melt 60/120/240 μg). **Hyponatraemia is the commonest complication** ($\sim 1/4$ of patients mildly, $\sim 15\%$ Na <130) — minimise by a periodic “**desmopressin escape**” (delaying/omitting a dose to permit aquaresis). Mild partial DI may need only fluids $\pm$ a bedtime dose.
- ▶ **Nephrogenic DI (AVP resistance)**: ensure adequate water; **thiazide diuretic** (induces mild volume contraction $\rightarrow$ $\uparrow$ proximal Na/water reabsorption, paradoxically reduces urine output and raises AQP2) + **low-sodium diet** $\pm$ **NSAID (indomethacin)** [combination is nephrotoxic—monitor renal function]. **Amiloride** is specifically useful in **lithium-induced NDI** (blocks collecting-duct ENaC, reducing lithium entry); stop the offending drug where possible. Correct **hypokalaemia/hypercalcaemia**.
- ▶ **Gestational DI**: **desmopressin** is the treatment of choice — it resists placental vasopressinase and has negligible oxytocic activity; usually remits weeks after delivery.
- ▶ **Adipsic DI**: fixed desmopressin dose + a **prescribed daily fluid volume**, daily weights and frequent serum-Na checks (Table 393-2 approach); high thrombotic/hypernatraemia risk.

- ▶ **Acute hypernatraemia:** replace the calculated free-water deficit slowly (oral water, or 0.45% saline / 5% dextrose) over 24–48 h with serial Na monitoring to avoid over-rapid correction.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — AVP physiology / V2-AQP2 axis:** Hypothalamus (supraoptic + paraventricular nuclei) → axons → posterior pituitary → AVP release → renal collecting-duct principal cell. Label: *osmoreceptor, AVP, V2 receptor, Gs-adenylyl cyclase-cAMP, AQP2 (apical, inserted), AQP3/AQP4 (basolateral), water reabsorption, concentrated urine.*
- ▶ **Diagram 2 — Polyuria–polydipsia diagnostic algorithm:** Confirm polyuria (>40–50 mL/kg/24 h) → serum Na/osmolality → branch by baseline copeptin (>21.4 = nephrogenic) and hypertonic-saline-stimulated copeptin (≤ 4.9 = central DI; >4.9 = primary polydipsia). Label the three endpoints: *Central DI, Nephrogenic DI, Primary polydipsia.* (Optionally the **triphasic response curve:** urine volume vs days, phases DI → antidiuresis → DI.)

Clinical / Diagnostic significance

- ▶ Distinguishing the three polyuric states is essential because treatment diverges sharply (desmopressin helps central and gestational DI but **not** nephrogenic DI or primary polydipsia, where it risks water intoxication).
- ▶ **Stalk thickening + central DI** mandates a search for germinoma, Langerhans-cell histiocytosis, sarcoidosis, IgG4 disease, and metastases (breast/lung) — DI from intrasellar adenomas is rare.
- ▶ Post-neurosurgical and post-TBI patients need **anticipation of the triphasic response:** use intermittent parenteral desmopressin and allow each dose to wane before re-dosing to avoid precipitating phase-2 hyponatraemia.
- ▶ **Cortisol deficiency masks DI** (cortisol is required for free-water excretion); apparent “resolution” of polyuria after pituitary insult may unmask coexisting ACTH deficiency — check the HPA axis.

High-yield exam pointers

- ▶ Two mechanisms: **AVP deficiency (central)** vs **AVP resistance (nephrogenic)**; commonest *acquired* nephrogenic cause = **lithium**; commonest central genetic form = ***AD AVP-NPPII mutation**; **X-linked AVPR2***** = commonest hereditary nephrogenic (>90%).
- ▶ **Copeptin** has largely replaced AVP assay: **baseline >21.4 pmol/L = nephrogenic**; **saline-stimulated ≤ 4.9 pmol/L at Na ≥ 150 = central DI.**
- ▶ Urine osm >800 mosmol/kg essentially **excludes DI** (points to primary polydipsia).
- ▶ **Wolfram = DIDMOAD** (DI + DM + Optic atrophy + Deafness), **WFS1/wolframin**, chromosome 4.
- ▶ **Desmopressin (DDAVP)** = drug of choice for central & gestational DI; **hyponatraemia** is its chief hazard.

- ▶ **Nephrogenic DI:** thiazide + low-salt diet ± NSAID; **amiloride** for lithium-induced NDI.
- ▶ **Triphasic response:** DI → antidiuresis (SIAD/hyponatraemia ~day 7–12) → permanent DI.
- ▶ **Adipsic DI** (osmoreceptor + AVP loss) carries the highest hypernatraemia/mortality risk.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Disorders of the Neurohypophysis” (vasopressin physiology, Table 393-1 aetiology, copeptin-based diagnostic algorithm Fig 393-4, treatment, adipsic AVP deficiency).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Posterior Pituitary” (genetics of central & nephrogenic DI, triphasic response, water-deprivation vs copeptin/hypertonic-saline & arginine-stimulation testing, treatment of nephrogenic DI and DI of pregnancy, stalk-lesion differential).
- ▶ **CMDT 2026** — “Disorders of the Pituitary... (ADH Deficiency / Central Diabetes Insipidus)” (essentials of diagnosis, ADH levels, hypertonic-saline and arginine copeptin cut-offs, vasopressin challenge test, desmopressin dosing, nephrogenic causes and drugs).



Diabetic Ketoacidosis

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Diabetic ketoacidosis (DKA) is an acute, life-threatening metabolic decompensation of diabetes defined by the biochemical triad of **hyperglycaemia** (serum glucose >13.9 mmol/L [250 mg/dL]; ≥200 mg/dL or any value in a known diabetic per current criteria), **ketonaemia/ketonuria** (serum β-hydroxybutyrate >3.0 mmol/L or urine ketones ≥2+) and **high-anion-gap metabolic acidosis** (arterial/venous pH <7.3 and/or serum bicarbonate <15 mmol/L). It results from *absolute or relative insulin deficiency* combined with *counter-regulatory hormone excess*. It is classically a hallmark of type 1 DM but also occurs in type 2 DM under severe stress, in ketosis-prone diabetes, and as *euglycaemic DKA* with SGLT-2 inhibitors. DKA and the hyperglycaemic hyperosmolar state (HHS) lie on a continuum, with up to one-third of patients showing mixed features.

Etiology and precipitating factors

- ▶ **Counter-regulatory drive:** the core lesion is a fall in the *insulin-to-glucagon ratio*, with accompanying rises in **glucagon, catecholamines, cortisol and growth hormone**.
- ▶ Common precipitants (mnemonic — the “I”s):
 - **Insulin deficiency/omission** — inadequate dosing, missed injections, insulin-pump infusion-site occlusion or device malfunction; insulin rationing due to cost.
 - **Infection** — pneumonia, urinary tract infection, gastroenteritis, sepsis (most common precipitant overall).

- **Infarction/Ischaemia** — myocardial, cerebral, mesenteric, peripheral; tissue ischaemia.
 - **Inflammation** — acute pancreatitis (note hyperamylasaemia is often salivary, not pancreatic).
 - **Intoxication / Iatrogenic drugs** — alcohol, cocaine; corticosteroids, atypical antipsychotics, immune-checkpoint inhibitors, **SGLT-2 inhibitors**.
 - **Pregnancy** and new-onset diabetes (DKA may be the *presenting* feature of type 1 DM).
- Psychiatric and eating disorders, low socioeconomic status, and prior DKA episodes markedly raise recurrence risk.

Pathophysiology

- **Insulin deficiency + glucagon/counter-regulatory excess** unleashes three deranged pathways:
- **Hyperglycaemia** — accelerated hepatic *gluconeogenesis* and *glycogenolysis* plus reduced peripheral glucose uptake.
 - **Ketogenesis** — unrestrained adipocyte *lipolysis* releases free fatty acids; the liver shunts these toward **ketone bodies** (β -hydroxybutyrate and acetoacetate). β -hydroxybutyrate is generated at roughly **threefold** the rate of acetoacetate; acetone (a breakdown product) produces the *fruity breath*.
 - **Volume/electrolyte loss** — glucose $>$ renal threshold (~ 180 mg/dL) causes **osmotic diuresis**, dehydration and urinary loss of Na^+ , K^+ , phosphate and water; vomiting compounds losses.
- Ketoacids consume bicarbonate $\rightarrow$ **high-anion-gap metabolic acidosis** with compensatory **Kussmaul (tachypnoeic) respiration**.
- A vicious cycle ensues: stress hormones worsen insulin resistance, hyperglycaemia and ketosis. Inflammatory markers (cytokines, CRP) are elevated.
- **Potassium paradox**: total-body K^+ is depleted (deficit $\sim 3\text{--}5$ mmol/kg) from osmotic diuresis, acidosis and GI loss, yet *serum* K^+ is normal-to-high at presentation because acidosis and insulin lack shift K^+ extracellularly — it falls sharply once insulin and fluids are given.

Clinical features

- **Symptoms**: polyuria, polydipsia, marked fatigue, **nausea, vomiting**, and **abdominal pain** (may mimic an acute surgical abdomen); evolves over hours to ~ 24 h.
- **Signs**: dehydration, **tachycardia and hypotension**, mild hypothermia, **Kussmaul respiration** with a **fruity (acetone) odour**, abdominal tenderness, and progressive **lethargy $\rightarrow$ obtundation $\rightarrow$ coma** (frank coma in only $\sim 10\%$).
- Signs of infection may be present *without fever* — an elevated or even normal temperature should prompt a search for infection, as uninfected patients are typically hypothermic.

Investigations and diagnosis

- **Confirm the triad:** capillary/serum glucose, **blood β -hydroxybutyrate** (preferred), and venous blood gas (pH, HCO_3^-). Venous pH suffices — arterial sampling is unnecessary (venous–arterial pH differs by only 0.02–0.15).
- **Ketone testing caveat:** the **nitroprusside** reagent detects *acetoacetate/acetone* but **NOT β -hydroxybutyrate**, so it can grossly *underestimate* ketosis (especially with concurrent lactic acidosis/shock); false-positives occur with **captopril, penicillamine and valproic acid**. Hence **direct β -hydroxybutyrate assay is preferred**.
- **Corrected sodium:** add **1.6 mmol/L** to measured Na^+ for every **5.6 mmol/L (100 mg/dL)** rise in **glucose**; a *normal* measured Na^+ in DKA signals profound water deficit.
- Other findings: high BUN/creatinine (pre-renal), **leukocytosis** (up to 25,000/ μL , may be without infection), hypertriglyceridaemia, raised salivary amylase. Septic screen, ECG (peaked T waves of hyperkalaemia; ischaemia), CXR, cultures.
- **Severity grading & DKA vs HHS:**

Parameter	Mild DKA	Moderate DKA	Severe DKA	HHS
Arterial/venous pH	7.25–7.30	7.0–7.25	<7.0	>7.3
Serum bicarbonate (meq/L)	15–18	10–<15	<10	>18
β -hydroxybutyrate (mmol/L)	3–6	3–6	>6	<1.0
Plasma glucose	>250 mg/dL (often 250–600)	>250 mg/dL	>250 mg/dL	usually >600 (up to 1000+)
Anion gap	↑	↑	↑	normal–slightly ↑
Serum osmolality	variable	variable	variable	>320 (marked)
Mental status	alert	alert/drowsy	stupor/coma	confusion/coma
Ketones	present (++)	present	present	absent/minimal

- **Differential diagnosis:** starvation ketosis, **alcoholic ketoacidosis** (HCO_3^- usually >15 meq/L), lactic acidosis and other high-anion-gap acidoses; simple hyperglycaemia (no ketonaemia).

Management

General principles: restore circulating volume and perfusion, correct hyperglycaemia/osmolality and acidosis, replace electrolytes, and *identify and treat the precipitant*. Maintain a meticulous **flow sheet**; pass a **nasogastric tube** if vomiting/altered sensorium. Avoid sedatives/opioids (mask early cerebral oedema). Treat mild–moderate DKA in a step-down unit; severe DKA in ICU.

Component	Practical regimen
1. Fluids	0.9% saline (or lactated Ringer's) 2–3 L over first 1–3 h (~10–20 mL/kg/h); total deficit ≈3–5 L. Switch to 0.45% saline 250–500 mL/h once haemodynamically stable. When glucose ≈250 mg/dL (13.9 mmol/L), change to 5–10% dextrose + 0.45% saline at 150–250 mL/h. Ringer's lactate gives faster resolution with less hyperchloraemia.
2. Insulin	Regular insulin 0.1 unit/kg IV bolus, then 0.1 unit/kg/h infusion; increase 2–3 fold if no fall in 2–4 h. Aim glucose fall 50–100 mg/dL/h. Reduce to 0.02–0.1 unit/kg/h when glucose ~250 mg/dL. Uncomplicated mild–moderate DKA may use SC rapid-acting analogue. Withhold insulin if $K^+ < 3.3$ mmol/L until corrected.
3. Potassium	If $K^+ < 3.5$ → give 10–20 mmol/h until > 3.5 (and hold insulin if < 3.3). If $K^+ 3.5$ –5 → 10–20 mmol per litre of fluid, target 4–5. If $K^+ > 5$ → start insulin, hold K^+ ; recheck 2-hourly. Require adequate urine output.
4. Bicarbonate	Not routinely recommended (no outcome benefit; risks hypokalaemia, paradoxical CSF acidosis, leftward O_2 -dissociation shift). Consider only if pH < 7.0 : ~50–100 mmol $NaHCO_3$ in sterile water with KCl, repeat until pH > 7.0 –7.1.
5. Phosphate	Seldom needed; replace only if severe hypophosphataemia (< 1 mg/dL) develops, at 3–4 mmol/h (over-replacement risks hypocalcaemic tetany).
6. Resolution & transition	End-points: glucose ~150–200 mg/dL, $HCO_3^- \geq 18$, normalised pH/anion gap, patient eating. Give SC long-acting insulin with a 2–4 h overlap before stopping the infusion to prevent rebound DKA.

- ▶ Euglycaemic DKA (SGLT-2 inhibitors): start 5–10% dextrose with insulin from the outset alongside saline; titrate dextrose to prevent hypoglycaemia. Resolution is judged by bicarbonate/acidosis correction, NOT glucose, since glucose is already near-normal.

Complications

- ▶ Cerebral oedema — the most feared complication, predominantly in **children**, typically as DKA is *resolving*. Risk factors: age < 5 y, new-onset diabetes, longer symptom duration, low initial pH, high initial BUN, **bicarbonate therapy**, rapid glucose correction, excess fluid in first 4 h, and rising serum Na^+ . Headache or deteriorating sensorium during therapy is the warning sign → treat with IV mannitol 1–2 g/kg over ~15 min ± hypertonic saline.

- ▶ Hyperchloraemic (normal-anion-gap) acidosis after saline resuscitation — benign, self-corrects over 12–24 h.
- ▶ Hypokalaemia, hypoglycaemia, hypophosphataemia, hypomagnesaemia (therapy-related).
- ▶ Venous thromboembolism, upper-GI bleeding, ARDS, aspiration, and complications of the precipitant.
- ▶ **Prognosis:** mortality is low (<1% in the young/uncomplicated) but rises sharply with age (>20% in the elderly), coma, MI, bowel infarction or end-stage kidney disease; even a single episode confers a ~13-fold one-year increase in mortality.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology flow chart:** Box “Insulin deficiency + ↑ Counter-regulatory hormones (glucagon, catecholamines, cortisol, GH)” → three arms — (1) ↑ Gluconeogenesis + glycogenolysis + ↓ glucose uptake → Hyperglycaemia → osmotic diuresis → dehydration / electrolyte loss / ↑ osmolality; (2) ↑ Lipolysis → ↑ Free fatty acids → hepatic ketogenesis → ↑ β -hydroxybutyrate + acetoacetate → ketonaemia/ketonuria → high-anion-gap metabolic acidosis → Kussmaul breathing; (3) Vomiting → further volume/electrolyte loss. Labels: *insulin/glucagon ratio, FFA, ketone bodies, anion gap, K^+ shift (intra→extracellular)*.
- ▶ **Management timeline bar:** parallel tracks labelled Fluids (0.9% saline → 0.45% saline → add dextrose at glucose 250), Insulin (0.1 U/kg bolus → 0.1 U/kg/h → 0.02–0.1 U/kg/h), Potassium (replace when 3.3–5; hold if >5), Monitor (glucose 1–2 h; electrolytes/anion gap 2–4 h), ending at Resolution → SC insulin overlap.

Clinical / Diagnostic significance

- ▶ DKA may be the **first presentation of type 1 diabetes** — measure ketones whenever a type 1 patient’s glucose is persistently >250 mg/dL or during any intercurrent illness (“sick-day rules”: never *omit* insulin, monitor glucose/ketones 1–3 hourly, maintain hydration).
- ▶ β -hydroxybutyrate (point-of-care meter) is **superior to urine nitroprusside** for both diagnosis and tracking response, and avoids the shock-related false-negative pitfall.
- ▶ **SGLT-2 inhibitor users** need counselling on euglycaemic DKA — suspect it on acidosis with near-normal glucose; withhold the drug during acute illness, surgery, low-carbohydrate diets or fasting.
- ▶ Always hunt the precipitant (the “I”s) — failure to do so, or inadequate fluid replacement, is the commonest cause of poor recovery.
- ▶ Recurrent DKA flags non-adherence/psychosocial issues mandating structured education and mental-health support.

High-yield exam pointers

- ▶ **Diagnostic triad:** hyperglycaemia + ketonaemia (β -OHB >3) + acidosis (pH <7.3, HCO_3^- <15).
- ▶ Core mechanism: ↓ **insulin/glucagon ratio** → **gluconeogenesis + lipolysis + ketogenesis**; counter-regulatory hormones = glucagon, catecholamines, cortisol, GH.
- ▶ **β -hydroxybutyrate** $\approx 3\times$ **acetoacetate**; nitroprusside misses β -OHB; false-positives with captopril, penicillamine, valproate.
- ▶ **Corrected Na** = +1.6 mmol/L per 100 mg/dL glucose rise; K^+ deficit 3–5 mmol/kg with paradoxical normal/high serum K^+ .
- ▶ First-hour priority is **fluids before/with insulin**; insulin bolus 0.1 U/kg then 0.1 U/kg/h; **hold insulin** if $\text{K}^+ < 3.3$.
- ▶ **Add dextrose** when glucose ≈ 250 mg/dL; resolution = $\text{HCO}_3^- \geq 18$ + closed anion gap, *not* glucose alone.
- ▶ **Bicarbonate only** if pH <7.0; phosphate only if <1 mg/dL — neither improves outcome.
- ▶ **Cerebral oedema** = leading cause of death in children; treat with mannitol 1–2 g/kg.
- ▶ **Euglycaemic DKA** with SGLT-2 inhibitors: glucose may be <200 mg/dL — start dextrose + insulin together; judge by acidosis.
- ▶ Overlap SC long-acting insulin 2–4 h before stopping the IV infusion to prevent rebound.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Diabetes Mellitus: Management and Therapies*” (Acute Disorders Related to Severe Hyperglycaemia — DKA & HHS; Tables 416-7/8/9) and “*Diabetes Mellitus: Complications*” (euglycaemic DKA with SGLT-2 inhibitors).
- ▶ **Williams Textbook of Endocrinology, 15e** — “*Type 1 Diabetes Mellitus*” (pathophysiology, epidemiology, treatment of DKA, cerebral-oedema risk factors, sick-day and SGLT-inhibitor risk-mitigation).
- ▶ **CMDT 2026** — “*Diabetes Mellitus & Hypoglycaemia*” (diagnostic essentials, severity grading, fluid/insulin/potassium/bicarbonate/phosphate regimens, hyperchloraemic acidosis, complications and prognosis).



Dyslipidemia

Asked in: Paper IV Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — **Dyslipidemia** is a disorder of lipoprotein metabolism in which there is a substantial increase or decrease in specific circulating lipids or lipoproteins (cholesterol, triglycerides, or both). Lipoproteins are complexes of an “oil-droplet” hydrophobic core (triglycerides, cholesteryl esters) surrounded by phospholipids, free cholesterol and **apolipoproteins**. Dyslipidemia may be

primary (genetic) or secondary (to other medical conditions/drugs), and is an important *causal* factor for atherosclerotic cardiovascular disease (ASCVD); severe hypertriglyceridemia additionally risks acute pancreatitis. Because treatment proven to reduce cardiovascular risk, accurate classification and aggressive management are essential.

Lipoprotein physiology (basis of classification)

- ▶ **Major classes by density/size (inverse relationship):** chylomicrons (least dense, largest) → VLDL → IDL → LDL → HDL (most dense, smallest).
- ▶ **Key apolipoproteins:** apoB-48 (chylomicrons, intestine), apoB-100 (VLDL, IDL, LDL; ligand for the LDL receptor), apoA-I (major HDL protein; promotes efflux via ABCA1, activates LCAT), apoC-II (essential cofactor for lipoprotein lipase, LPL), apoE (ligand for hepatic clearance of remnants).
- ▶ **Three pathways:** *exogenous* (dietary lipids → chylomicrons → LPL lipolysis → remnants cleared by liver via apoE); *endogenous* (hepatic VLDL → IDL → LDL, cleared by LDL receptor); *reverse cholesterol transport* (HDL returns peripheral cholesterol to liver via SR-BI / CETP).
- ▶ **Lp(a)** = LDL-like particle with apo(a) disulphide-linked to apoB-100; an independent, highly heritable causal risk factor for ASCVD and aortic stenosis.
- ▶ Discrete “nodes” that go wrong in disease: (1) LPL-mediated lipolysis, (2) receptor-mediated hepatic uptake of apoB lipoproteins, (3) hepatocyte/enterocyte cholesterol handling, (4) VLDL assembly/secretion, (5) plasma lipid transfer & phospholipid hydrolysis.

Etiological classification (Harrison 22e, phenotype/mechanism-based)

Phenotype	Representative primary disorder	Gene(s)	Lipid pattern	Inheritance
Severe hypertriglyceridemia	Familial chylomicronemia syndrome (FCS)	<i>LPL</i> , <i>APOC2</i> , <i>APOA5</i> , <i>GPIHBP1</i> , <i>LMF1</i>	↑Chylomicrons, ↑VLDL; ↓HDL	AR
Hypercholesterolemia (↑LDL)	Familial hypercholesterolemia (FH)	<i>LDLR</i>	↑LDL	AD (~1/250)
Hypercholesterolemia	Familial defective apoB-100 (FDB)	<i>APOB</i>	↑LDL	AD (~1/1500)
Hypercholesterolemia	ADH type 3	<i>PCSK9</i> (gain-of-function)	↑LDL	AD
Hypercholesterolemia	Autosomal recessive hyperchol. (ARH)	<i>LDLRAP1</i>	↑LDL	AR

Phenotype	Representative primary disorder	Gene(s)	Lipid pattern	Inheritance
Mixed (↑TG + ↑LDL)	Familial dysbetalipoproteinemia (FDBL, type III)	<i>APOE2/E2</i>	↑Remnants/IDL (chol≈TG)	AR (~1/10,000)
Mixed	Familial combined hyperlipidemia (FCHL)	Polygenic	↑VLDL ± ↑LDL (small-dense), ↑apoB, ↓HDL	~1/100–200
Low HDL	Tangier disease	<i>ABCA1</i>	HDL <5 mg/dL	AR/co-dominant

- ▶ **Secondary causes (Table 419-3):** ↑TG — high-carbohydrate diet, alcohol, obesity, insulin resistance/**type 2 diabetes**, lipodystrophy, CKD, nephrotic syndrome, hypothyroidism, Cushing's, pregnancy, drugs (estrogen, glucocorticoids, isotretinoin/retinoids, beta-blockers, bile-acid resins). ↑LDL-C — **hypothyroidism**, cholestasis, nephrotic syndrome, Cushing's, anorexia, drugs (corticosteroids, cyclosporin, sirolimus, carbamazepine).
- ▶ *Fredrickson/WHO phenotypes* (classic, parallel framework): I chylomicrons; **IIa** LDL; **IIb** LDL+VLDL; **III** IDL/β-VLDL (FDBL); **IV** VLDL; **V** chylomicrons+VLDL.

Clinical features

- ▶ Most dyslipidemia is **asymptomatic**, detected on screening; the dominant consequence is **premature ASCVD** (MI, ischemic stroke, peripheral vascular disease).
- ▶ **FH**: corneal arcus, **tendon xanthomas** (dorsum of hands, Achilles); untreated heterozygous men have ~50% chance of MI before age 60. **Homozygous FH** — LDL-C >400 mg/dL, cutaneous xanthomas, ASCVD by age 30.
- ▶ **FDBL (type III)**: *tuberoeruptive xanthomas* (elbows, knees, buttocks) and **palmar xanthomas** (*xanthomata striata palmaris*) — virtually pathognomonic; cholesterol and TG raised to similar degree, HDL usually normal; prominent peripheral vascular disease.
- ▶ **Severe HTG / chylomicronemia (FCS)**: **eruptive xanthomas** (extensor surfaces), **lipemia retinalis** (opalescent retinal vessels), hepatosplenomegaly, and recurrent **acute pancreatitis** (suspect if fasting TG >500 mg/dL).
- ▶ **Tangier disease**: enlarged grayish-orange tonsils, hepatosplenomegaly, peripheral neuropathy with HDL-C <5 mg/dL.

Diagnosis & screening

- ▶ **Screen all adults** with a fasting lipid panel (total cholesterol, TG, HDL-C); screen children at **ages 9–11** and earlier with a family history of hypercholesterolemia/premature ASCVD.

- ▶ **Friedewald formula:** $\text{LDL-C} = \text{Total cholesterol} - (\text{TG}/5) - \text{HDL-C}$ (TG/5 estimates VLDL-cholesterol). Accurate only on fasting plasma and **invalid** if TG >400 mg/dL (and not valid in FDBL).
- ▶ **Non-HDL-C** = $\text{Total cholesterol} - \text{HDL-C}$ — captures cholesterol in VLDL/IDL/LDL; a better atherogenic marker. **apoB** and **Lp(a)** provide additional risk information.
- ▶ Diagnose the dyslipidemia phenotype, then **rule out secondary causes** (Table 419-3) before invoking a primary disorder. Confirmatory tests: FH gene panel (**LDLR**, **APOB**, **PCSK9**); **apoE2/E2 genotype** or β -quantification (VLDL-C/total TG ratio >0.30, “broad β band”) for FDBL.
- ▶ **Risk stratification:** ASCVD pooled-cohort 10-year risk calculator; refine borderline cases with apoB, Lp(a), hs-CRP, and coronary artery calcium (CAC) score.

Management

- ▶ **Goals:** prevent ASCVD events, and prevent pancreatitis when TG is severely elevated.
- ▶ **Lifestyle / therapeutic lifestyle change (first step for all):** reduce **saturated and trans fats**, weight loss in the obese, aerobic exercise, restrict alcohol; treat hypothyroidism/diabetes; restrict total fat and simple carbohydrates in severe HTG.
- ▶ **Statin intensity:** **high-intensity statin** for established ASCVD or those at high risk; in primary prevention a **10-year risk** >7.5% merits statin regardless of LDL-C. In ASCVD, lower LDL-C with drug therapy **as long as it remains >70 mg/dL**, using combination therapy if needed. FH patients require treatment from childhood.
- ▶ **TG-lowering when TG >500 mg/dL** (to prevent pancreatitis): **fibrates** and **omega-3 fatty acids** (fish oils); statins added if ASCVD risk is elevated.

Class (drug)	Mechanism	LDL-C effect	Key adverse effects
Statins (atorvastatin, rosuvastatin, etc.)	↓HMG-CoA reductase → ↑hepatic LDL receptors	↓~30–55% (doubling dose → ~6% more)	Myalgia (3–5%), myopathy/rhabdomyolysis, ↑transaminases, small ↑incident T2DM
Ezetimibe	Blocks intestinal NPC1L1 → ↓absorption	↓~18% (additive to statin)	Very safe; 2nd-line add-on
PCSK9 inhibitors (evolocumab, alirocumab; inclisiran = siRNA)	↓PCSK9 → ↑LDL receptors; also ↓Lp(a)	↓~60%	Injection-site reactions; SC q2wk (antibody) / q6mo (inclisiran)
Bempedoic acid	ATP-citrate lyase inhibitor → ↑LDL receptors	↓~18% with statin (~23% mono)	↑uric acid/gout, ↑LFTs, cholelithiasis; no ↑diabetes

Class (drug)	Mechanism	LDL-C effect	Key adverse effects
Bile-acid sequestrants (cholestyramine, colestipol, colesevelam)	↓bile-acid reabsorption → ↑LDL receptors	↓LDL but ↑TG	Bloating, constipation; avoid in HTG
Fibrates (fenofibrate, gemfibrozil)	PPARα agonist → ↑LPL, ↓apoC-III, ↓VLDL	TG ↓~30%	Myopathy (esp. with statin), gallstones, ↑creatinine, warfarin potentiation
Omega-3 (EPA/DHA, icosapent ethyl)	↓VLDL synthesis	TG ↓~30% (3–4 g/day)	Dyspepsia; icosapent ethyl ↓CV events in HTG

- ▶ **Homozygous FH / refractory cases:** add **lomitapide** (MTP inhibitor), **mipomersen** (apoB antisense), **evinacumab** (ANGPTL3 antibody), **LDL apheresis**, and rarely liver transplantation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Lipoprotein metabolic pathways:** label *Intestine* → *Chylomicron* → *LPL (with apoC-II)* → *Chylomicron remnant* → *Liver (apoE-mediated uptake)* for the exogenous arm; *Liver* → *VLDL* → *IDL* → *LDL* → *LDL receptor* for the endogenous arm; and *Peripheral cell* → *ABCA1* → *nascent HDL* → *LCAT* → *mature HDL* → *SR-BI/CETP* → *Liver* for reverse cholesterol transport. Label **LPL**, **apoB-100**, **apoE**, **LDL receptor**, **PCSK9**, **HDL**, **SR-BI**, **CETP**.
- ▶ **Xanthoma plate:** label **tendon xanthoma** (Achilles, FH), **tuberoeruptive + palmar xanthoma** (FDBL), **eruptive xanthoma + lipemia retinalis** (chylomicronemia), **corneal arcus**.

Clinical / Diagnostic significance

- ▶ LDL-C reduction provides robust, dose-dependent reduction in MI, stroke and total mortality — “lower is better” within tolerated limits.
- ▶ **Cascade screening** of first-degree relatives is highly effective in FH (50% of siblings/children affected).
- ▶ Severe HTG mandates urgent TG lowering to avert pancreatitis; **low HDL-C** (<40 mg/dL men, <50 mg/dL women) is an independent risk marker but is **no longer a therapeutic target** for pharmacologic raising.
- ▶ A discordantly elevated **apoB** (relative to LDL-C) flags small-dense LDL of FCHL/metabolic syndrome and warrants aggressive therapy.

High-yield exam pointers

- ▶ **Friedewald formula** and its limitation (invalid if TG >400 mg/dL or in FDBL); learn **non-HDL-C** = TC – HDL-C.

- ▶ **FH** = autosomal dominant, *LDLR/APOB/PCSK9*, LDL-C usually **>190 mg/dL**, tendon xanthomas, prevalence ~1/250.
- ▶ **FDBL (type III)** = **apoE2/E2**, **palmar + tuberoeruptive xanthomas** (pathognomonic), chol ≈ TG, broad-β band, VLDL-C/TG ratio **>0.30**.
- ▶ **FCS** = LPL/apoC-II axis defect, TG >500 mg/dL, eruptive xanthomas, lipemia retinalis, **pancreatitis** risk.
- ▶ **Statins** first-line; **high-intensity** for ASCVD/high risk; LDL target driven by risk, treat ASCVD while LDL **>70 mg/dL**.
- ▶ Add-on order: statin → **ezetimibe** → **PCSK9 inhibitor**; **bempedoic acid** for statin-intolerant.
- ▶ **Fibrates + fish oil** for TG >500 mg/dL to prevent pancreatitis; **bile-acid resins** raise TG (avoid in HTG).
- ▶ Statin caution: myopathy risk ↑ with **gemfibrozil**, macrolides, azole antifungals, ciclosporin; slight ↑ incident diabetes outweighed by CV benefit.
- ▶ Always **exclude secondary causes** (hypothyroidism, nephrotic syndrome, DM, cholestasis, drugs) before labelling a primary genetic disorder.

SOURCE & COVERAGE

Harrison 22e — Ch 419 “Disorders of Lipoprotein Metabolism” (D.J. Rader). *Coverage note:* All classifications, drugs, doses, eponyms and numbers above are grounded in Ch 419. Harrison 22e organises dyslipidemia by **mechanism/phenotype** (severe HTG, hypercholesterolemia, mixed hyperlipidemia, low HDL) rather than the classic **Fredrickson/WHO Types I–V**; the Fredrickson scheme is included as a universally accepted parallel framework for exam completeness (Harrison explicitly names only “type III hyperlipoproteinemia” = FDBL).



Myxedema Coma (Myxedema Crisis): Risk Factors, Triggers, Clinical Manifestations and Treatment

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — Myxedema coma is the **decompensated, life-threatening end-stage of severe, long-standing hypothyroidism**, in which failing thyroid hormone-dependent homeostasis produces depressed consciousness, hypothermia and multi-organ slowing. It is an *endocrine emergency* of the elderly, almost always **primary** in origin, and carries a high mortality (Harrison quotes **20–40%**, CMDT **30–100%**) despite intensive care. The term “coma” is in fact a *misnomer* — the conscious level ranges from simple lethargy and obtundation through somnolence to true coma — hence the newer term **myxedema crisis**. Outcome is *independent of the absolute T4 and TSH levels* and depends chiefly on early recognition and treatment.

Pathophysiology — how chronic hypothyroidism decompensates

- ▶ Long-standing thyroid hormone deficiency lowers basal metabolic rate, thermogenesis, cardiac output, ventilatory drive and hepatic drug metabolism; an acute stress then overwhelms this fragile reserve and tips the patient into crisis.
- ▶ **Alveolar hypoventilation** is the central event: depressed central ventilatory response to hypoxia and hypercapnia, plus respiratory-muscle weakness and obstructive sleep apnoea, lead to **CO₂ retention and CO₂ narcosis** with resultant hypoxia — a major driver of the depressed sensorium.
- ▶ **Hypothermia** results from reduced thermogenesis; the cold itself further slows metabolism, creating a vicious cycle (temperature may fall to 23 °C / 74 °F).
- ▶ **Dilutional hyponatraemia** (SIADH-like, from reduced free-water clearance and inappropriate vasopressin secretion) and **hypoglycaemia** add to cerebral dysfunction.
- ▶ **Impaired adrenal reserve** (relative adrenocortical insufficiency) coexists, especially as metabolic demand rises with treatment.
- ▶ Reduced hepatic/renal clearance means sedatives, opioids and anaesthetics accumulate — both a *trigger* and a *perpetuating factor*.

Risk factors and precipitating triggers

Crisis develops when a precipitant is superimposed on a high-risk host. CMDT data: 94% have primary hypothyroidism, ~50% were previously **undiagnosed**, and ~80% are women.

Host / risk factors	Precipitating triggers
Elderly (almost always), female	Drugs impairing respiration/CNS — sedatives, hypnotics, anaesthetics, antidepressants, opioids
Severe long-standing or undiagnosed hypothyroidism	Infection / sepsis — especially pneumonia
Non-adherence to / discontinuation of levothyroxine	Cold exposure (winter presentation, hypothermia)
Post-radioiodine, post-thyroidectomy, autoimmune (Hashimoto)	Cardiac events — congestive heart failure, myocardial infarction
Coexisting cardiac/cerebrovascular disease	Cerebrovascular accident (stroke) , trauma , surgery
	Gastrointestinal bleeding , metabolic stress, hypoglycaemia

- ▶ Sedatives/anaesthetics/opioids are doubly dangerous — their metabolism is *slowed* in hypothyroidism, so they further depress cognition and respiratory drive and can precipitate **respiratory arrest**.

Clinical manifestations

The picture is **decompensated hypothyroidism plus altered sensorium**; features superimpose on the chronic stigmata of myxedema (dry, cool, doughy non-pitting skin, puffy facies, periorbital oedema, macroglossia, hoarse voice, alopecia, loss of outer third of eyebrows).

System	Features
Neurological	Reduced level of consciousness (lethargy → coma); seizures/convulsions ; delayed relaxation of deep tendon reflexes (may be absent if areflexic); impaired memory/psychosis (“myxedema madness”); abnormal CNS signs
Thermoregulatory	Hypothermia — subnormal temperature, may reach 23 °C; patient may be afebrile despite serious infection
Respiratory	Hypoventilation → hypoxia + hypercapnia (CO ₂ narcosis); respiratory-muscle weakness; pleural effusion; sleep apnoea
Cardiovascular	Bradycardia , hypotension , reduced contractility/stroke volume, low voltage ECG, pericardial effusion
Renal / metabolic	Dilutional hyponatraemia , hypoglycaemia , rhabdomyolysis , acute kidney injury (AKI)
Gastrointestinal	Ileus, megacolon, constipation, faecal impaction, urinary retention

- ▶ CMDT frequencies at presentation: **hyponatraemia ~65%**, **hypothermia ~50%**, **hypotension ~40%**, **bradycardia ~20%**, **hypoglycaemia ~15%**.

Diagnosis

- ▶ **Clinical diagnosis** — do not wait for confirmatory tests; *delay in therapy worsens prognosis*. Send serum FT4 and TSH rapidly, then **treat empirically** on clinical grounds.
- ▶ Expected biochemistry: **low FT4** with **markedly elevated TSH** in primary disease (TSH may be low/normal in central hypothyroidism).
- ▶ Supportive labs: hyponatraemia, hypoglycaemia, raised CPK, hypercapnia/hypoxia on ABG, hypercholesterolaemia, anaemia, raised lactate dehydrogenase.
- ▶ **Diagnostic scoring systems** (e.g., the *Popoveniuc* scoring system) aid recognition but are an adjunct to, not a replacement for, clinical judgement.
- ▶ Exclude/treat coexisting **adrenal insufficiency** — check cortisol; hyponatraemia in any hypothyroid patient mandates evaluation for adrenal insufficiency.

Treatment

Management is **ICU-based** and combines thyroid hormone replacement with aggressive correction of physiological disturbances. Because gut/IM/SC absorption is unpredictable in the hypometabolic state, give drugs **intravenously** wherever possible.

1. Thyroid hormone replacement

- ▶ **Levothyroxine (T4)**: IV loading bolus **200–400 µg** (Harrison) / **200–500 µg** (Williams) / **500 µg** (CMDT) to replete the peripheral pool — may improve within hours; then daily **IV/oral T4 ~1.6 µg/kg/day** (reduce IV dose by ~25%), or **50–100 µg IV daily** (lower dose if suspected coronary artery disease).
- ▶ **Liothyronine (T3)**: because peripheral **T4 → T3 conversion is impaired**, adding T3 is rational. Loading **5–20 µg** then **2.5–10 µg every 8 h** (Harrison); CMDT: **10–20 µg bolus** then **10 µg every 8–12 h** for the first 48 h. Use **lower doses** in small, elderly or cardiac-risk patients — excess T3 can provoke **arrhythmias**.

2. Glucocorticoid

- ▶ **Hydrocortisone** — parenteral **50 mg every 6 h** (Harrison) / **5–10 mg/h** (Williams) — for presumed **relative adrenal insufficiency**, ideally before/with T4.

3. Supportive / corrective measures

- ▶ **Ventilatory support** — assisted ventilation with controlled O₂; **regular ABG** monitoring, usually needed for the **first 48 h** (hypercapnia is an indication to admit/ventilate).
- ▶ **Passive rewarming with blankets only**; **avoid active external warming** — peripheral vasodilatation can precipitate **cardiovascular collapse** (external warming considered only if temperature <30 °C, with space blankets to prevent further heat loss).
- ▶ **Hyponatraemia/hypoglycaemia**: use **hypertonic saline** and **IV glucose (5% dextrose)** for severe derangements; **avoid hypotonic fluids** (worsen water intoxication/dilutional hyponatraemia).
- ▶ **Treat the precipitant**: early **broad-spectrum antibiotics** pending exclusion of infection; correct cardiac events, bleeding, metabolic upset.
- ▶ **Avoid sedatives**; if unavoidable, use reduced doses and monitor levels (impaired drug metabolism).
- ▶ General comatose care: frequent turning, aspiration precautions, attention to faecal impaction and urinary retention; switch to **oral levothyroxine** once consciousness/oral intake returns.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Vicious-cycle flow diagram of myxedema coma pathogenesis**. Centre box: *Severe long-standing hypothyroidism*. Arrows to four limbs, each labelled: (1) **Hypoventilation → hypoxia + hypercapnia (CO₂ narcosis)**; (2) **Reduced thermogenesis → hypothermia**; (3) **Reduced free-water clearance → dilutional hyponatraemia**; (4) **Impaired adrenal reserve + hypoglycaemia**. All four converge on a central output box: **Depressed consciousness /**

coma → death. Add an external arrow labelled **Precipitant** (infection, cold, sedatives, MI/CHF, stroke) feeding the central box.

- ▶ **Management box** (“4 pillars”). Four labelled columns: (i) IV Levothyroxine ± Liothyronine, (ii) IV Hydrocortisone, (iii) Ventilation + passive rewarming (blankets), (iv) Correct Na⁺/glucose + treat precipitant.

Clinical / Diagnostic significance

- ▶ A **high index of suspicion** in any obtunded, hypothermic, bradycardic elderly patient — *especially in winter or after sedation* — is life-saving; treat before biochemical confirmation.
- ▶ **Always co-treat for adrenal insufficiency** with hydrocortisone *before/with* thyroid hormone — starting T4 alone can precipitate adrenal crisis.
- ▶ Patients may be **afebrile despite severe sepsis**; sepsis/pneumonia must be actively sought and empirically covered.
- ▶ **Hyponatraemia mandates** evaluation for adrenal insufficiency and avoidance of hypotonic fluids.
- ▶ Prognosis hinges on early therapy, control of the precipitant and ventilatory support — *not* on the absolute hormone levels.

High-yield exam pointers

- ▶ **Endocrine emergency**; mortality 20–40% (Harrison), up to 30–100% (CMDT) — *treat empirically, do not await TSH/FT4*.
- ▶ Triad/hallmarks: **altered sensorium + hypothermia + hypoventilation** (CO₂ narcosis), on a background of myxedema.
- ▶ **94% primary hypothyroidism**, ~50% undiagnosed, ~80% women (CMDT); almost always elderly.
- ▶ **Commonest precipitants**: infection (**pneumonia**), **cold exposure**, sedatives/opioids/anaesthetics, MI/CHF, stroke, GI bleed, drug non-adherence.
- ▶ **Loading IV levothyroxine 200–500 µg**, then daily T4; **add IV liothyronine (T3)** because T4→T3 conversion is impaired; watch for **arrhythmia**.
- ▶ **IV hydrocortisone** for relative adrenal insufficiency — give *with/before* thyroxine.
- ▶ **Passive rewarming (blankets) only** — active external warming → **cardiovascular collapse**.
- ▶ **Avoid hypotonic fluids**; correct hyponatraemia (hypertonic saline) and hypoglycaemia (dextrose); ventilate for hypercapnia.
- ▶ “Myxedema coma” is a **misnomer** — consciousness ranges from lethargy to coma (myxedema crisis).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Hypothyroidism” (clinical features, myxedema-coma pathogenesis, levothyroxine/liothyronine and hydrocortisone dosing, warming and fluid rules, mortality figures).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Hypothyroidism and Thyroiditis” (myxedema-coma definition, predisposing factors, alternate T4/T3 regimens, gastric rewarming, diagnostic scoring systems, supportive care).
- ▶ **CMDT 2026** — “Disorders of the Pituitary, Thyroid, & Adrenal Glands” (myxedema-crisis epidemiology, presenting frequencies of hyponatraemia/hypothermia/hypotension/bradycardia/hypoglycaemia, IV levothyroxine 500 µg + liothyronine regimen, mortality 30–100%, admission criteria).
- ▶ *Coverage note:* The corpus references diagnostic scoring systems (e.g., Popoveniuc) but does not reproduce the individual point values; these are therefore named but not tabulated, to avoid fabricating specifics.



Syndrome of Inappropriate Antidiuresis (SIADH/SIAD)

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — The **syndrome of inappropriate antidiuresis (SIAD/SIADH)** is a disorder of water homeostasis in which arginine vasopressin (AVP/ADH) is secreted — or its renal action is sustained — at plasma osmolalities that should normally suppress it, in the *absence* of an osmotic or appropriate haemodynamic (hypovolaemic/hypervolaemic) stimulus. The cardinal biochemical hallmark is **hypotonic, euvolaemic hyponatraemia** with inappropriately concentrated urine. It is the single most common cause of hypoosmolality in clinical practice (20–40% of all hypoosmolar patients) and is fundamentally a **diagnosis of exclusion**, defined since 1967 by the **Schwartz–Bartter criteria**.

Etiology

SIAD results either from pituitary (eutopic) hypersecretion of AVP driven by CNS/pulmonary disease and drugs, or from ectopic (paraneoplastic) AVP production. A small subset have a gain-of-function *V2-receptor* mutation (**nephrogenic SIAD**) with undetectable AVP. Causes fall into five groups:

Category	Representative causes
Malignancy (ectopic AVP)	Small-cell lung carcinoma (≈75% of malignancy-associated SIAD; ~10% present with Na <130), mesothelioma, head & neck/oropharyngeal, GI (stomach, duodenum, pancreas), GU (ureter, bladder, prostate), thymoma, lymphoma, Ewing sarcoma

Category	Representative causes
Pulmonary disease	Bacterial/viral pneumonia, tuberculosis, lung abscess, aspergillosis, empyema, advanced COPD, positive-pressure ventilation, respiratory failure
CNS disorders	Subarachnoid haemorrhage, head trauma, meningitis, encephalitis, brain abscess/tumour, subdural haematoma, stroke, hydrocephalus, Guillain-Barré, SLE, acute intermittent porphyria, MS
Drugs	SSRIs, tricyclics, carbamazepine/oxcarbazepine, chlorpropamide, vincristine, cyclophosphamide/ifosfamide, NSAIDs, antipsychotics, nicotine, clofibrate, MDMA (“Ecstasy/Molly”), AVP analogues (desmopressin, oxytocin)
Other	Hereditary nephrogenic SIAD (V2R gain-of-function), HIV/AIDS, prolonged endurance exercise, pain, nausea, stress, general anaesthesia, post-operative state, idiopathic (common in the elderly)

Pathophysiology

- ▶ Persistent AVP action on renal **V2 receptors** → **aquaporin-2** insertion in collecting-duct principal cells → water retention, free-water excretion fails, and intake of free water (at thirst thresholds shifted downward) generates hyponatraemia.
- ▶ **Not truly euvoelaemic** but *subclinically volume-expanded*; this triggers two adaptive escapes that limit oedema: (1) **secondary natriuresis** (volume expansion, not AVP, drives urinary Na^+ loss → patients reach a new steady state in neutral Na^+ balance — the basis of so-called “renal salt wasting”), and (2) **AVP/renal escape** — hypotonicity downregulates V2-receptor and aquaporin-2 expression.
- ▶ Proximal-tubular urate and urea handling is suppressed by the volume-expanded state → characteristic **hypouricaemia** ($<4 \text{ mg/dL}$) and low BUN ($<10 \text{ mg/dL}$).
- ▶ **Four patterns of AVP secretion** (independent of cause): (1) random/erratic hypersecretion ($\sim 1/3$); (2) non-suppressible basal AVP with normal osmotic response; (3) **reset osmostat** (left-shifted threshold; AVP suppresses and urine dilutes if Na^+ falls low enough); (4) low/undetectable AVP (**nephrogenic SIAD**, constitutive V2R activation). A fifth copeptin-defined “barostat reset” pattern is described.

Clinical features

- ▶ Reflect **cerebral oedema** from osmotic water shift into brain cells, and depend on severity and *rate* of fall in Na^+ .

- ▶ **Acute** (<48 h): headache, nausea/vomiting, lethargy → seizures, obtundation, brainstem herniation, neurogenic (non-cardiogenic) pulmonary oedema, coma, death. Premenopausal women are especially vulnerable.
- ▶ **Chronic** (>48 h): often labelled “asymptomatic” owing to brain organic-osmolyte efflux/volume regulation, but causes subtle gait/cognitive impairment, **falls, fractures** (with reduced bone density) and increased mortality.

Evaluation / Diagnosis

Schwartz–Bartter diagnostic criteria (essential):

- ▶ **Decreased effective plasma osmolality** (<275 mOsm/kg; exclude pseudo- and translocational hyponatraemia).
- ▶ **Inappropriate urinary concentration** — urine osmolality >100 mOsm/kg (not maximally dilute) at some level of hypoosmolality.
- ▶ **Clinical euvolaemia** (no orthostasis/tachycardia/dry membranes; no oedema/ascites).
- ▶ **Elevated urinary sodium** (>30–40 mmol/L) on normal salt and water intake.
- ▶ **Exclusion** of hypothyroidism, glucocorticoid deficiency (secondary/primary adrenal insufficiency), renal failure and diuretic use.

Supportive (non-essential): hypouricaemia (<4 mg/dL), low BUN, failure to excrete a standard water load, and AVP/copeptin inappropriately elevated for osmolality. **Measurement of AVP/copeptin is generally NOT clinically useful** (10–20% have undetectable AVP; levels overlap with hypovolaemic states).

Key investigations: serum osmolality (exclude pseudohyponatraemia from hyperlipidaemia/hyperproteinaemia and translocational from hyperglycaemia/mannitol), paired urine osmolality and urine Na⁺, serum uric acid, BUN/creatinine, glucose, TFT and **0900 cortisol/short Synacthen test**, and imaging (chest CT for occult small-cell lung cancer in smokers; MRI brain) to find the cause.

Critical differentials by urine Na⁺ and volume status:

- ▶ **Cerebral salt wasting (CSW)** — hypovolaemic hyponatraemia with high urine Na⁺ in intracranial disease (esp. SAH); distinguished by *clinical hypovolaemia* and *responds to saline repletion* (the opposite of SIAD). Modern series suggest true CSW is exceedingly rare; most SAH hyponatraemia is SIAD.
- ▶ **Hypovolaemic hyponatraemia** (urine Na⁺ <20–30; hyperuricaemic) corrects with normal saline.
- ▶ **Hypervolaemic hyponatraemia** (heart failure, cirrhosis; urine Na⁺ <10).
- ▶ **Glucocorticoid deficiency and hypothyroidism** mimic SIAD and must be excluded first.

Management

1. Acute / severely symptomatic (seizures, coma) — medical emergency:

- ▶ **Hypertonic 3% NaCl (513 mmol/L):** a 100-mL bolus over ~10–15 min, repeated up to 2–3 times until symptoms abate; each bolus raises Na^+ by ~1–2 mmol/L. Aim for a prompt rise of only 4–6 mmol/L — sufficient to relieve cerebral oedema. Less severe symptoms: 3% saline 0.5–2 mL/kg/h.
- ▶ Monitor serum Na^+ every 1–2 h; supplemental O_2 /ventilatory support for neurogenic pulmonary oedema.

2. Chronic hyponatraemia — treat the cause + raise Na^+ safely:

- ▶ Withdraw causative drugs; treat tumour/pneumonia; replace glucocorticoid/thyroid if deficient.
- ▶ **Fluid restriction (500–1000 mL/day, all fluids)** is first-line but often fails. The **Furst ratio** ($\text{UNa} + \text{UK})/\text{PNa} > 1$ (i.e. urine osmolality > 500 mOsm/L) predicts failure → escalate.
- ▶ **Increase solute load:** oral salt tablets $\pm$ furosemide 20 mg BD (blunts the medullary gradient); oral urea 30–60 g/day (osmotic aquaresis; palatable bicarbonate/citrate formulations).
- ▶ **AVP-receptor antagonists (vaptans):** **tolvaptan** (oral V_2 antagonist; low-dose 7.5 mg preferred to limit overcorrection) and **conivaptan** (IV $\text{V}_1\text{A}/\text{V}_2$). Start in hospital, liberalise fluids > 2 L/day, monitor closely; limit duration to < 1 –2 months (hepatotoxicity); avoid in cirrhosis.
- ▶ **SGLT2 inhibitors** (glycosuric osmotic diuresis) raise Na^+ in SIAD and **demeclocycline** (induces nephrogenic DI; nephrotoxic, photosensitivity — avoided in cirrhosis) are alternatives.

3. Avoid osmotic demyelination syndrome (ODS):

- ▶ Do **not** correct Na^+ by > 8 mmol/L in 24 h (and < 18 mmol/L over 48 h); high-risk patients ($\text{Na}^+ < 120$, alcoholism, malnutrition, **hypokalaemia**, liver disease) target only 4–6 mmol/L/day.
- ▶ Correct hypokalaemia cautiously (raises Na^+ independently). If overcorrection occurs/anticipated, **re-lower** with IV 5% dextrose and/or a **DDAVP “clamp”** (desmopressin) to prevent aquaresis.
- ▶ ODS (central pontine + extrapontine myelinolysis) presents 2–6 days later with dysarthria, dysphagia, para-/quadriplegia, “locked-in” syndrome.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm for hyponatraemia** (flowchart): Box “Hyponatraemia ($\text{Na}^+ < 135$) → measure serum osmolality” → branches: *Pseudo/translocational* (normal/high osm) vs *True hypotonic* (< 275). Hypotonic branch → assess **volume status**: **Hypovolaemic** (Urine $\text{Na}^+ < 20$ = extrarenal loss; > 20 = renal loss/diuretics/Addison/CSW) | **Euvolaemic** (Urine $\text{Na}^+ > 20$ → exclude hypothyroidism, glucocorticoid deficiency → SIAD) | **Hypervolaemic** (CHF, cirrhosis, nephrotic, renal failure). Label each box with the urine Na^+ cut-off.
- ▶ **SIAD pathophysiology loop:** AVP → V_2 receptor → aquaporin-2 $\uparrow$ → water retention → $\downarrow$ plasma Na^+ /osmolality + subclinical volume expansion → secondary natriuresis (high urine

Na^+) + AVP/renal escape (AQP2 down-regulation). Label: AVP, V2 receptor, AQP2, collecting duct, hypouricaemia.

Clinical / Diagnostic significance

- ▶ Hypouricaemia (<4 mg/dL) and low BUN are quick bedside discriminators of SIAD from hypovolaemic hyponatraemia (which is hyperuricaemic).
- ▶ New-onset unexplained SIAD in a smoker mandates **CT thorax** to exclude **small-cell lung cancer**.
- ▶ Always **exclude adrenal insufficiency and hypothyroidism** before labelling SIAD — glucocorticoid replacement alone may correct euvolaemic hyponatraemia from secondary adrenal failure.
- ▶ **Thiazide-induced** hyponatraemia mimics SIAD; defer the SIAD diagnosis until 1–2 weeks after stopping the thiazide.
- ▶ The *rate* of correction, not just the target, governs outcome — ODS is iatrogenic and preventable.

High-yield exam pointers

- ▶ SIAD = euvolaemic hypotonic hyponatraemia + inappropriately concentrated urine + high urine Na^+ + hypouricaemia; a diagnosis of exclusion.
- ▶ **Schwartz–Bartter (1967)**: ↓plasma osm <275, urine osm >100, euvolaemia, urine Na^+ >40, exclude thyroid/adrenal/renal/diuretic causes.
- ▶ **SCLC** = commonest malignant cause (75%); **SSRIs/carbamazepine** = commonest drug causes; **SAH** classic CNS cause.
- ▶ **Four AVP patterns**, including **reset osmostat** and AVP-negative **nephrogenic SIAD** (V2R gain-of-function).
- ▶ Acute symptomatic: **3% saline 100 mL bolus**, target rise **4–6 mmol/L**; chronic: **fluid restriction** → **urea/tolvaptan 7.5 mg/SGLT2i**.
- ▶ **Never correct >8 mmol/L/24 h** (4–6 in high-risk) → prevents **osmotic demyelination** (central pontine myelinolysis).
- ▶ **Distinguish CSW** (hypovolaemic, saline-responsive) from SIAD; **AVP/copeptin assay is not diagnostically useful**.
- ▶ Overcorrection → re-lower with **D5W ± DDAVP clamp**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Fluid and Electrolyte Disturbances” (hyponatraemia classification, SIAD pathophysiology, causes table, diagnostic approach)

and treatment including hypertonic saline, vaptans, urea, furosemide, ODS/correction limits) and “Disorders of the Neurohypophysis” (SIAD clinical features, differential diagnosis, treatment — 100-mL 3% saline bolus, urea, tolvaptan 7.5 mg, demeclocycline, SGLT2 inhibitors).

- ▶ **Williams Textbook of Endocrinology, 15e** — “Posterior Pituitary” (Schwartz–Bartter criteria, four/five patterns of AVP secretion, nephrogenic SIAD, secondary natriuresis, renal escape/aquaporin-2, cerebral salt wasting, therapy principles, ODS correction goals).
- ▶ **CMDT 2026** — “Electrolyte & Acid-Base Disorders” (SIADH diagnostic criteria, Furst ratio, symptomatic vs chronic management, vaptans/urea/SGLT2i, ODS risk factors and correction limits, DDAVP clamp).



Etiology, Clinical Features, Diagnosis, Complications and Management of Obesity

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Obesity is a chronic, relapsing, multifactorial disease defined as *a state of excess adipose-tissue mass that adversely affects health*. Because direct fat measurement is impractical, the **body-mass index (BMI = weight in kg / height in m²)** is used as a proxy: the WHO classifies BMI ≥ 30 kg/m² as obesity and 25–29.9 kg/m² as overweight. It arises from a sustained imbalance of energy intake over expenditure on a strong genetic and obesogenic-environmental background, and it predisposes to type 2 diabetes, cardiovascular disease, several cancers and reduced life expectancy.

Etiology and Pathogenesis

- ▶ **Fundamental basis — energy imbalance:** Obesity develops when energy intake chronically exceeds expenditure; because it is *cumulative*, a surplus as small as **~7 kcal/day** can produce obesity over years. Excess energy is stored as triglyceride in the unilocular lipid droplet of adipocytes (and ~10% of fat cells turn over yearly).
- ▶ **Genetic predisposition:** Twin/adoption studies show adiposity is strongly heritable (CMDT: genetics explain 40–90% of weight variation). Up to **20% of children with severe obesity** carry a chromosomal abnormality or highly penetrant mutation. Most common obesity is **polygenic**.
- ▶ **Leptin–melanocortin (central) pathway** — the hypothalamus integrates signals of energy stores:
 - **Leptin** (from adipose tissue) rises with fat mass; a *fall* below habitual level is a powerful drive to eat. It stimulates **POMC** neurons in the arcuate nucleus and inhibits **AGRP/NPY/GABA** neurons.
 - POMC-derived **α -/β-MSH act on the MC4 receptor** in the paraventricular nucleus → ↓intake and ↑expenditure; **AGRP** antagonises MC4R. *BDNF/TrkB* and *SIM1* act downstream.

- “**Leptin resistance**” at high levels (blunted response to leptin excess) explains why leptin does not prevent obesity.
- ▶ **Gut/pancreatic (peripheral) signals:** Ghrelin (stomach) increases hunger pre-meal; GLP-1, GIP, PYY, oxyntomodulin, CCK and insulin/amylin promote satiety after a meal — the rationale for incretin-based drugs.
- ▶ **Monogenic obesity** (severe, early-onset, hyperphagic): mutations in **leptin** (treatable with recombinant leptin), **leptin receptor**, **POMC** (with red hair, ACTH deficiency), **PCSK1**, **carboxypeptidase E**, **MC4R** (the *commonest* — heterozygous variants in 5–6% of severe early-onset obesity, ~1 in 300 of the population), **SIM1**, **BDNF**, **TrkB**, **SH2B1**.
- ▶ **Syndromic obesity:** **Prader-Willi** (commonest syndrome, ~1 in 25,000; paternal chromosome-15 deletion; hypotonia, hyperphagia, hypogonadism), **Bardet-Biedl** (AR ciliopathy; polydactyly, retinal dystrophy, renal disease), **Albright hereditary osteodystrophy** / **pseudohypoparathyroidism** (*GNAS1*), Cohen, Carpenter, Alström, Tubby.
- ▶ **Secondary / acquired causes** — always exclude:
 - Endocrine: **hypothyroidism**, **Cushing’s syndrome**, **PCOS**, **insulinoma**, **hypothalamic damage** (craniopharyngioma, trauma, inflammation).
 - **Drug-induced:** insulin, sulfonylureas, thiazolidinediones; glucocorticoids; antipsychotics (clozapine, olanzapine, risperidone); lithium; antidepressants (tricyclics, MAOIs, paroxetine, mirtazapine); antiepileptics (valproate, gabapentin, carbamazepine).
- ▶ **Obesogenic environment:** cheap, energy-dense, aggressively-marketed food in large portions, plus mechanisation, sedentary work and reduced thermoregulatory expenditure — drives the population-level rise.

Clinical Features

- ▶ **Anthropometric:** raised BMI; **central (android) adiposity** — increased waist circumference and waist-to-hip ratio **>0.9 in women, >1.0 in men** (independent marker of metabolic risk).
- ▶ **Symptoms of excess mass:** exertional dyspnoea, fatigue, mechanical low-back pain and knee pain, immobility, daytime somnolence/snoring (sleep apnoea).
- ▶ **Skin:** **acanthosis nigricans** (velvety hyperpigmentation of axilla/groin/nape — marker of hyperinsulinaemia), skin tags (acrochordons), striae distensae, intertrigo/fungal infection, **hidradenitis suppurativa**, stasis pigmentation, lymphoedema.
- ▶ **Reproductive:** in women — irregular menses, anovulatory infertility, hirsutism (PCOS); in men — **central hypogonadism** with low testosterone and inappropriately low/normal LH-FSH.
- ▶ **Distribution matters:** visceral/central obesity carries far higher cardiometabolic risk than gluteofemoral (lower-body) fat — the latter being relatively protective.

Diagnosis and Evaluation

The four steps are: (1) obesity-focused **history**, (2) **physical examination** for degree and type of obesity, (3) assessment of **complications/comorbidities**, and (4) assessment of **readiness to change** (motivational interviewing, 0–10 confidence/importance scale). Use neutral language (“weight,” “BMI,” “unhealthy weight”).

Classification	BMI (kg/m ²)	Obesity class	Disease risk
Underweight	<18.5	—	—
Healthy weight	18.5–24.9	—	—
Overweight	25.0–29.9	—	Increased
Obesity	30.0–34.9	I	High
Obesity	35.0–39.9	II	Very high
Extreme obesity	≥40	III	Extremely high

- ▶ **BMI limitations:** measures size, not body composition/fat distribution; over-estimates fat in the very muscular; **lower thresholds apply to Asia-Pacific populations** (risk at lower BMI).
- ▶ **Waist circumference** (surrogate for visceral fat; measure horizontally above iliac crest, most useful when BMI ≤35) — **ethnic-specific cut-offs:** Europeans — men >94 cm, women >80 cm; **South Asians & Chinese** — men >90 cm, women >80 cm; Japanese — men >85 cm, women >90 cm.
- ▶ **Routine investigations for all:** fasting lipid profile (total, LDL, HDL, triglycerides), chemistry panel, HbA1c, blood pressure; thyroid function (TSH) and, where suspected, screening for Cushing’s (24-h urine free cortisol / dexamethasone suppression), PCOS work-up and obstructive-sleep-apnoea screening.
- ▶ **Severity staging (beyond BMI):**
 - **AACE/ACE staging:** Stage 0 = obesity by BMI, no complications; Stage 1 = ≥1 mild–moderate complication; Stage 2 = ≥1 severe complication — guides aggressiveness of therapy.
 - **Edmonton Obesity Staging System (EOSS):** five grades (0–4) across **medical, functional and psychological domains**, *independent of BMI*.

Complications

- ▶ **Metabolic/endocrine:** insulin resistance/hyperinsulinaemia, **metabolic syndrome**, **type 2 diabetes**, atherogenic **dyslipidaemia** (high triglycerides, low HDL), hyperuricaemia/**gout**, PCOS, male hypogonadism.
- ▶ **Cardiovascular:** hypertension, coronary artery disease, stroke, **heart failure (diastolic dysfunction/HFpEF)**, atrial fibrillation, varicose veins, venous thromboembolism.

- ▶ **Respiratory:** obstructive sleep apnoea, obesity-hypoventilation (**Pickwickian**) syndrome, asthma, cor pulmonale, exertional dyspnoea.
- ▶ **Hepato-gastrointestinal:** MAFLD/NAFLD → NASH → fibrosis/cirrhosis/HCC, GERD/reflux oesophagitis, cholelithiasis (and cholecystitis, pancreatitis, gallbladder cancer), hernias.
- ▶ **Musculoskeletal:** osteoarthritis of knees/hips, low back pain, carpal tunnel syndrome, immobility.
- ▶ **Malignancy:** colorectal, kidney, pancreatic, oesophageal adenocarcinoma, and (in women) endometrial and breast cancer — each 5 kg/m² BMI rise raises cancer mortality ~10%.
- ▶ **Neuro-psychological:** idiopathic intracranial hypertension, meralgia paraesthetica, increased dementia and stroke risk; depression, low self-esteem, body-image disturbance, social stigmatisation.
- ▶ **Renal/GU:** obesity-related glomerulopathy, stress incontinence, pregnancy complications.
- ▶ **Other:** worse outcomes from infection (e.g., SARS-CoV-2), surgical-wound infection; rare association with thrombotic thrombocytopenic purpura.

Management

Therapy is escalated by BMI category and comorbidity (Table 414-4): lifestyle for all, drugs from BMI ≥27 with comorbidity / ≥30, surgery from BMI ≥35 with comorbidity / ≥40. A realistic initial goal is 8–10% loss over 6 months; even 5–10% loss yields dose-related improvement in glycaemia, BP and lipids.

- ▶ **1. Lifestyle management** (modest ~3–5 kg loss; the foundation):
 - **Diet:** create a deficit of **500–750 kcal/day** (≈1200–1500 kcal/day for women, 1500–1800 for men) targeting ~1–2 lb/week loss; macronutrient ratio matters less than total calorie reduction and adherence; use low-energy-density foods, meal replacements; **very-low-calorie diets** (≤800 kcal/day) for selected motivated patients (e.g., DiRECT trial achieved diabetes remission).
 - **Physical activity:** **150 min/week moderate (or 75 min vigorous); >300 min/week** often needed to lose and maintain; key role in *maintenance*; reduce sedentary time.
 - **Behavioural therapy / CBT:** self-monitoring, stimulus control, stress management, problem-solving, cognitive restructuring.
- ▶ **2. Pharmacotherapy** (BMI ≥30, or ≥27 with comorbidity; adjunct to lifestyle):

Drug	Mechanism	Note (placebo-subtracted weight loss)
Phentermine	Sympathomimetic (↑CNS noradrenaline)	Short-term use only; ~4.4%
Orlistat 120 mg tid	GI lipase inhibitor (blocks ~30% dietary fat)	Steatorrhea; supplement fat-soluble vitamins; ~4.1%

Drug	Mechanism	Note (placebo-subtracted weight loss)
Phentermine/topiramate	Sympathomimetic + GABA/carbonic-anhydrase	~8.0%; teratogenic (oral cleft)
Naltrexone SR/bupropion SR	Opioid antagonist + DA/NA reuptake inhibitor (POMC activation)	~5.1%
Liraglutide 3.0 mg SC daily	GLP-1 receptor agonist	~5.4%
Semaglutide 2.4 mg SC weekly	GLP-1 receptor agonist	~12.5%; SELECT trial: 20% ↓ MACE
Tirzepatide SC weekly	Dual GLP-1/GIP agonist	~17.8% (SURMOUNT) — most effective
Setmelanotide SC	MC4R agonist	For monogenic/syndromic obesity (POMC, PCSK1, LEPR, Bardet-Biedl)

GLP-1/GIP agonists are contraindicated with personal/family history of medullary thyroid carcinoma or MEN-2; pancreatitis is a caution. Common adverse effects are gastrointestinal (nausea, vomiting, diarrhoea, constipation).

- ▶ **3. Bariatric/metabolic surgery** (BMI ≥40, or ≥35 with comorbidity):
 - **Restrictive:** laparoscopic adjustable gastric banding (largely abandoned); sleeve gastrectomy (~80% greater curvature removed).
 - **Restrictive-malabsorptive:** Roux-en-Y gastric bypass, biliopancreatic diversion ± duodenal switch — typically 28–33% total-body-weight loss.
 - Benefits act partly via altered gut hormones (ghrelin, GLP-1, PYY); **Swedish Obese Subjects study:** 78% reduction in incident type 2 diabetes; reduced all-cause and cardiovascular mortality. Mortality usually <1%.
 - Risks: stomal stenosis/marginal ulcer (RYGB), and **lifelong micronutrient deficiency** (vitamin B12, iron, folate, calcium, vitamin D) after malabsorptive procedures.
- ▶ **4. Endoscopic options** (treatment gap / poor surgical candidates): intragastric balloon (6–12% loss, removed at 6 months); endoscopic sleeve gastroplasty (~18% at 2 years).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hypothalamic energy-balance circuit:** Adipose tissue → Leptin → Arcuate nucleus (stimulates POMC, inhibits AGRP/NPY) → α/β-MSH → MC4R in Paraventricular nucleus → “↓Food intake, ↑Energy expenditure”; gut hormones into brainstem — label Ghrelin (stomach, hunger), GLP-1, GIP, PYY, CCK, oxyntomodulin, Insulin, Amylin, Vagus nerve.

- **Obesity-complication body map:** central figure labelled with **Dementia/Stroke, Sleep apnoea, Hypertension, Ischaemic heart disease, Heart failure, NAFLD/NASH, Type 2 diabetes, Dyslipidaemia, Gallstones, Reflux oesophagitis, PCOS, Osteoarthritis, Gout, Cancers (oesophagus/colon/endometrium/pancreas/kidney).**

Clinical / Diagnostic significance

- Use **BMI + waist circumference + complication staging** together — BMI alone under-estimates risk in South Asians, hence the lower waist cut-offs (men >90 cm, women >80 cm) relevant to Indian practice.
- **Acanthosis nigricans** at the bedside flags insulin resistance and warrants HbA1c/lipids.
- Always **screen for and treat secondary/iatrogenic causes** (thyroid, Cushing's, obesogenic drugs) before labelling "simple" obesity.
- Weight loss is **disease-modifying**: 5–10% improves glycaemia/BP/lipids; semaglutide (SELECT) and bariatric surgery (SOS) provide *hard cardiovascular and diabetes outcome* benefit.

High-yield exam pointers

- BMI ≥ 30 = obesity; ≥ 40 = extreme (class III); Asia-Pacific thresholds are lower.
- Waist-hip ratio **>0.9 (women), >1.0 (men)** = adverse risk; visceral > subcutaneous fat for metabolic harm.
- **MC4R** = commonest monogenic obesity gene; **Prader-Willi** = commonest syndromic cause.
- **Leptin deficiency is the only fully treatable monogenic obesity** (recombinant leptin); leptin-receptor deficiency is not.
- **Setmelanotide** (MC4R agonist) for POMC/PCSK1/LEPR/Bardet-Biedl obesity.
- Drug ladder potency: **tirzepatide > semaglutide > phentermine-topiramate > liraglutide $\approx$ naltrexone-bupropion > orlistat/phentermine.**
- GLP-1/GIP agonists contraindicated in **MEN-2 / medullary thyroid cancer**.
- Surgery thresholds: **BMI ≥ 40 , or ≥ 35 with comorbidity**; RYGB/sleeve give 28–33% weight loss; supplement **B12, iron, folate, Ca, vitamin D** lifelong.
- Treatment target: **8–10% loss over 6 months**; even 5% improves comorbidities.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "*Pathobiology of Obesity*" (O'Rahilly & Farooqi; etiology, leptin-melanocortin pathway, monogenic/syndromic causes, complications) and "*Evaluation and Management of Obesity*" (Kushner; classification tables, AACE/ACE & Edmonton staging, antiobesity drugs, bariatric surgery).

- ▶ **CMDT 2026** — “*Nutrition, Nutritional Disorders, & Obesity*” (diagnostic approach, weight-loss thresholds, pharmacotherapy and surgical/endoscopic referral criteria).
- ▶ Coverage note: All specifics (BMI/waist cut-offs, drug doses and placebo-subtracted weight-loss figures, trial names — DiRECT, SELECT, SURMOUNT, STEP, SOS) are verbatim from the Harrison and CMDT obesity chapters. The dedicated subspecialty text (Williams Textbook of Endocrinology, “Obesity and Neuroendocrine Control of Energy Stores”) was consulted but added no specifics beyond those already grounded above; corpus coverage of this topic is thorough.



Evaluation and Treatment of Diabetic Peripheral Neuropathy

Asked in: Paper III Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Diabetic neuropathy is a group of clinically distinct syndromes resulting from damage to peripheral somatic and autonomic nerves by chronic hyperglycaemia and associated metabolic-syndrome factors. It occurs in roughly **50% of individuals with long-standing type 1 or type 2 DM** and is the most common cause of peripheral neuropathy in the developed world. **Distal symmetric polyneuropathy (DSPN)** is by far the commonest form. Diagnosis is essentially clinical and is one of *exclusion* — other causes (B12 deficiency, paraproteinaemia, hypothyroidism, alcohol) must be ruled out before attributing neuropathy to diabetes.

Classification (ADA / Toronto Consensus)

- ▶ **A. Diffuse neuropathy** (commonest group)
 - **Distal symmetric polyneuropathy (DSPN)** — small-fibre predominant, large-fibre predominant, or *mixed* (most common).
 - **Autonomic neuropathy** — cardiovascular (CAN), gastrointestinal, urogenital, sudomotor, hypoglycaemia unawareness, abnormal pupillary function.
- ▶ **B. Mononeuropathy / mononeuritis multiplex** — isolated cranial (III, IV, VI, VII) or peripheral nerve (median, ulnar, peroneal, femoral); entrapment syndromes.
- ▶ **C. Radiculopathy / polyradiculopathy** — lumbosacral radiculoplexus neuropathy (*diabetic amyotrophy / Bruns–Garland syndrome*), thoracic (truncal) radiculopathy.
- ▶ Special form: **treatment-induced neuropathy of diabetes (TIND / “insulin neuritis”)** — acute painful small-fibre neuropathy after rapid glycaemic correction.

Risk factors and pathogenesis

- ▶ **Risk factors:** duration of diabetes and poor glycaemic control (HbA1c); high BMI/central obesity; smoking; coexistent retinopathy and nephropathy; hypertension, hypertriglyceridaemia and ASCVD. In T2D the wider **metabolic syndrome** drives neuropathy as much as glucose itself.
- ▶ **Pathogenesis** — hyperglycaemia-driven microvascular and metabolic injury to both myelinated and unmyelinated fibres, with a unifying theme of mitochondrial **oxidative stress / bioenergetic failure**:
 - **Polyol pathway** — aldose reductase (AKR1B1) reduces glucose to **sorbitol** (then fructose via sorbitol dehydrogenase), consuming NADPH and depleting glutathione.
 - **Advanced glycation end-products (AGEs)** — the dicarbonyl **methylglyoxal** modifies proteins and, via Nav1.8 sodium channels on C-fibres, contributes to neuropathic pain; AGE–RAGE signalling activates inflammation.
 - **Protein kinase C (PKC)** activation and flux through the **hexosamine pathway**.
 - Defective resolution of inflammation and nerve ischaemia (vasa nervorum) — relevant to acute mononeuropathies.

Clinical features

- ▶ **DSPN:** insidious **stocking-and-glove** sensory loss beginning in the toes, ascending up the legs and later into the fingers (“length-dependent”). Small-fibre symptoms — burning, tingling, lancinating/stabbing pain, hyperaesthesia, dysaesthesia — typically *worse at rest and at night*. Up to 50% are **asymptomatic**, making screening essential. As it progresses pain may subside, leaving sensory deficit, **loss of protective sensation (LOPS)**, and later motor signs (foot-drop, small-muscle wasting, clawing of toes).
- ▶ **Signs:** reduced 10-g monofilament/vibration perception, **absent ankle reflexes**, impaired proprioception, distal weakness, foot deformity.
- ▶ **Autonomic:** resting tachycardia, reduced heart-rate variability, **orthostatic hypotension**, gastroparesis, diabetic diarrhoea/constipation, neurogenic bladder (cystopathy), erectile dysfunction/retrograde ejaculation, anhidrosis of feet with hyperhidrosis of trunk, **hypoglycaemia unawareness**, prolonged QTc and risk of sudden death.
- ▶ **Mononeuropathy:** acute painful **third-nerve palsy** that is *pupil-sparing* (ptosis + ophthalmoplegia, pupil intact), or VI/IV/VII (Bell’s) palsy; self-limiting over 6–12 weeks.
- ▶ **Diabetic amyotrophy (Bruns–Garland):** severe unilateral low-back/hip/thigh pain with proximal quadriceps wasting and weakness, often heralded by marked weight loss; raised CSF protein and ESR; gradual self-limited recovery over 6–18 months.
- ▶ **Diabetic neuropathic cachexia:** symmetric painful neuropathy with profound weight loss; good prognosis, recovers within ~1 year.

Evaluation and diagnosis

- ▶ **When to screen:** annual examination beginning **5 years after diagnosis of T1DM** and at **diagnosis of T2DM**, aimed at detecting LOPS (the major risk factor for ulceration, falls and amputation).
- ▶ **Bedside small-fibre tests** — pinprick (sharp/dull discrimination on dorsum of toe), temperature (cool tuning-fork on cheek vs toe), cotton-wisp light touch.
- ▶ **Bedside large-fibre tests** — **128-Hz tuning-fork** vibration at the great toe, ankle (Achilles) reflexes, proprioception at the first MTP joint.
- ▶ **10-g Semmes–Weinstein monofilament (5.07 filament)** — assesses LOPS / ulcer risk; recommended as a **three-site test** (plantar great toe, 3rd and 5th metatarsal heads).
- ▶ **Validated screening scores:** Michigan Neuropathy Screening Instrument (MNSI), Modified Toronto Clinical Neuropathy Score, Neuropathy Impairment Score, Utah Early Neuropathy Score; questionnaires (DN4, LANSS) help identify *neuropathic pain*.
- ▶ **Confirmatory / atypical-case tests:**
 - **Nerve conduction studies (NCS)** — gold standard for **large-fibre** neuropathy; reduced amplitudes with mild–moderate slowing (sural, peroneal, tibial). Sural abnormality plus one other nerve = large-fibre neuropathy.
 - **Intra-epidermal nerve-fibre density (IENFD)** on 3-mm skin punch biopsy (PGP 9.5 staining) — gold standard for **small-fibre** neuropathy.
 - Quantitative sensory testing, autonomic testing (heart-rate variability, QSART/sudomotor, sympathetic skin response), corneal confocal microscopy (research).
- ▶ **Toronto Consensus severity grading:** *possible* → *probable* (≥ 2 of: neuropathic symptoms, decreased distal sensation, reduced/absent ankle reflexes) → *confirmed* (symptom/sign **plus** abnormal NCS or validated small-fibre measure) → *subclinical* (abnormal tests, no symptoms/signs).
- ▶ **Exclude mimics (AAN):** serum protein electrophoresis with immunofixation, **vitamin B12** (metformin lowers B12), TFTs; consider HIV, alcohol, paraneoplastic. Up to **10% of neuropathy in diabetics is non-diabetic** (Rochester study). *Red flags for an alternative diagnosis:* asymmetry, motor > sensory involvement, or rapid/aggressive course.

Treatment

- ▶ **A. Disease-modifying / preventive (the foundation):**
 - **Glycaemic control** — tight, near-normal glycaemia *prevents and slows* DSPN dramatically in T1DM (DCCT). In T2DM intensive glucose control alone is only **modestly effective**; multifactorial risk-factor control is required.
 - **Treat the metabolic syndrome** — dyslipidaemia, hypertension, hypertriglyceridaemia, obesity; smoking and alcohol cessation; exercise and weight loss; correct B12/folate deficiency.

- **Caution:** lower HbA1c gradually — a fall >1% **per month** risks treatment-induced neuropathy (TIND) and accelerated retinopathy.
- **Foot protection** — daily foot inspection, appropriate footwear/accommodative insoles, callus/ulcer prevention, podiatry referral; mechanical off-loading and debridement for neuropathic ulcers.
- ▶ **B. Symptomatic treatment of painful DSPN** — start one agent, titrate to effect or side-effects, then add a second from a different class; ~two-thirds obtain relief:
 - **Voltage-gated $\alpha 2\delta$ ligands** — **pregabalin** (50–100 mg tid; FDA-approved) and **gabapentin** (300–1200 mg tid).
 - **SNRIs** — **duloxetine** (30–60 mg/day; FDA-approved), **venlafaxine** (37.5–150 mg/day).
 - **Tricyclic antidepressants** — secondary amines preferred: **amitriptyline** / **nortriptyline** / **desipramine** (10–100 mg qhs); limited by anticholinergic effects.
 - **Topical** — 5% **lidocaine** patch, **capsaicin** 0.075% cream; **alpha-lipoic acid** 600 mg/day (antioxidant, used in Europe); TENS as adjuvant.
 - **Sodium-channel blockers** (carbamazepine, mexiletine) as later-line; treat coexistent sleep and mood disorders.
 - **Tapentadol** is FDA-approved but, like other **opioids**, is **discouraged** (modest efficacy, addiction risk) — refer to a pain clinic if uncontrolled.

Class	Examples	Typical dose
$\alpha 2\delta$ ligand	Pregabalin / Gabapentin	50–100 mg tid / 300–1200 mg tid
SNRI	Duloxetine / Venlafaxine	30–60 mg/day / 37.5–150 mg/day
TCA	Amitriptyline / Nortriptyline	10–100 mg qhs
Topical	Lidocaine 5% patch / Capsaicin 0.075%	Apply to painful area

- ▶ **C. Autonomic neuropathy (organ-directed):**
 - **Orthostatic hypotension** — adequate salt/fluids, compression stockings, head-up tilt, slow standing; **fludrocortisone** 0.1–0.2 mg/day, **midodrine** 10 mg tid, **droxidopa**.
 - **Gastroparesis** — small, frequent low-fat/low-fibre meals; **metoclopramide** (short-term), **erythromycin** 250 mg tid (motilin agonist); avoid opioids/GLP-1 agonists; gastric electrical stimulation in refractory cases.
 - **Diabetic diarrhoea** — rifaximin/metronidazole if bacterial overgrowth, loperamide; constipation — stimulant laxatives.
 - **Cystopathy** — scheduled voiding, bethanechol, self-catheterisation.
 - **Erectile dysfunction** — **PDE5 inhibitors** (sildenafil, tadalafil, vardenafil); contraindicated with nitrates.

- ▶ **D. Focal forms:** mononeuropathies and amyotrophy are largely self-limiting (analgesia + glycaemic control); entrapment (carpal tunnel) — wrist splint, NSAIDs, surgical decompression; glucocorticoids are sometimes used for severe radiculoplexus pain (unproven).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Stocking-and-glove sensory loss diagram** — outline of a body with shaded distal lower limbs (feet/calves) and hands/fingers; labels: *Distal symmetric “stocking-and-glove” pattern, length-dependent (longest nerves first), small fibres (pain/temperature) before large fibres (vibration/proprioception).*
- ▶ **Foot examination / screening sites** — sole of foot showing the **three monofilament test sites** (plantar great toe, 3rd metatarsal head, 5th metatarsal head); add labels: *10-g Semmes–Weinstein monofilament (LOPS), 128-Hz tuning fork at great toe (vibration), Achilles reflex, pinprick/temperature (small fibre).*

Clinical / Diagnostic significance

- ▶ DSPN with LOPS is the leading cause of **foot ulceration**, **Charcot neuroarthropathy** (“**rocker-bottom**” foot) and **non-traumatic lower-limb amputation** — annual foot screening is mandatory.
- ▶ **Cardiovascular autonomic neuropathy (CAN)** predicts silent ischaemia, perioperative instability, prolonged QTc and **sudden death** — assess heart-rate variability and orthostatic BP.
- ▶ Always exclude mimics (B12, paraproteinaemia, hypothyroidism) — ~10% of “diabetic” neuropathy is non-diabetic; atypical features mandate neurology referral and NCS.
- ▶ Pre-operative cardiac evaluation is prudent because **silent ischaemia** is common in autonomic neuropathy.

High-yield exam pointers

- ▶ Occurs in ~50% of long-standing DM; DSPN is the commonest form; up to 50% **asymptomatic**.
- ▶ Screen **annually**: from 5 years after T1DM diagnosis and **at diagnosis** of T2DM.
- ▶ **10-g Semmes–Weinstein monofilament (5.07)** detects LOPS; **128-Hz tuning fork** tests large fibre; **IENFD on skin biopsy** = gold standard for small-fibre; **NCS** = gold standard for large-fibre.
- ▶ **Toronto Consensus**: possible → probable → confirmed → subclinical.
- ▶ Diabetic 3rd-nerve palsy is **pupil-sparing**; diabetic amyotrophy = **Bruns–Garland syndrome**.
- ▶ Tight glycaemic control prevents DSPN strongly in T1DM, only modestly in T2DM.
- ▶ Painful DSPN first-line classes: **$\alpha 2\delta$ ligands** (pregabalin/gabapentin), **SNRIs** (duloxetine), **TCAs**; FDA-approved = pregabalin, duloxetine, tapentadol; **avoid opioids**.

- ▶ Avoid lowering HbA1c >1%/month — risk of **treatment-induced neuropathy** (TIND / “insulin neuritis”).
- ▶ Orthostatic hypotension: **midodrine** / **fludrocortisone**; gastroparesis: **metoclopramide** / **erythromycin**; ED: PDE5 inhibitors.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Diabetes Mellitus: Complications” and “Peripheral Neuropathy” (including Table: *Treatment of Painful Sensory Neuropathies*).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Complications of Diabetes Mellitus” (diabetic neuropathies — classification per ADA/Pop-Busui position statement, Toronto Consensus criteria, Box 38.3 diagnosis, disease-modifying and painful-DSPN treatment, pathogenesis: polyol pathway/AGEs/PKC/hexosamine).
- ▶ **CMDT 2026** — “Diabetes Mellitus & Hypoglycemia” (current management of peripheral and autonomic neuropathy, Charcot foot, drug doses).



Gestational Diabetes Mellitus

Asked in: Paper IV Dec 2023 · Paper IV Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — **Gestational diabetes mellitus (GDM)** is glucose intolerance with onset or first recognition during the **second or third trimester** of pregnancy that is not clearly overt (pre-existing) diabetes. It complicates roughly **8% of pregnancies** (the International Diabetes Federation estimated in 2021 that ~**16% of pregnancies worldwide** are affected by GDM or pre-existing diabetes), and it arises when maternal pancreatic β -cell insulin secretion fails to compensate for the physiological insulin resistance of pregnancy. By current **ADA** convention, hyperglycaemia *diagnosed in the first trimester* is reclassified as **pre-existing (pregestational) diabetes**, not GDM. GDM matters because it is both an immediate threat to mother and fetus and a powerful marker of future maternal type 2 diabetes (T2DM) and cardiovascular disease.

Classification and definitional boundaries

- ▶ **ADA aetiologic classification of diabetes** places GDM as a distinct category (Type IV) alongside: I — Type 1 DM; II — Type 2 DM; III — Specific/”other” types (MODY/monogenic, exocrine pancreatic disease, endocrinopathies, drug-/chemical-induced, etc.); IV — **Gestational diabetes mellitus**.
- ▶ **Pregestational (pgDM)** = type 1 or type 2 diabetes antedating pregnancy (complicates ~1% of pregnancies; prevalence is higher in obese vs normal-weight women, ~2.2% vs 0.5%). The crucial clinical separation: **pgDM is teratogenic** because hyperglycaemia is present during

organogenesis (first 5–8 weeks), whereas **GDM** appears after organogenesis and so chiefly causes *fetal overgrowth* rather than malformation.

- ▶ Glucose tolerance in GDM is typically **bidirectional** — most women revert to normal (or impaired) glucose tolerance postpartum.

Pathophysiology and risk factors

- ▶ **Physiology of normal pregnancy:** the fetoplacental unit drives major metabolic change — glucose and amino acids are shunted to the fetus while the mother shifts to ketones/triglycerides, producing “**accelerated starvation**” / **accelerated ketosis** on fasting (lower glucose, higher β -hydroxybutyrate and acetoacetate). Progressive **insulin resistance** develops, mediated by placental production of **steroids, a placental growth-hormone variant, and human placental lactogen** (other candidates: placenta-derived pro-inflammatory exosomes and miRNAs).
- ▶ **β -cell compensation:** to maintain euglycaemia, maternal insulin secretion rises by up to **~250%**. **GDM develops when this β -cell compensation is inadequate** for the rising insulin resistance.
- ▶ That the driver is *placental* (not merely weight gain) is shown by the fact that **euglycaemia returns within days of delivery** once the placenta is removed.
- ▶ **Risk factors:** prepregnancy **obesity** (a major risk factor), excessive gestational weight gain, advancing age, ethnicity (South Asian, etc.), prior GDM, prior macrosomic infant, family history of T2DM, PCOS/insulin-resistant states, and offspring of women who had diabetes in pregnancy (intergenerational transmission).

Screening and diagnosis

- ▶ **Universal screening** of asymptomatic pregnant women at **24–28 weeks** is routine prenatal care (USPSTF grade **B** recommendation). Women with high-risk features may be screened earlier; if hyperglycaemia meets standard non-pregnant diabetes criteria in the **first trimester**, label as pre-existing diabetes.
- ▶ Two validated approaches exist. The **two-step (ACOG-preferred)** strategy is detailed in the corpus; the **one-step (IADPSG/ADA)** 75-g test is the widely-used alternative.

Strategy	Test	Diagnostic thresholds	Rule for diagnosis
Two-step — Step 1 (screen)	50-g oral glucose challenge, non-fasting; 1-h plasma glucose	≥ 130 – 140 mg/dL (7.2–7.8 mmol/L)*	If abnormal $\rightarrow$ proceed to Step 2
Two-step — Step 2 (diagnostic)	100-g 3-h OGTT (fasting) — <i>Carpenter–Coustan</i>	Fasting ≥ 95 ; 1-h ≥ 180 ; 2-h ≥ 155 ; 3-h ≥ 140 mg/dL	GDM if ≥ 2 values met/exceeded
One-step (IADPSG/ADA)	75-g 2-h OGTT (fasting)	Fasting ≥ 92 ; 1-h ≥ 180 ; 2-h ≥ 153 mg/dL	GDM if ≥ 1 value met/exceeded

- ▶ The 50-g screen cut-off is given as >130 mg/dL (Harrison) or ≥ 140 mg/dL* (CMDT/ACOG); 135 mg/dL is also used — higher cut-offs trade sensitivity for specificity.
- ▶ The 100-g OGTT is performed after an **overnight fast (8–14 h)**, following ≥ 3 days of unrestricted diet (>150 g carbohydrate/day); the patient stays seated and does not smoke.
- ▶ HbA1c is **unreliable for monitoring** in pregnancy (high red-cell turnover gives falsely low values), so it is not used for serial glycaemic monitoring.

Maternal, fetal and neonatal complications

- ▶ The mechanistic link is the **Pedersen hypothesis**: maternal hyperglycaemia crosses the placenta → fetal hyperinsulinaemia → fetal overgrowth and, at delivery, neonatal hypoglycaemia.

Domain	Complications
Maternal	Preeclampsia, polyhydramnios, increased caesarean delivery , birth trauma/lacerations; long-term T2DM and cardiovascular disease
Fetal / obstetric	Macrosomia (birth weight >4000 g) → shoulder dystocia , brachial plexus injury (Erb palsy) and birth trauma; large-for-gestational-age fetus, polyhydramnios
Neonatal	Hypoglycaemia (fetal hyperinsulinaemia), hyperbilirubinaemia , polycythaemia , respiratory distress syndrome

- ▶ In **pgDM** (contrast for the exam) add: spontaneous abortion, **congenital malformations** (cardiac, skeletal, neural-tube defects; *caudal regression/sacral agenesis* is the classically associated anomaly), stillbirth and worsening of maternal nephropathy/retinopathy. These reflect first-trimester hyperglycaemia and are **not** features of pure GDM.

Management

- ▶ **Goal-directed glycaemic targets (pregnancy)**: fasting <95 mg/dL (5.3 mmol/L), 1-h postprandial <140 mg/dL (7.8 mmol/L), 2-h postprandial <120 mg/dL (6.7 mmol/L); aim HbA1c $<6\%$. Self-monitor capillary glucose ~ 4 times/day (fasting + post-meals).
- ▶ **Step 1 — Medical nutrition therapy (MNT)** and appropriate gestational weight gain control normalise glucose in the **majority** of women; combine with physical activity.
- ▶ **Step 2 — Pharmacotherapy if targets exceeded**: **insulin is the preferred/first-line agent** (does not cross the placenta, low treatment-failure rate). Use a **basal–bolus regimen** — intermediate/short-acting combinations such as **NPH + regular**, or rapid analogues **lispro/aspart** (placenta-impermeant).
- ▶ **Oral agents — metformin and glyburide** are alternatives when insulin is declined or impractical. Contemporary data show **metformin** gives **lower mean birth weight**, **less gestational weight gain** and **less preeclampsia** than glyburide or insulin; however, both are **off-label**, cross the

placenta, and metformin's uncertain long-term offspring effects (higher childhood adiposity) keep insulin first-line.

- ▶ **Insulin requirements** rise through gestation in diabetic pregnancy: ~0.7–0.8 U/kg/day (1st trimester) → 0.8–1.0 (2nd) → 0.9–1.2 U/kg/day (3rd) as placental insulin resistance increases.
- ▶ **Fetal surveillance:** serial ultrasound for growth/macrosomia and polyhydramnios (markers of suboptimal control). **Timing/mode of delivery:** induction often in the early-term window (37–39 weeks) when indicated; caesarean considered for estimated fetal weight ≥4500 g to avoid shoulder dystocia. **Tight intrapartum control** minimises neonatal hypoglycaemia.
- ▶ **Benefit of treatment:** randomised data show treating GDM reduces preeclampsia, birth weight >4000 g and shoulder dystocia.

Postpartum and long-term follow-up

- ▶ GDM usually resolves immediately after delivery, but it unmasks a high lifetime risk of dysglycaemia: a 7- to 10-fold increased risk of T2DM, with ~10% developing diabetes within 5 years; ~35–60% develop diabetes over 10–20 years (and 50–70% over 15–25 years in some series — a 10- to 18-fold increase).
- ▶ **Postpartum re-test:** a 75-g 2-h OGTT at 4–12 weeks after delivery to detect persisting diabetes or impaired glucose tolerance, then lifelong screening at least every 3 years.
- ▶ **Risk reduction:** breastfeeding, weight loss, exercise and metformin reduce progression to T2DM; counsel on cardiovascular risk and the need for primary-care follow-up.
- ▶ **Offspring** of GDM pregnancies carry increased risk of childhood obesity, metabolic syndrome and later T2DM — an intergenerational, partly *in-utero-programmed* effect attenuated by good maternal control.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Two-step GDM screening/diagnosis flowchart:** Box 1 “All pregnant women, 24–28 wk” → “50-g GCT (non-fasting), 1-h glucose” → decision node “≥130–140 mg/dL?” → if No “Normal — no GDM”; if Yes → “100-g 3-h OGTT (fasting)” → list thresholds “Fasting 95 / 1-h 180 / 2-h 155 / 3-h 140 mg/dL” → decision “≥2 values exceeded?” → “GDM” vs “Not GDM”. Add a side branch “One-step 75-g OGTT: 92 / 180 / 153 → ≥1 value = GDM”.
- ▶ **Pathophysiology schematic:** “Placenta → human placental lactogen + placental GH-variant + steroids” → arrow “maternal insulin resistance ↑” → “β-cell secretion ↑ up to 250% (compensation)”; a second arrow showing “inadequate compensation → GDM → maternal hyperglycaemia → (placental transfer) → fetal hyperinsulinaemia → macrosomia, and at birth → neonatal hypoglycaemia (*Pedersen hypothesis*)”.

Clinical / Diagnostic significance

- ▶ Distinguishing **GDM from pgDM** changes the whole risk profile: pgDM mandates **preconception** optimisation (target HbA1c <6%, insulin before conception) to cut malformation risk; GDM care centres on third-trimester glycaemia and macrosomia prevention.
- ▶ A positive GDM diagnosis is an **opportunity for cardiometabolic prevention** — the postpartum OGTT and triennial screening identify future diabetes early.
- ▶ HbA1c's unreliability in pregnancy means **SMBG/continuous glucose monitoring**, not HbA1c, guides titration.
- ▶ Ultrasound estimated fetal weight and polyhydramnios are **surrogate alarms** for inadequate control and drive delivery planning.

High-yield exam pointers

- ▶ GDM = glucose intolerance **first recognised in 2nd/3rd trimester**; first-trimester hyperglycaemia = **pre-existing diabetes**, not GDM.
- ▶ Screen **all** women at **24–28 weeks** (USPSTF grade B).
- ▶ **Two-step**: 50-g GCT (≥ 130 – 140 mg/dL) $\rightarrow$ 100-g 3-h OGTT, ≥ 2 of 95/180/155/140 mg/dL = GDM. **One-step**: 75-g 2-h OGTT, ≥ 1 of 92/180/153 mg/dL = GDM.
- ▶ Targets: **fasting <95, 1-h <140, 2-h <120 mg/dL**, HbA1c <6%.
- ▶ **Insulin is first-line** drug therapy; metformin/glyburide are off-label alternatives; lispro, aspart, regular and NPH **do not cross the placenta**.
- ▶ Key sequelae via **fetal hyperinsulinaemia**: macrosomia $\rightarrow$ shoulder dystocia/Erb palsy; neonatal hypoglycaemia, hyperbilirubinaemia, polycythaemia, RDS.
- ▶ **Caesarean** considered at EFW ≥ 4500 g; treating GDM lowers preeclampsia, macrosomia and shoulder dystocia.
- ▶ Postpartum 75-g OGTT at **4–12 weeks**; lifelong screening **every 3 years**; **7–10 $\times$ risk of T2DM** (~10% within 5 years).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Medical Disorders During Pregnancy” (Endocrine/Metabolic Disorders — Gestational Diabetes); “Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology” (Gestational DM, ADA classification, screening recommendations).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Pathophysiology of Type 2 Diabetes Mellitus” (gestational diabetes / pregnancy insulin resistance, β -cell compensation ~250%, placental drivers) and “Therapeutics of Type 2 Diabetes Mellitus” (pregnancy management, postpartum risk).

- ▶ **CMDT 2026** — “Obstetrics & Obstetric Disorders” (GDM screening/diagnostic criteria table, glycaemic targets, insulin and oral-agent therapy, postpartum 75-g OGTT) and “Diabetes Mellitus & Hypoglycemia” (pregnancy targets).
- ▶ **Coverage note:** The corpus fully supports the two-step (50-g/100-g Carpenter–Coustan) pathway, targets, complications and management. The **one-step IADPSG/ADA 75-g criteria (92/180/153 mg/dL)**, the eponyms **Pedersen hypothesis** and **caudal regression/sacral agenesis**, and **Erb palsy** as the brachial-plexus lesion are universally accepted standard internal medicine added for completeness but are not stated verbatim in these chapters. The historical **White classification** of diabetes in pregnancy is not covered in this corpus and is omitted.



GLP-1 Analogues

Asked in: Paper IV Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — **Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs)**, also called *incretin mimetics* or *GLP-1 analogues*, are injectable (and now oral) peptide drugs that are homologs or analogues of the gut incretin hormone GLP-1, engineered to resist degradation by *dipeptidyl peptidase-4 (DPP-4)*. They lower glucose in a **glucose-dependent** manner, produce **weight loss** without intrinsic hypoglycaemia, and several confer proven **cardiovascular and renal protection**. They have transformed the management of type 2 diabetes mellitus (T2DM) and obesity, and now occupy a preferred place in glucose-lowering and weight-management algorithms.

Incretin physiology and rationale (mechanism of action)

- ▶ The “**incretin effect**”: an oral glucose load evokes a far greater insulin response than an equivalent intravenous load, because of gut-derived hormones released with nutrient ingestion — **GLP-1** (from intestinal **L-cells**) and **glucose-dependent insulintropic polypeptide (GIP)**, a 42-amino-acid peptide from duodenal/jejunal **K-cells**. This incretin effect is *blunted* in T2DM.
- ▶ Native GLP-1 is rapidly inactivated by the enzyme **DPP-4** (half-life ~1–2 min) and cleared by the kidney, so it cannot be used as a drug; analogues are made DPP-4-resistant or are given as DPP-4 inhibitors (incretin *enhancers*) instead.
- ▶ **Pleiotropic actions of GLP-1RAs:**
 - **Pancreas** — potentiate *glucose-dependent* insulin secretion from beta cells and suppress postprandial **glucagon** (alpha-cell) secretion; insulintropy ceases as glucose falls toward normal, hence minimal hypoglycaemia.
 - **Stomach** — **delay gastric emptying**, flattening postprandial glucose excursions.

- CNS — stimulate GLP-1 receptors in the hypothalamic **arcuate nucleus**, the brainstem **nucleus tractus solitarius** and connected appetite-relay nuclei to promote **satiety** and reduce energy intake → weight loss.
- Additional benefits: improved lipid profile, lower blood pressure, anti-inflammatory/anti-atherogenic endothelial effects, and reduction of hepatic steatosis.

Classification

Group	Agents	Salient feature
Short-acting GLP-1RA	Exenatide (synthetic <i>exendin-4</i>), Lixisenatide	Dominant effect on <i>postprandial</i> glucose via gastric slowing; more nausea per unit HbA1c fall
Long-acting GLP-1RA	Liraglutide (daily); Dulaglutide, exenatide-ER, Semaglutide (weekly)	Greater <i>fasting</i> glucose & HbA1c reduction; CV outcome benefit; better tolerated
Oral GLP-1RA	Oral semaglutide (with absorption enhancer SNAC)	First peptide GLP-1RA absorbed enterally
Dual incretin (GIP/GLP-1) agonist	Tirzepatide	“Twincretin”; superior HbA1c & weight loss

- **Origin pearl:** *exendin-4* is a naturally occurring peptide in the saliva of the *Gila monster* (*Heloderma suspectum*), shares ~53% sequence identity with human GLP-1, and is intrinsically DPP-4-resistant; **exenatide** is its synthetic form and was the first GLP-1RA approved (2004). **Liraglutide** has 97% homology with human GLP-1.

Individual agents — dosing and pharmacology

Agent	Route / frequency	Typical dose	Half-life	HbA1c fall
Exenatide	SC twice daily (before breakfast & dinner)	5–10 mcg BD	~2.4 h (≤6 h action)	~1.0%
Lixisenatide	SC once daily (before breakfast)	10–20 mcg OD	~3 h	~0.4–0.6%
Liraglutide	SC once daily	0.6 → 1.2 → 1.8 mg (3.0 mg for obesity)	~12–15 h	~0.6–1.5%
Dulaglutide	SC once weekly	0.75 → up to 4.5 mg	~5 days	~1.5–1.8%
Semaglutide (SC)	SC once weekly	0.25 → 0.5 → 1 → 2 mg (2.4 mg for obesity)	~1 week	~1.5–2.1%

Agent	Route / frequency	Typical dose	Half-life	HbA1c fall
Semaglutide (oral)	Oral once daily, fasting, ≥ 30 min before food	3 $\rightarrow$ 7 $\rightarrow$ 14 mg	~1 week	comparable to injectable
Tirzepatide (GIP/GLP-1)	SC once weekly	2.5 $\rightarrow$ up to 15 mg	~117 h	up to ~2.3%

- Doses are **titrated slowly** (over weeks) to limit gastrointestinal intolerance.
- **Fixed-ratio combinations with basal insulin:** *liraglutide/degludec* (*Xultophy*) and *lixisenatide/glargine* (*Soliqua*).
- **Tirzepatide** is engineered from the GIP backbone with agonist activity at both receptors; its GLP-1-receptor affinity is ~5-fold weaker than native GLP-1, while GIP agonism equals native GIP — central GIP action appears to act synergistically with GLP-1 to magnify weight loss.

Clinical efficacy and cardiovascular / renal outcomes

- **Glycaemia & weight:** the most effective non-insulin injectables for HbA1c lowering; consistent weight loss (≈ 2 –6 kg with most agents; ≥ 10 –15% with semaglutide 2.4 mg and tirzepatide). Only **liraglutide 3.0 mg** and **semaglutide 2.4 mg** are licensed specifically for chronic weight management; **tirzepatide** is approved for obesity (and obstructive sleep apnoea in obesity).
- **Head-to-head:** tirzepatide 5/10/15 mg gave superior HbA1c reduction versus semaglutide 1 mg (SURPASS-2); the 15 mg dose lowered HbA1c ~2.3% from a baseline of 8.3% with >10% weight loss in 57%.
- **Cardiovascular outcome trials (CVOTs) — long-acting agents (MACE = CV death, non-fatal MI, non-fatal stroke):**

Trial	Agent	MACE HR (95% CI)	Key extra findings
LEADER	Liraglutide	0.87 (0.78–0.97)	↓CV death (0.78), ↓all-cause death (0.85), ↓albuminuria
SUSTAIN-6	Semaglutide (SC)	0.74 (0.58–0.94)	↓stroke (0.61); transient ↑retinopathy signal
REWIND	Dulaglutide	0.88 (0.79–0.99)	↓stroke (0.76); primary-prevention population
EXSCEL	Exenatide-ER	0.91 (0.83–1.00)	Not statistically significant for MACE
HARMONY	Albiglutide	0.78 (0.68–0.90)	↓MI

- ▶ CV benefit is a **class property of long-acting agents** in high-risk T2DM; *short-acting* agents have not shown it consistently. Notably, GLP-1RAs reduced **atherosclerotic (MI/stroke)** events but **not heart-failure hospitalisation**.
- ▶ **Beyond diabetes:** SELECT showed a 20% reduction in MACE with semaglutide 2.4 mg in patients with established CV disease and obesity/overweight **without** diabetes; STEP-HFpEF improved heart-failure symptoms and exercise capacity in obesity-related HFpEF.
- ▶ **Renoprotection:** GLP-1RAs reduce albuminuria; dedicated trial data (semaglutide in CKD) demonstrate slowing of kidney-disease progression, supporting renal benefit.

Adverse effects, contraindications and precautions

- ▶ **Gastrointestinal (commonest):** nausea (11–40%), vomiting (4–13%), diarrhoea (9–17%), constipation, abdominal pain — dose-related, usually mild/transient, mitigated by slow titration; ~1–5% discontinue.
- ▶ **Hypoglycaemia:** not caused by GLP-1RAs alone, but occurs when combined with a **sulfonylurea or insulin** — pre-emptively reduce the secretagogue, and reduce insulin by ~20% (unless HbA1c >8%).
- ▶ **Pancreatitis:** post-marketing reports; advise patients to stop the drug and seek care for severe, persistent abdominal pain. (Avoid in prior pancreatitis.)
- ▶ **Medullary thyroid carcinoma / MEN-2:** rodent C-cell tumours seen pre-clinically; **contraindicated** with personal/family history of medullary thyroid cancer or MEN type 2.
- ▶ **Renal:** acute kidney injury (usually pre-renal, from volume depletion due to nausea/vomiting) — stop if unable to tolerate fluids >4 h. **Exenatide** is renally cleared and contraindicated at **eGFR <30 mL/min**; liraglutide/dulaglutide/semaglutide are proteolytically metabolised and preferred in renal impairment.
- ▶ **Diabetic retinopathy:** transient worsening (SUSTAIN-6) attributed to rapid glucose lowering.
- ▶ **Others:** cholelithiasis (with rapid weight loss); caution with gastroparesis and drugs that slow GI motility; a regulatory caution regarding mood change/suicidal ideation is under review.
- ▶ **Absolute contraindications:** type 1 DM / DKA, medullary thyroid carcinoma or MEN-2; relative — pancreatitis history, confirmed gastroparesis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **GLP-1 action diagram** — label: *intestinal L-cell* → *GLP-1 release on nutrient ingestion*; arrows to **pancreatic beta cell** (↑ **glucose-dependent insulin**), **alpha cell** (↓ **glucagon**), **stomach** (↓ **gastric emptying**), **brain/hypothalamus** (↑ **satiety**, ↓ **appetite**); show **DPP-4** degrading native GLP-1 (with GLP-1RA = DPP-4-resistant).

- ▶ **Classification tree** — *GLP-1RA* → branches: **short-acting** (exenatide, lixisenatide) / **long-acting** (liraglutide; dulaglutide, semaglutide, exenatide-ER) / **oral** (semaglutide-SNAC) / **dual GIP-GLP-1** (tirzepatide).

Clinical / Diagnostic significance

- ▶ **Place in therapy (T2DM):** preferred add-on (or first-line with metformin) when **atherosclerotic CVD, high CV risk, CKD, or obesity** predominates; combine with SGLT2 inhibitors for layered cardiorenal benefit.
- ▶ **Do not co-prescribe** a GLP-1RA with a **DPP-4 inhibitor** (mechanistically redundant).
- ▶ **Weight management:** semaglutide 2.4 mg, liraglutide 3.0 mg and tirzepatide give clinically meaningful, durable weight loss with cardiometabolic improvement, including in non-diabetic obesity.
- ▶ **Monitoring/counselling:** titrate slowly; counsel on GI symptoms, dehydration-related AKI, pancreatitis warning signs; screen for MTC/MEN-2 history before starting; review at intervals for efficacy and tolerability.

High-yield exam pointers

- ▶ **Exenatide** = **exendin-4** from *Gila monster* saliva; DPP-4-resistant; first GLP-1RA. **Liraglutide** 97% homologous to human GLP-1.
- ▶ Mechanism quartet: ↑ **glucose-dependent insulin**, ↓ **glucagon**, ↓ **gastric emptying**, ↑ **satiety**.
- ▶ **No hypoglycaemia alone**; cause **weight loss**; effective HbA1c reduction (~1–2%).
- ▶ Weekly long-acting agents: **dulaglutide, semaglutide, exenatide-ER**; daily: **liraglutide**; oral **semaglutide** uses absorption enhancer SNAC.
- ▶ **CVOTs:** LEADER (liraglutide), SUSTAIN-6 (semaglutide), REWIND (dulaglutide) positive; EXSCEL (exenatide) **neutral**; benefit on **atherosclerotic events, not HF hospitalisation**.
- ▶ **Tirzepatide** = dual GIP/GLP-1 agonist (“twincretin”), most potent for HbA1c and weight.
- ▶ Key cautions: **medullary thyroid carcinoma / MEN-2, pancreatitis, exenatide in eGFR <30**, transient **retinopathy** worsening, AKI from volume depletion.
- ▶ **SELECT trial** — CV benefit of semaglutide in obesity **without diabetes**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Diabetes Mellitus: Management and Therapies” and “Evaluation and Management of Obesity.”
- ▶ **Williams Textbook of Endocrinology, 15e** — “Therapeutics of Type 2 Diabetes Mellitus” (GLP-1 receptor agonists, GIP/GLP-1 dual agonist, CVOT tables) and “Physiology of Insulin Secretion” (incretin effect).

- CMTD 2026 — “Diabetes Mellitus & Hypoglycemia” (current dosing, safety) and “Nutrition, Nutritional Disorders, & Obesity.”



Graves' Disease

Asked in: Paper IV Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Graves' disease* is an organ-specific **autoimmune disorder** caused by **thyroid-stimulating immunoglobulins (TSIs)** — IgG antibodies directed against the **TSH receptor (TSH-R)** that mimic TSH and drive unregulated thyroid hormone synthesis. It is the commonest cause of **thyrotoxicosis**, accounting for **60–80%** of cases, and is the only cause that classically combines **goitre**, **ophthalmopathy (thyroid eye disease)**, **dermopathy (pretibial myxoedema)** and **acropachy**. Thyrotoxicosis (thyroid-hormone excess) must be distinguished from hyperthyroidism (excessive *gland function*) — Graves' produces both.

Epidemiology & Pathogenesis

- **Epidemiology:** affects up to **2% of women**, one-tenth as frequent in men; peak onset **20–50 years**; high dietary iodine intake increases prevalence. Concordance in **monozygotic twins** is **20–30%** versus **<5%** in dizygotic twins, confirming a strong genetic component.
- **Susceptibility genes:** polymorphisms in **HLA-DR**, immunoregulatory genes **CTLA-4**, **CD25**, **CD40**, **PTPN22**, **FCRL3**, **CD226**, and the **TSH-R** gene itself.
- **Environmental triggers:** smoking (a moderate risk for Graves' but a **major risk for ophthalmopathy**), stress, sudden iodine load, the **postpartum period** (threefold rise), and immune reconstitution after HAART, **alemtuzumab**, or **immune checkpoint inhibitors** (nivolumab, pembrolizumab).
- **Mechanism of hyperthyroidism:** TSIs / **TRAb** synthesised by intrathyroidal, marrow and lymph-node lymphocytes bind and activate the TSH-R → continuous stimulation of hormone synthesis and gland growth, *unrestrained by feedback*. Coexisting **TPO** and **thyroglobulin (Tg) antibodies** are present in up to **80%**; because lymphocytic thyroiditis coexists, there is **no direct correlation** between TSI titre and hormone level.
- **Ophthalmopathy mechanism:** activated T-cell infiltration of extraocular muscles → release of **IFN- γ** , **TNF**, **IL-1** → fibroblast activation and **glycosaminoglycan** deposition that traps water → muscle swelling; increased orbital fat adds to retrobulbar expansion. The **TSH-R** is a **shared orbital autoantigen**, and aberrant signalling via the **insulin-like growth factor-1 receptor (IGF-1R)** on orbital fibroblasts underpins disease and is the target of **teprotumumab**.

Clinical Features

- ▶ **General thyrotoxic features** (descending frequency): hyperactivity, irritability, **heat intolerance and sweating**, palpitations, fatigue, **weight loss with increased appetite**, diarrhoea, oligomenorrhoea. Signs: **sinus tachycardia / atrial fibrillation** (esp. >50 y), fine **tremor**, goitre, warm moist skin, **proximal myopathy**, lid retraction/lag.
- ▶ In the elderly, presentation may be subtle — **apathetic thyrotoxicosis** (fatigue, weight loss, AF) mistaken for depression or malignancy.
- ▶ **Cardiovascular**: high-output state — bounding pulse, widened pulse pressure, aortic flow murmur; AF reverts to sinus rhythm in up to 75% once euthyroid.
- ▶ **Neuromuscular**: hyperreflexia, proximal myopathy without fasciculation; **thyrotoxic hypokalaemic periodic paralysis** — sudden flaccid paralysis, common in **Asian/American-Indian men** (~15%; up to 30× commoner in men), often after carbohydrate/dextrose load or exercise.
- ▶ **Graves'-specific signs (diagnostic triad clues)**:
 - **Goitre** — diffuse, firm, 2–3× **enlarged**, often with a **bruit/thrill** at the inferolateral poles (hypervascularity).
 - **Ophthalmopathy / thyroid eye disease (TED)** — clinically present in ~**one-third**; grittiness, excess tearing, **proptosis**, periorbital oedema, chemosis, scleral injection, **diplopia**, and, most seriously, **optic-nerve compression** at the orbital apex → visual loss. Occurs **without hyperthyroidism in 10%** (euthyroid Graves' ophthalmopathy); onset within 1 year of thyrotoxicosis in 75%.
 - **Thyroid dermopathy (pretibial myxoedema)** — <5% (CMDT ~3%); non-inflamed indurated plaque, “**orange-peel**” appearance, over anterolateral shins; almost always with moderate-severe eye disease.
 - **Thyroid acropachy** — <1%; clubbing with phalangeal periostitis, virtually always with dermopathy.

Classification of Ophthalmopathy (NO SPECS & CAS)

Class	“NO SPECS” feature (Werner)
0	No signs or symptoms
1	Only signs (lid retraction/lag), no symptoms
2	Soft tissue involvement (periorbital oedema)
3	Proptosis (>22 mm)
4	Extraocular muscle involvement (diplopia)
5	Corneal involvement
6	Sight loss (optic nerve)

- ▶ *NO SPECS* is a useful mnemonic but inadequate for monitoring; activity is better graded by the **7-point Clinical Activity Score (CAS)** of EUGOGO (spontaneous retrobulbar pain, pain on gaze, lid redness, conjunctival redness, lid swelling, caruncle/plica swelling, chemosis). **CAS ≥ 3 = active disease**; the EUGOGO system grades severity (mild / moderate-to-severe / sight-threatening).

Laboratory Evaluation & Differential Diagnosis

- ▶ **First-line:** suppressed TSH with raised free (and total) T4 and T3. In 2–5% only T3 is raised (*T3 toxicosis*); rarely *T4 toxicosis* (iodine-induced).
- ▶ **Confirm aetiology:** measure TRAb/TSI (high sensitivity & specificity for Graves'; also predicts neonatal thyrotoxicosis in pregnancy and GO course). Positive **TPO antibodies** in ~80%.
- ▶ **Radionuclide ($^{24}\text{Tc}/^{123}\text{I}/^{131}\text{I}$) scan & uptake:** *diffuse, high uptake* in Graves' — distinguishes it from **destructive thyroiditis, factitia and iodine excess (low uptake)** and from focal uptake of toxic adenoma/toxic MNG. **Colour-flow Doppler** (increased flow) is a radiation-free alternative.
- ▶ **Ancillary abnormalities:** mild rise in bilirubin, transaminases, ferritin, alkaline phosphatase; mild **hypercalcaemia/hypercalciuria**; microcytic anaemia; thrombocytopenia.
- ▶ **Differential:** toxic MNG, toxic adenoma, subacute/silent thyroiditis, factitious thyrotoxicosis, struma ovarii, TSH-secreting pituitary adenoma (non-suppressed TSH + diffuse goitre), and non-thyroid mimics (panic, pheochromocytoma, malignancy). A **normal TSH excludes Graves'**.

Management

- ▶ **Three definitive options** — antithyroid drug (ATD), radioiodine (^{131}I) and surgery; ATD is first-line in Europe/Japan/India and increasingly the USA.
- ▶ **Antithyroid (thionamide) drugs** — inhibit **thyroid peroxidase** ($\downarrow$ organification); also lower antibody levels:
 - **Methimazole/carbimazole** preferred: start **10–20 mg q12h**, maintenance 2.5–10 mg; PTU 100–200 mg q6–8h. PTU uniquely blocks peripheral **T4 $\rightarrow$ T3 conversion** but has short half-life (90 min vs 6 h) and **hepatotoxicity** — now restricted to **first-trimester pregnancy, thyroid storm, and methimazole intolerance**.
 - **Titration** regimen (most common) or **block-and-replace** (high ATD + LT4). Review at 4–6 weeks (titrate to free T4; TSH stays suppressed for months). **Remission 30–60% by 12–18 months**, higher if TRAb becomes undetectable.
 - **Side effects:** rash/urticaria/arthritis (1–5%); rare major — **agranulocytosis** ($<1\%$, idiosyncratic; **stop drug, urgent CBC for sore throat/fever**), hepatitis (PTU), cholestasis, vasculitis.
- ▶ **β -blockers** for adrenergic relief: **propranolol 20–40 mg q6h** (or atenolol); also for thyrotoxic periodic paralysis.

- ▶ **Radioiodine (^{131}I):** progressive ablation; typical dose 370 MBq (10 mCi) – 555 MBq (15 mCi); stop methimazole 2–3 days prior. Risks: transient worsening of thyrotoxicosis, **GO flare in smokers** (cover with prednisone 0.3–0.5 mg/kg/day), and inevitable **hypothyroidism (10–20% first year, ~5%/yr thereafter)**. **Absolutely contraindicated in pregnancy and lactation** (conceive only ≥ 6 months later); avoid in active moderate-to-severe eye disease.
- ▶ **Surgery (total/near-total thyroidectomy):** for large goitre, relapse, or patient preference. Render euthyroid with ATD, then **potassium iodide (SSKI 1–2 drops tid $\times$ 10 days)** to reduce vascularity. Complications: bleeding, laryngeal oedema, **hypoparathyroidism**, **recurrent laryngeal nerve injury**.
- ▶ **Pregnancy:** PTU until 14–16 weeks (avoids methimazole embryopathy — **aplasia cutis, choanal atresia, tracheo-oesophageal fistula**), then switch to methimazole; titrate to keep free T4 at/just above the upper reference range; monitor TRAb (transplacental TSI $\rightarrow$ fetal/neonatal thyrotoxicosis if $>3\times$ normal).
- ▶ **Ophthalmopathy:** stop smoking, restore euthyroidism, artificial tears, selenium for mild disease. **Active moderate-to-severe GO $\rightarrow$ IV methylprednisolone (cumulative 4.5 g: 500 mg weekly $\times 6$ then 250 mg weekly $\times 6$, $\pm$ mycophenolate).** **Teprotumumab** (anti-IGF-1R) is now first-line for active disease with significant proptosis/diplopia; rituximab/tocilizumab are second-line. **Sight-threatening GO** (optic neuropathy/corneal breakdown) $\rightarrow$ high-dose IV methylprednisolone $\pm$ orbital decompression.

Thyrotoxic Crisis (Thyroid Storm)

- ▶ Life-threatening decompensated thyrotoxicosis precipitated by infection, surgery, trauma, DKA, parturition or ^{131}I in untreated patients; **mortality 4–17%**. Features: hyperpyrexia, delirium/coma, seizures, vomiting, diarrhoea, jaundice, **high-output cardiac failure/arrhythmia**. Severity graded by the **Burch-Wartofsky point scale**.
- ▶ **Treatment (combine all):** PTU 500–1000 mg load then 250 mg q4h (blocks T4 $\rightarrow$ T3); **iodide** (SSKI 5 drops q6h) given ≥ 1 h after PTU (Wolff-Chaikoff block of release); **propranolol** 60–80 mg PO q4h or 2 mg IV q4h; **hydrocortisone** 300 mg IV then 100 mg q8h; plus cooling, oxygen, IV fluids, treat the trigger; **cholestyramine** sequesters hormone.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis of Graves' disease** — draw a thyroid follicular cell with a **TSH receptor**; a plasma cell/B-lymphocyte releasing TSI (TRAb, IgG) binding the receptor $\rightarrow$ arrow to “**unregulated T3/T4 synthesis & goitre**”. Side arrow showing the same antibody/IGF-1R acting on **orbital fibroblast $\rightarrow$ GAG deposition $\rightarrow$ proptosis**. Labels: *TSH receptor, TSI/TRAb, B-cell/plasma cell, T-cell + cytokines (IFN- γ , TNF, IL-1), IGF-1R, orbital fibroblast, glycosaminoglycans, extraocular muscle swelling*.

- ▶ **Evaluation-of-thyrotoxicosis algorithm** — Box 1: “↓TSH, ↑free T4” → Box 2: “Features of Graves’? (diffuse goitre, TRAb+, TPO+, ophthalmopathy, dermopathy)” → Yes = Graves’; No → **radionuclide uptake**: *diffuse high = Graves’, focal/patchy = toxic nodule/MNG, low/absent = thyroiditis, iodine excess, factitia*. Labels: TSH, free T4, free T3, TRAb, RAIU, $^{24}\text{Tc}/^{123}\text{I}$ scan.

Clinical / Diagnostic significance

- ▶ TRAb is the confirmatory autoantibody: clinches Graves’ when eye/skin signs are absent, predicts relapse after ATD, and guides pregnancy monitoring (neonatal thyrotoxicosis risk).
- ▶ Distinguishing Graves’ (high RAIU) from destructive thyroiditis (low RAIU) is decisive — the latter is *not* treated with thionamides.
- ▶ Untreated thyrotoxicosis risks AF, thromboembolism, osteoporosis, high-output failure and thyroid storm; AF often reverts with euthyroidism, so rate control + anticoagulation (CHA₂DS₂-VASc) is interim.
- ▶ New-onset AF, unexplained weight loss, or proximal myopathy in any adult warrants TSH testing.

High-yield exam pointers

- ▶ Commonest cause of thyrotoxicosis (60–80%); autoimmune, driven by TSI/TRAb against TSH-R; F:M ≈ 10:1.
- ▶ Classic tetrad: diffuse goitre + ophthalmopathy + dermopathy + acropachy; goitre bruit signifies hypervascularity.
- ▶ Smoking is the key modifiable risk for ophthalmopathy progression and ^{131}I -induced flare.
- ▶ NO SPECS (0–6) and CAS (≥3 = active) classify eye disease; proptosis cut-off >22 mm.
- ▶ Methimazole first-line; PTU only in first-trimester pregnancy, thyroid storm, methimazole intolerance; watch agranulocytosis (<1%).
- ▶ ^{131}I contraindicated in pregnancy/lactation and active severe GO; causes hypothyroidism.
- ▶ Teprotumumab = anti-IGF-1R monoclonal, first-line for active moderate-severe GO.
- ▶ Thyroid storm: PTU → iodide (≥1 h later) → β-blocker → steroid; mortality up to ~17%.
- ▶ T3 toxicosis in 2–5%; thyrotoxic hypokalaemic periodic paralysis classically in Asian men.

SOURCE & COVERAGE

- ▶ Harrison’s Principles of Internal Medicine, 22e — “Hyperthyroidism and Other Causes of Thyrotoxicosis” (epidemiology, pathogenesis, NO SPECS, antithyroid-drug regimens, radioiodine, surgery, pregnancy, thyroid storm).

- ▶ **Williams Textbook of Endocrinology, 15e** — “Hyperthyroid Disorders” (TSH-R/IGF-1R immunopathology, Clinical Activity Score, EUGOGO severity grading, IV methylprednisolone protocol, teprotumumab/OPTIC data, first-line treatment patterns).
- ▶ **CMDT 2026** — “Disorders of the Pituitary, Thyroid, & Adrenal Glands” (current drug doses, dermopathy/acropachy frequency, thyrotoxic-crisis presentation and management, hypokalaemic periodic paralysis).



Gynaecomastia

Asked in: Paper IV Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Gynaecomastia is the benign enlargement of the male breast due to proliferation of true **glandular** (ductal–stromal) tissue, clinically palpable as a firm, rubbery, mobile, often tender disc extending concentrically from beneath the nipple–areola. It results from an **increased estrogen-to-androgen ratio** acting on breast tissue and must be distinguished from *pseudogynaecomastia* (excess adipose tissue, soft and diffuse, common in obesity) and from **male breast carcinoma**. It may be a benign physiological variant or the first clue to serious endocrine, systemic or neoplastic disease.

Hormonal basis & pathogenesis

- ▶ **Estrogens** stimulate growth and differentiation of ductal epithelium (ductal hyperplasia); **progesterone** drives acinar/glandular bud formation; **androgens inhibit** breast growth and differentiation. GH, IGF-1, insulin, thyroid hormone and cortisol play permissive roles; prolactin promotes milk production in already-developed glands.
- ▶ The unifying mechanism is a **raised estrogen : androgen ratio** at the breast, achieved by *estrogen excess*, *androgen deficiency/resistance*, or both. Even small rises in serum estradiol (within the normal male range) produce large proportional effects on breast tissue.
- ▶ *Galactorrhoea is rare* even with hyperprolactinaemia, because male progesterone levels are too low for acinar development/lactogenesis.
- ▶ In primary hypogonadism (e.g. *Klinefelter syndrome*), high **LH** stimulates aromatase in Leydig cells → relatively more estradiol than testosterone. In obesity/ageing, increased adipose **aromatase** raises peripheral androgen→estrogen conversion.

Natural history & histological phases

- ▶ **Florid / proliferative (early, <6 months)**: ductal proliferation, periductal inflammation and oedema, subareolar fat accumulation → tender, painful; **responsive to medical therapy**.

- **Inactive / fibrotic (late, >6–12 months):** progressive stromal fibrosis, hyalinisation; non-tender; only partial spontaneous regression and generally **unresponsive to drugs** — requires surgery.
- Absence of breast tenderness usually signals the chronic fibrotic stage that will not remit.

Classification of causes

Category	Representative causes
Physiologic	Neonatal (transplacental maternal/placental estrogens; in 60–90%, resolves in weeks); pubertal (transient ↑estrogen:testosterone, ~60% of boys by age 14, regresses in 1–2 yr); ageing/obesity (↑aromatase, ↓testosterone; up to ~65% of men aged 50–80)
Estrogen excess	Exogenous estrogens (diethylstilbestrol for prostate Ca, estrogen creams/cosmetics, phytoestrogens, lavender/tea-tree oils); ER agonists (marijuana, digitoxin); estrogen-secreting tumours — adrenal carcinoma, Leydig/Sertoli cell tumours (Sertoli ± <i>Peutz-Jeghers</i> , <i>Carney complex</i>); hCG-secreting tumours — germ cell, lung, hepatic, gastric, renal; familial/sporadic aromatase excess syndrome
Androgen deficiency / resistance	Primary or secondary hypogonadism (incl. Klinefelter 47,XXY); androgen insensitivity syndromes; hyperprolactinaemia (suppresses GnRH → hypogonadism)
Drug-induced (~20% of adult cases)	Spirolactone (common), AR antagonists (flutamide, bicalutamide, enzalutamide), 5α-reductase inhibitors (finasteride/dutasteride), ketoconazole, cimetidine/H2 blockers , GnRH agonists, digitalis, HAART/efavirenz , anabolic steroids, ketoconazole, CCBs, amiodarone, TCAs/SSRIs, alcohol, opioids, methadone, isoniazid, metoclopramide, antipsychotics
Systemic disease	Hepatic cirrhosis (↓androstenedione catabolism, ↑SHBG → ↑free E2/T), CKD stage 4–5 (often with dialysis), hyperthyroidism (↑SHBG, ↑LH-driven E2), acromegaly, Cushing syndrome, refeeding after starvation/chronic illness (“second puberty”)

Clinical evaluation

- **History:** speed of onset and growth, pain/tenderness, drugs & substances (above), alcohol, recreational drugs, cosmetics/supplements; symptoms of hypogonadism (low libido, ED); features of liver/renal/thyroid disease, weight change, recent refeeding.

- ▶ **Examination (technique):** with thumb and forefinger as pincers, palpate the subareolar disc both **seated and supine** and compare with nearby fat. **True glandular tissue** is firm, rubbery, finely lobular, mobile, concentric to the nipple; **pseudogynaecomastia** is soft, diffuse, non-discrete adipose tissue.
- ▶ Also assess **virilisation, testicular size and masses** (orchidometer; small/firm testes → Klinefelter; a testicular mass → tumour), penis for hypospadias.
- ▶ **Red flags for carcinoma:** unilateral/markedly asymmetric, eccentric (not directly sub-areolar), rock-hard or fixed, skin dimpling (*peau d'orange*), nipple retraction, bloody discharge, axillary lymphadenopathy.
- ▶ **Thresholds:** glandular tissue **>4 cm** (Harrison) or **≥5 cm** with recent/rapid onset, tenderness or suspicious features warrants work-up; non-tender lesions **≤2.5 cm** are a common normal variant; up to two-thirds of pubertal boys and ~half of hospitalised men have benign palpable glandular tissue.

Investigations

- ▶ **First-line hormonal panel:** total and free testosterone, LH, FSH, estradiol (E2), β -hCG, TSH/FT4, prolactin.
- ▶ **Interpretation:** $\downarrow$ T + $\uparrow$ LH → **primary hypogonadism** (do karyotype for Klinefelter if testes very small); $\downarrow$ T + low/normal LH → **secondary hypogonadism**; $\uparrow$ T + $\uparrow$ LH → partial androgen insensitivity; $\uparrow$ hCG → testicular germ-cell/Sertoli tumour or ectopic (lung, liver); $\uparrow$ E2 with **suppressed LH** → estrogen-secreting testicular/adrenal tumour.
- ▶ **Organ work-up:** liver and renal function; TSH for thyrotoxicosis.
- ▶ **Imaging/biopsy:** **testicular ultrasound** if hCG/E2 elevated; **CT adrenal** for high E2 with normal testes, **CT chest/abdomen** for hCG-source search; **mammography ± ultrasound-guided FNA/biopsy** for any features suspicious of malignancy. (Note: routine commercial E2 assays are inaccurate at male levels — prefer **mass spectrometry**; use an assay detecting total hCG/ β -subunit.)
- ▶ Despite full evaluation, the cause is established in only a minority — many adult cases remain **idiopathic**.

Treatment

- ▶ **Treat the cause:** stop/replace the offending drug; correct hypogonadism, thyrotoxicosis, liver/renal disease, tumour. If addressed early, gynaecomastia usually subsides over months.
- ▶ **Reassurance/observation:** physiological neonatal and pubertal gynaecomastia regress spontaneously (pubertal in ~90% by age 18, within 1–2 yr).
- ▶ **Medical therapy (effective only in the early proliferative phase, <6 months):**

- **SERMs** — *Tamoxifen* 10–20 mg/day (reduces volume >50% in ~60%) and *Raloxifene* 60 mg/day (>50% reduction in ~90%); tamoxifen also prevents/treats antiandrogen-induced gynaecomastia in prostate-cancer patients.
- **Aromatase inhibitors** — *Anastrozole* (e.g. 0.5 mg thrice weekly, titrated to mid-range male E2) helps some early/pubertal cases but in a randomised trial was **no better than placebo** for *established* gynaecomastia; avoid long-term AI in adolescents (risk of osteoporosis and delayed epiphyseal fusion).
- ▶ **Prevention:** prophylactic low-dose breast irradiation ($\approx 10\text{--}15$ Gy over 1–3 days) or tamoxifen before androgen-deprivation therapy in prostate cancer.
- ▶ **Surgery:** definitive for long-standing (>6–12 months), fibrotic, large, painful, disfiguring or drug-refractory disease, or when malignancy is suspected — **subcutaneous mastectomy $\pm$ liposuction (reduction mammoplasty).**

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hormonal pathophysiology schematic:** central box “ $\uparrow$ Estrogen : Androgen ratio at breast $\rightarrow$ ductal proliferation” with three feeding arrows — (1) *Estrogen excess* (tumour E2 / hCG-driven aromatisation / exogenous estrogen / $\uparrow$ peripheral aromatase in fat); (2) *Androgen deficiency* (primary & secondary hypogonadism, hyperprolactinaemia); (3) *Drugs* (spironolactone, AR blockers, 5-ARIs, cimetidine). Label “Estrogen $\rightarrow$ ductal hyperplasia”, “Progesterone $\rightarrow$ acini”, “Androgen $\perp$ inhibits”.
- ▶ **Evaluation algorithm (Harrison Fig. 403-7):** Breast enlargement $\rightarrow$ *true glandular* vs *adipose (pseudogynaecomastia)* $\rightarrow$ if glandular, measure **Total/Free T, SHBG, LH, FSH, E2, TSH, hCG** $\rightarrow$ four branches: $\downarrow T + \uparrow E2:T$ ratio = T-deficiency; $\uparrow E2$ with low/normal T = search testis/adrenal tumour; $\uparrow \beta\text{-hCG}$ = ultrasound testis + CT for hCG tumour; very high SHBG = check free T/E2.

Clinical / Diagnostic significance

- ▶ New, rapidly growing, tender gynaecomastia **in a lean adult** demands evaluation — may signal a testicular/adrenal tumour or hCG-secreting malignancy.
- ▶ **Klinefelter syndrome (47,XXY):** classic gynaecomastia with small firm testes; carries an **increased risk of male breast cancer** $\rightarrow$ periodic **mammographic surveillance** is recommended.
- ▶ Gynaecomastia is a sensitive physical sign of **chronic liver disease** and **chronic kidney disease**, and a flag for drug toxicity (spironolactone, digoxin, antiretrovirals).
- ▶ The relative risk of **male breast carcinoma** is increased in men with gynaecomastia (absolute risk small) — unilateral, hard, eccentric or bloody-discharge lesions must be imaged/biopsied.

High-yield exam pointers

- ▶ Core mechanism = ↑ **estrogen : androgen ratio**; estrogen → ducts, progesterone → acini, androgen inhibits.
- ▶ **True (glandular, ≥4 cm, tender, mobile disc)** vs **pseudogynaecomastia (fatty, soft, obese)** vs **carcinoma (hard, fixed, eccentric, peau d'orange, nipple bleed)**.
- ▶ Three physiological peaks: **neonatal, pubertal, ageing/obesity**.
- ▶ ~20% of adult cases are **drug-induced**; remember **spironolactone, ketoconazole, cimetidine, 5-ARIs, AR antagonists, digoxin, marijuana, efavirenz/HAART, anabolic steroids**.
- ▶ First-line tests: **testosterone, LH, FSH, estradiol, β-hCG, TSH, prolactin**; karyotype if small testes (Klinefelter).
- ▶ ↑hCG → **germ-cell/ectopic tumour**; ↑E2 + suppressed LH → **estrogen-secreting tumour**.
- ▶ Drugs (SERMs/AI) work only in the **early proliferative phase (<6 months)**; **tamoxifen 10–20 mg/day, raloxifene 60 mg/day**; fibrotic disease needs **subcutaneous mastectomy**.
- ▶ **Refeeding gynaecomastia** — first described in liberated WWII prisoners of war; “second puberty” mechanism.
- ▶ **Familial aromatase excess syndrome** — CYP19 activation (chromosome 15q21) → prepubertal gynaecomastia, advanced bone age, short stature.
- ▶ Spironolactone causes it; **eplerenone does not**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Disorders of the Testes and Male Reproductive System” (Gynecomastia section; evaluation Fig. 403-7).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Testicular Disorders” (Gynecomastia: pathophysiology, Table 17.3 Causes of Gynecomastia, evaluation and treatment).
- ▶ **CMDT 2026** — “Male Hypogonadism & Gynecomastia” (Essentials of diagnosis, Table 31–3, current SERM/aromatase-inhibitor regimens).



Hirsutism

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — **Hirsutism** is the presence of excessive **terminal hair** (long, coarse, pigmented) growing in a **male (androgen-dependent) pattern** in a woman — face (upper lip, chin), chest, upper abdomen, midline, and back. It affects roughly **10%** of reproductive-age women and is most often **idiopathic** or due to **androgen excess from polycystic ovary syndrome (PCOS)**; less commonly it reflects **nonclassic congenital adrenal hyperplasia (NCCAH)** or, rarely, an **androgen-secreting tumour**. It must be distinguished from **hypertrichosis** (androgen-independent, generalised vellus hair) and from **virilization** (a more severe androgenic state with masculinising features).

Hair biology and androgen physiology

- ▶ Hair is **vellus** (fine, soft, non-pigmented) or **terminal** (long, coarse, pigmented). Androgens drive the conversion of vellus to terminal hair within the **pilosebaceous unit (PSU)** at androgen-sensitive sites (face, chest, upper abdomen, back).
- ▶ Hair-growth cycle has three phases: **anagen** (growth), **catagen** (involution) and **telogen** (rest). Paradoxically, scalp androgen excess shortens anagen, causing **androgenetic alopecia/thinning**.
- ▶ **Testosterone** is the principal circulating androgen in hirsutism, but it is a *precursor*: it is converted in the PSU by **5 α -reductase** to **dihydrotestosterone (DHT)** — a more potent androgen (higher affinity, slower dissociation from the androgen receptor) that is the **primary local mediator**. Two isoenzymes: **type 2** (prostate, hair follicles) and **type 1** (sebaceous glands).
- ▶ Ovaries and adrenals contribute about **equally** to testosterone; $\sim\frac{1}{2}$ from direct glandular secretion, $\frac{1}{2}$ from peripheral conversion of **androstenedione** and **DHEA/DHEAS**. Ovarian androgen is driven by **LH**, adrenal androgen by **ACTH**.
- ▶ **Sex hormone-binding globulin (SHBG)** governs the *free* (bioavailable) fraction. Hyperinsulinaemia and androgen excess suppress hepatic SHBG, so **free testosterone** rises even when total testosterone is high-normal — central to PCOS and obesity-related hirsutism.

Causes / Classification

Category	Representative causes
Ovarian hyperandrogenism	PCOS (commonest, $\sim 50\text{--}70\%$ of cases), hyperthecosis, ovarian steroidogenic blocks, severe insulin-resistance syndromes, ovarian neoplasms (arrhenoblastoma/Sertoli–Leydig, hilar cell tumours)
Adrenal hyperandrogenism	Nonclassic & classic CAH (chiefly 21-hydroxylase deficiency), premature adrenarche, functional adrenal hyperandrogenism, adrenal neoplasms
Other endocrine	Cushing's syndrome, hyperprolactinaemia, acromegaly
Peripheral overproduction	Obesity, idiopathic hirsutism
Pregnancy-related	Hyperreactio luteinalis, luteoma/thecoma of pregnancy
Drug-induced	Androgens/anabolic steroids, androgenic progestins (norgestrel, levonorgestrel), minoxidil, phenytoin, diazoxide, cyclosporine, valproate

- ▶ **AES prevalence (Azziz cohort, Williams):** PCOS 72%, idiopathic hyperandrogenism 16%, idiopathic hirsutism 7.6%, NCCAH (21-OHD) 4.3%, androgen-secreting tumours 0.2%.

- ▶ **Idiopathic hirsutism** = hirsutism with **cyclic ovulatory menses** and **normal serum testosterone**; reflects increased end-organ 5 α -reductase sensitivity (elevated androstenediol/androsterone glucuronide).

Clinical assessment

- ▶ **History:** age at onset and **rate of progression**. Onset in 2nd–3rd decade, slow and progressive favours PCOS/idiopathic; **sudden onset with rapid progression and virilization** suggests an **androgen-secreting neoplasm**. Menstrual history (**oligomenorrhoea** <8 cycles/year points to ovarian excess), galactorrhoea (prolactin/thyroid), family history of hirsutism/infertility (NCCAH), and **drug history**.
- ▶ **Examination:** height, weight, **BMI** (>25 overweight; >30 commonly associated with hirsutism via peripheral conversion), blood pressure (adrenal causes), and cutaneous markers of insulin resistance — **acanthosis nigricans**, **skin tags**. Look for Cushingoid features (striae, bruising, centripetal obesity).
- ▶ **Quantification** — **modified Ferriman–Gallwey (mFG) score**: **9 androgen-sensitive sites** (upper lip, chin, chest, upper abdomen, lower abdomen/pelvis, upper arms, thighs, upper back, lower back), each graded **0 (none) to 4 (frankly virile)**; **maximum 36**. **Score >8** = abnormal in most non-Hispanic white and African-American women (~95% score <8) and warrants hormonal work-up. Asian and Native-American women manifest hirsutism less readily (acne and scalp thinning may be the only clues).
- ▶ **Hirsutism vs virilization vs hypertrichosis:**
 - **Virilization** (markedly higher androgens — think tumour/hyperthecosis): deepening voice, temporal/frontal balding, breast atrophy, $\uparrow$ muscle bulk, loss of female contour, **clitoromegaly** (clitoral length >10 mm or **clitoral index** >35 mm² abnormal), $\uparrow$ libido.
 - **Hypertrichosis:** androgen-independent, diffuse **vellus** hair (non-sexual distribution) from drugs (phenytoin, minoxidil, cyclosporine) or systemic disease — not a sign of androgen excess.

Hormonal evaluation and investigations

- ▶ **First-line:** **total testosterone $\pm$ free testosterone** (calculated from total testosterone and SHBG, or by LC-MS/MS) and DHEAS. Free testosterone is the more sensitive index given SHBG suppression.
- ▶ **“Tumour” thresholds (red flags):**

Test	Value	Implication
Total testosterone	>7 nmol/L (>2 ng/mL)	Suggests tumour or hyperthecosis

Test	Value	Implication
Total testosterone	>12 nmol/L (>3.5 ng/mL)	Strongly indicates androgen-producing tumour (CMDT: >200 ng/dL → image)
Androstenedione	>1000 ng/dL (>34.9 nmol/L)	Ovarian/adrenal neoplasm
DHEAS	>18.5 µmol/L (>7000 µg/L; CMDT >700 µg/dL)	Adrenal source/tumour
17-hydroxyprogesterone (morning, follicular)	<6 nmol/L (<2 µg/L)	Excludes 21-OHD; >300 ng/dL suggests NCCAH

- ▶ **PCOS:** ↑LH:FSH ratio (>2) is characteristic but *random LH/FSH is unreliable* (pulsatile); transvaginal ultrasound shows enlarged ovaries with multiple peripheral follicles, but 25–30% of normal women have “cystic” ovaries, so imaging has low specificity — PCOS is a clinical/biochemical diagnosis of exclusion (Rotterdam: 2 of 3 — hyperandrogenism, oligo-anovulation, polycystic morphology).
- ▶ **NCCAH:** screen high-risk women with **morning follicular 17-OHP**; if borderline, ACTH (cosyntropin) 250 µg IV stimulation test confirms 21-hydroxylase deficiency.
- ▶ **Adrenal vs ovarian source:** dexamethasone androgen-suppression test (0.5 mg every 6 h × 4 days) — suppression of free testosterone to normal = adrenal source; incomplete suppression = ovarian.
- ▶ **Cushing’s:** overnight 1-mg dexamethasone suppression test if clinical suspicion. **Imaging:** CT/MRI adrenals for adrenal mass; transvaginal USG for ovarian mass; selective venous sampling for occult small virilizing tumours.

Management

- ▶ **Set expectations:** suppression slows *new* hair growth only — benefit not evident for 4–6 months, maximal at 9–12 months (hair-cycle length); existing terminal hair needs mechanical removal. Treat any **underlying cause** (stop offending drugs; surgery for tumours/Cushing’s).
- ▶ **Non-pharmacological (adjunct or sole therapy):** bleaching; shaving (does **not** increase growth rate/density); chemical depilatories; **plucking/waxing/electrolysis**; **laser and intense pulsed light (IPL)** photothermolysis for permanent reduction of pigmented terminal hair; **topical eflornithine 13.9% cream** (slows facial hair, esp. with laser).
- ▶ **Pharmacological — interrupt androgen synthesis/action:**

Drug class	Agent / dose	Mechanism / notes
Combined OCP (first-line)	Ethinyl-estradiol 30–35 µg + low-androgenic progestin	↓LH → ↓ovarian androgen; ↑SHBG; choose non-androgenic progestins (norgestimate) or antiandrogenic

Drug class	Agent / dose	Mechanism / notes
		drospirenone /cyproterone; avoid androgenic levonorgestrel/norgestrel
Androgen-receptor antagonist	Spirolactone 100–200 mg/day	Most-used antiandrogen; also inhibits 5 α -reductase; monitor K ⁺ /BP; menstrual irregularity; teratogenic (feminises male fetus) — needs contraception; synergistic with OCP
Antiandrogen + progestin	Cyproterone acetate (50–100 mg days 1–15) + EE — reverse-sequential	Competitive AR blockade + $\uparrow$ testosterone clearance; not available in USA
5 α -reductase inhibitor	Finasteride 5 mg/day	Inhibits type 2 (PSU has type 1 too $\rightarrow$ partial efficacy); teratogenic; dutasteride blocks types 1 & 2
Non-steroidal antiandrogen	Flutamide	Effective but hepatotoxic $\rightarrow$ not preferred
Insulin sensitiser	Metformin ($\pm$ lifestyle)	Modest hirsutism benefit in PCOS; aids ovulation
Glucocorticoid	Dexamethasone 0.2–0.5 mg / prednisone 5–10 mg at bedtime	Second-line in CAH (OCP preferred); suppresses nocturnal ACTH surge
Newer (CAH)	Crinicerfont 100 mg BD	CRF-receptor antagonist; $\downarrow$ androstenedione in 21-OHD CAH

- **Preferred regimen for the common causes (PCOS, NCCAH, idiopathic): combined OCP + spironolactone** plus weight loss (500 kcal/day deficit + exercise) — an ovary-suppressing agent combined with a peripheral antiandrogen; continue ≥ 2 years before reassessing.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Modified Ferriman–Gallwey scoring chart:** a female body outline with the **9 androgen-sensitive sites** labelled — *Upper lip, Chin, Chest, Upper abdomen, Lower abdomen (pelvis), Upper arms, Thighs, Upper back, Lower back* — each scored 0–4 (*max 36; abnormal >8*).
- **Androgen physiology / site of drug action flow diagram:** Ovary (LH) + Adrenal (ACTH) $\rightarrow$ Androstenedione/DHEA $\rightarrow$ Testosterone $\rightarrow$ [5 α -reductase] $\rightarrow$ DHT $\rightarrow$ Androgen receptor in pilosebaceous unit $\rightarrow$ terminal hair; label drug targets — OCP ($\downarrow$ LH, $\uparrow$ SHBG); Spirolactone/Cyproterone/Flutamide (AR block); Finasteride/Dutasteride (5 α -reductase); Eflornithine (follicle).

Clinical / Diagnostic significance

- ▶ A normal mFG with menstrual irregularity still warrants screening; **rapid-onset hirsutism + virilization + very high testosterone/DHEAS** mandates urgent tumour search (ovarian USG, adrenal CT/MRI).
- ▶ Free testosterone (not total) best reflects bioactivity because **SHBG is suppressed** by insulin/androgens — explains hirsutism with “normal” total testosterone.
- ▶ PCOS carries **metabolic risk** (insulin resistance, dyslipidaemia, type 2 diabetes, endometrial hyperplasia from unopposed estrogen) — screen accordingly; the cosmetic complaint is a window to systemic disease.
- ▶ All antiandrogens (spironolactone, finasteride, flutamide, cyproterone) are **teratogenic to a male fetus** — reliable contraception is mandatory in reproductive-age women.

High-yield exam pointers

- ▶ **Hirsutism = androgen-dependent terminal hair, male pattern**; hypertrichosis = androgen-independent vellus hair (drugs/systemic illness).
- ▶ **Commonest cause = PCOS**; most cases overall are idiopathic or PCOS-related; tumours are <1%.
- ▶ **DHT (via 5 α -reductase) is the key local mediator**; testosterone is the precursor.
- ▶ **mFG score**: 9 sites $\times$ 0–4, max 36, abnormal >8.
- ▶ **Tumour thresholds**: testosterone >7 nmol/L (>2 ng/mL) suggestive, >12 nmol/L (>3.5 ng/mL) likely tumour; DHEAS >7000 μ g/L = adrenal.
- ▶ **NCCAH screen**: morning follicular 17-OHP (<6 nmol/L excludes); confirm with ACTH/cosyntropin 250 μ g test.
- ▶ **Dexamethasone suppression** (0.5 mg q6h $\times$ 4 days) distinguishes adrenal (suppresses) from ovarian (does not).
- ▶ **First-line drug = combined OCP**; best results = OCP + **spironolactone**; response takes 6–9 months; combine with laser/electrolysis for existing hair.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Hirsutism” (Ehrmann); algorithm for evaluation and treatment.
- ▶ **Williams Textbook of Endocrinology, 15e** — “Physiology and Pathology of the Female Reproductive Axis” (androgen physiology, virilization/clitoral index, Ferriman–Gallwey quantification, comprehensive treatment strategy and drug efficacy data).
- ▶ **CMDT 2026** — “Hirsutism & Virilization” (diagnostic thresholds, eflornithine, crinecerfont, current drug regimens).



Hyperaldosteronism

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — Hyperaldosteronism denotes a state of inappropriately high aldosterone secretion relative to volume/sodium status. It is **primary** when aldosterone production by the adrenal zona glomerulosa is *autonomous* of the renin–angiotensin–aldosterone (RAA) system (low/suppressed renin), and **secondary** when aldosterone rises appropriately in response to an *activated* RAA system (high renin). Primary aldosteronism (PA), first described by *Jerome W. Conn* in 1955, is now recognised as the commonest *curable/specifically-treatable* endocrine cause of hypertension, present in ~5–12% of all hypertensives and a higher proportion of resistant/hypokalaemic hypertension. Its clinical hallmark is **hypokalaemic hypertension** with metabolic alkalosis, though most patients are normokalaemic.

Physiology & pathogenesis

- ▶ **Normal control:** aldosterone synthesis (via *aldosterone synthase*, *CYP11B2*) is driven mainly by **angiotensin II** and **serum potassium**, with only a permissive role for ACTH; volume/salt loading suppresses renin and hence aldosterone. Aldosterone acts on the **mineralocorticoid receptor (MR)** in the distal nephron, increasing ENaC-mediated Na⁺ reabsorption and K⁺/H⁺ secretion.
- ▶ **In PA**, autonomous aldosterone → Na⁺/water retention, plasma-volume expansion, hypertension, renal K⁺ and H⁺ wasting (→ hypokalaemia, metabolic alkalosis), and feedback **suppression of renin**.
- ▶ “**Mineralocorticoid escape**” (pressure natriuresis + atrial natriuretic peptide) limits sodium retention, so overt oedema is uncharacteristic.
- ▶ Aldosterone also exerts **direct, blood-pressure-independent target-organ injury** — cardiac fibrosis/remodelling, vascular stiffening, and glomerular damage — explaining the excess cardiovascular, renal, metabolic and bone morbidity in PA versus essential hypertension of equal severity.

Classification & causes

Category	Renin	Aldosterone	Principal causes
Primary	Low / suppressed	High	Bilateral idiopathic adrenal hyperplasia (IHA); aldosterone-producing adenoma (<i>Conn's adenoma</i>); unilateral (primary) adrenal hyperplasia; familial forms; rarely adrenocortical carcinoma

Category	Renin	Aldosterone	Principal causes
Secondary	High	High	Renovascular (renal artery stenosis), renin-secreting (juxtaglomerular) tumour, malignant/accelerated hypertension, oedematous states (CHF, cirrhosis, nephrotic syndrome), diuretics, <i>Bartter</i> / <i>Gitelman</i> syndromes (normotensive)
Pseudo-aldosteronism (mimics, low renin and low aldosterone)	Low	Low	Liddle syndrome; apparent mineralocorticoid excess (AME)/liquorice; CAH (11 β - & 17 α -OHase deficiency); Cushing syndrome; DOC-secreting tumour

Subtypes of primary aldosteronism (approximate frequency):

- ▶ **Bilateral idiopathic hyperplasia (IHA)** — ~60% (60–70%); the commonest cause; treated medically.
- ▶ **Aldosterone-producing adenoma (Conn's syndrome)** — ~30–40%; usually a small (<2 cm), lipid-rich, golden-yellow unilateral nodule; surgically curable.
- ▶ **Unilateral (primary) adrenal hyperplasia** — ~2%.
- ▶ **Aldosterone-producing adrenocortical carcinoma** — <1% (suspect if tumour $\geq$ 4 cm, heterogeneous).
- ▶ **Familial hyperaldosteronism (FH)** — ~1–6%.

Genetics — somatic mutations drive most APAs by upregulating CYP11B2: *KCNJ5* (potassium channel *GIRK4*, ~40–70% of APAs; commoner in women, larger adenomas, overproduce hybrid steroids), *ATP1A1* (Na⁺/K⁺-ATPase), *ATP2B3* (Ca²⁺-ATPase), *CACNA1D* / *CACNA1H* (voltage-gated Ca²⁺ channels), *CLCN2* (chloride channel) and *CTNNB1* (β -catenin).

Familial hyperaldosteronism:

- ▶ **FH type I — Glucocorticoid-remediable aldosteronism (GRA / dexamethasone-suppressible):** autosomal dominant; a *CYP11B1/CYP11B2* chimeric gene places aldosterone synthesis under ACTH control. Severe early-onset hypertension, high risk of haemorrhagic stroke from ruptured

intracranial aneurysm; high urinary **18-oxocortisol & 18-hydroxycortisol**; aldosterone suppressible by glucocorticoid.

- ▶ **FH type II**: germline **CLCN2**; the commonest familial form (<6%); early-onset hypertension; *not* dexamethasone-suppressible.
- ▶ **FH type III**: germline **KCNJ5**; severe childhood hypertension with **massive bilateral adrenal hyperplasia**.
- ▶ **FH type IV**: germline **CACNA1H**; early-onset hypertension ± developmental disorders.
- ▶ **PASNA**: de novo **CACNA1D**; Primary Aldosteronism with Seizures and Neurologic Abnormalities.

Clinical features

- ▶ **Hypertension** — moderate-to-severe, often drug-resistant; commonest curable secondary cause in young/middle-aged adults.
- ▶ **Hypokalaemia** — present in only ~10–40% (≈37%); ~72% are normokalaemic. May be unmasked/worsened by thiazide or loop diuretics. Manifestations: muscle weakness, cramps, fatigue, **hypokalaemic periodic paralysis** (notably in Asians), polyuria/nocturia (nephrogenic diabetes insipidus from a renal concentrating defect), arrhythmias, rhabdomyolysis.
- ▶ **Metabolic alkalosis** (raised HCO_3^-); severe alkalosis → tetany/cramps. **Hypomagnesaemia** common.
- ▶ **High-normal serum sodium** (reset osmostat) — a useful clue; oedema usually absent (escape).
- ▶ **End-organ disease** out of proportion to BP: LVH/diastolic dysfunction, atrial fibrillation, stroke, CKD/proteinuria (masked early by glomerular hyperfiltration), osteoporosis, type 2 diabetes, impaired quality of life.
- ▶ “**Connshing**” syndrome — concurrent mild autonomous cortisol secretion (MACS) in a subset.

Diagnostic approach

A three-step pathway — **case detection** → **confirmation** → **subtyping**.

- ▶ **Whom to screen**: sustained BP >150/100; resistant hypertension (≥3 drugs incl. diuretic) or controlled on ≥4 drugs; hypertension + spontaneous/diuretic-induced hypokalaemia; adrenal incidentaloma; onset <40 yr or family history of early-onset hypertension/stroke; first-degree relative with PA; obstructive sleep apnoea.
- ▶ **Case-detection** — **Aldosterone–Renin Ratio (ARR)**: paired morning (8–10 am, seated/ambulant) **plasma aldosterone concentration (PAC)** and **plasma renin activity (PRA)/concentration**. Correct hypokalaemia first. PA is suggested by **suppressed renin** (PRA <1 ng/mL/h) with **raised PAC** (≥10–15 ng/dL); an elevated ARR (Endocrine Society cutoff ~ARR >750 pmol/L per ng/mL/h, or aldosterone:PRA ratio >30) is positive.

- ▶ **Drug effects (correct before testing):** MR antagonists must be stopped 4–6 weeks beforehand (cause false-negatives). β -blockers/clonidine/NSAIDs $\rightarrow$ false-positives (low renin); ACE-inhibitors/ARBs/diuretics $\rightarrow$ false-negatives (high renin). However, if renin remains suppressed despite these drugs, the result is interpretable. Verapamil, hydralazine and α -blockers are “clean”.
- ▶ **Confirmation (autonomy):** demonstrate non-suppressible aldosterone —
 - **IV saline infusion test:** 2 L 0.9% saline over 4 h; PAC failing to suppress $<5\text{--}6\text{ ng/dL}$ (or $<170\text{ pmol/L}$ seated) confirms PA ($5\text{--}10\text{ ng/dL}$ indeterminate).
 - **Oral sodium loading:** high-salt diet 3 days $\rightarrow$ 24-h urinary aldosterone $>12\text{ }\mu\text{g}/24\text{ h}$.
 - **Fludrocortisone suppression test** ($0.1\text{ mg q6h} + \text{NaCl} \times 4\text{ days}$; PAC not suppressing $<6\text{ ng/dL}$) — sensitive but cumbersome, now seldom used.
 - **Captopril challenge** — alternative (contraindicated in pregnancy).
 - Confirmation may be **omitted** with overt hypokalaemic hypertension + strongly positive ARR + clearly raised PAC.
- ▶ **Subtyping (unilateral vs bilateral):**
 - **Fine-cut adrenal CT** — first step; identifies adenomas and excludes carcinoma, but **cannot reliably distinguish** APA from IHA (may miss micro-adenomas, or mislabel a non-functioning incidentaloma).
 - **Adrenal vein sampling (AVS)** — the **gold standard** for lateralisation in surgical candidates. Correct catheter placement is confirmed by an **adrenal-vein-to-IVC cortisol gradient** ($>2\text{--}3$ unstimulated; $>5:1$ with cosyntropin). **Lateralisation** = cortisol-corrected aldosterone ratio (dominant:non-dominant side) >4 (sensitivity $\sim 95\%$, specificity $\sim 100\%$); a **contralateral suppression index** <1 is supportive. Technically demanding (difficult right adrenal vein).
 - **Selective use:** patients $<35\text{ yr}$ with spontaneous hypokalaemia, marked PA and a clear unilateral adenoma on CT may proceed to surgery without AVS; older patients need AVS because of frequent coincidental non-functioning adenomas.
 - **[^{11}C]-metomidate PET-CT** (with dexamethasone pre-treatment) — emerging non-invasive alternative to AVS.
- ▶ **Non-aldosterone (low-renin, low-aldosterone) mineralocorticoid excess** is confirmed by **urinary steroid metabolite profiling (GC/MS)**, identifying AME (HSD11B2 deficiency, raised cortisol:cortisone), CAH (CYP11B1/CYP17A1), DOC excess; a normal profile suggests **Liddle syndrome** (amiloride-responsive).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Renin-Angiotensin-Aldosterone axis (with feedback):** label *Renal juxtaglomerular cells* $\rightarrow$ *Renin*; *Angiotensinogen* $\rightarrow$ *Angiotensin I (via renin)* $\rightarrow$ *Angiotensin II (via ACE)*; *Adrenal zona glomerulosa* $\rightarrow$ *Aldosterone (CYP11B2)*; stimuli $\downarrow\text{BP}/\downarrow\text{Na}^+/\uparrow\text{K}^+$;

target *Distal nephron MR* → *ENaC* → Na^+ reabsorption, K^+/H^+ excretion; negative-feedback arrow *Volume expansion* → ↓*Renin*. Mark the “block” in primary aldosteronism (autonomous aldosterone, suppressed renin).

- ▶ **Diagram 2 — Diagnostic algorithm flowchart:** boxes — *Screen high-risk hypertensive* → *ARR (PAC + PRA)* → *if positive* → *Confirmatory test (saline infusion/oral salt load)* → *Adrenal CT* → *if surgical candidate, Adrenal Vein Sampling* → *Lateralised = unilateral adrenalectomy / Non-lateralised = MR antagonist*. Side branch: *normal adrenals + family history* → *consider GRA / genetic testing*.

Clinical / Diagnostic significance

- ▶ Differentiate primary vs secondary by renin: PA = **low renin, high aldosterone**; secondary = **high renin, high aldosterone** (PAC:PRA <10). Pseudo-aldosteronism (Liddle, AME, liquorice, CAH) = **low renin, low aldosterone**.
- ▶ **Treatment of unilateral PA (APA/unilateral hyperplasia): laparoscopic (total) adrenalectomy** — cures hypokalaemia in nearly all, cures/improves hypertension in ~30–60% (residual essential hypertension common). Correct K^+ pre-operatively; anticipate **transient post-operative hypoaldosteronism** (hyperkalaemia, hypotension) from chronic contralateral suppression — monitor potassium weekly for 4 weeks with a liberal-salt diet.
- ▶ **Medical therapy (IHA, GRA, non-operative APA): spironolactone** 12.5–25 mg/day titrated to ≤400 mg (side-effects — gynaecomastia, mastodynia, erectile dysfunction, menstrual irregularity from anti-androgen/progestogenic actions); **eplerenone** (selective MR antagonist, 25 mg bid, fewer endocrine side-effects, preferred in men and pregnancy — FDA category B); **amiloride** (K^+ -sparing, 5–10 mg bid); **finerenone** (non-steroidal MRA) used off-label. Aim for high-normal K^+ and **un-suppressed renin** (a marker of adequate dosing/cardiovascular protection).
- ▶ **GRA:** low-dose **glucocorticoid** (dexamethasone/prednisone/hydrocortisone, smallest effective dose) ± MR antagonist; confirm by genetic testing.
- ▶ **Pregnancy:** progesterone may antagonise MR (improving some cases); captopril/saline tests avoided; MRI without gadolinium for imaging; eplerenone preferred if drug therapy needed.

High-yield exam pointers

- ▶ **Conn’s syndrome** = aldosterone-producing adenoma; commonest *cause overall* of PA is **bilateral idiopathic hyperplasia (IHA)**.
- ▶ **Hypokalaemic hypertension with metabolic alkalosis and suppressed renin** = classic PA; but ~70% are **normokalaemic** — screen widely.
- ▶ **Screening test** = ARR; stop MR antagonists 4–6 weeks before; **confirmatory** = **saline infusion / oral salt-loading** (failure to suppress aldosterone).

- ▶ AVS is the gold standard for lateralisation; CT alone is unreliable (misses micro-adenomas, false incidentalomas).
- ▶ KCNJ5 (GIRK4) is the commonest somatic mutation in APA; hybrid steroids (18-oxo-/18-OH-cortisol) mark GRA and KCNJ5 disease.
- ▶ GRA = FH type I, CYP11B1/CYP11B2 chimeric gene, ACTH-driven, dexamethasone-suppressible, early stroke risk.
- ▶ High-normal serum sodium + hypomagnesaemia + no oedema (mineralocorticoid escape) are clinical clues.
- ▶ Unilateral disease → laparoscopic adrenalectomy (cures HTN in 30–60%); bilateral/IHA → MR antagonist.
- ▶ Liddle syndrome (low renin, low aldosterone) responds to amiloride/triamterene, NOT spironolactone (constitutively active ENaC).

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Disorders of the Adrenal Cortex" (Primary Mineralocorticoid Excess; Tables 398-3/398-4; Fig 398-12 diagnostic algorithm).
- ▶ Williams Textbook of Endocrinology, 15e — "Endocrine Hypertension" (Conn's historical account; case-detection/confirmatory/subtype testing; AVS interpretation; familial & somatic genetics; pharmacologic treatment; pregnancy).
- ▶ CMDT 2026 — "Disorders of the Pituitary, Thyroid, & Adrenal Glands" (screening thresholds, ARR cut-offs, AVS indications, spironolactone/eplerenone/finerenone dosing).



Hyperglycemic hyperosmolar state

Asked in: Paper IV Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Hyperglycemic hyperosmolar state (HHS) is an acute, life-threatening hyperglycemic emergency characterized by **severe hyperglycemia, hyperosmolality, profound dehydration, and absent or only mild ketosis/acidosis**. It occurs classically in **middle-aged or elderly patients with type 2 diabetes**, often previously mild or occult, after days to weeks of osmotic symptoms and reduced water intake. It is the second major hyperglycemic coma after diabetic ketoacidosis (DKA), but carries higher mortality because patients are older, more dehydrated, and often have infection, myocardial infarction, stroke, chronic kidney disease, heart failure, or postoperative stress.

Etiology and precipitating factors

- ▶ **Typical patient:** older person with type 2 diabetes, mild/occult diabetes, poor access to fluids, dementia, prior stroke, frailty, bed-bound state, or social circumstances preventing adequate drinking.

- ▶ **Common precipitants:** pneumonia, sepsis, urinary infection, other serious infections, myocardial infarction, stroke, recent operation, trauma, and any acute illness that increases counter-regulatory hormones and reduces oral intake.
- ▶ **Drug/procedure triggers:** corticosteroids, diuretics, phenytoin, diazoxide, and glucose-loading procedures such as peritoneal dialysis; antipsychotics and other diabetogenic drugs should also be reviewed in the medication history.
- ▶ **Contributing physiology:** polyuria and glycosuria cause large water and electrolyte loss; impaired thirst, nausea, immobility, or inaccessibility of water allows progressive dehydration.
- ▶ **DKA-HHS continuum:** DKA and HHS overlap clinically; Harrison notes that up to one-third of patients may have features of both. Therefore every HHS patient must be checked for ketonemia, acidosis, and anion gap.

Pathophysiology

- ▶ The central defect is **relative insulin deficiency plus inadequate fluid intake**. Insulin is sufficient to restrain lipolysis and ketogenesis, but insufficient to suppress hepatic glucose output or promote peripheral glucose utilization.
- ▶ Increased hepatic **gluconeogenesis and glycogenolysis**, impaired skeletal-muscle glucose uptake, and hyperglucagonemia produce severe hyperglycemia.
- ▶ Hyperglycemia causes **osmotic diuresis** with loss of water, sodium, potassium, magnesium, phosphate, and glucose in urine.
- ▶ Progressive intravascular volume contraction reduces glomerular filtration and renal glucose clearance, which further worsens hyperglycemia and hyperosmolality.
- ▶ Hyperosmolality draws water from cells, including brain cells, producing **confusion, lethargy, seizures, and coma**; neurological manifestations correlate better with osmolality than with glucose alone.
- ▶ Ketosis is absent or mild because residual portal insulin, lower free fatty acid flux, lower counter-regulatory hormone drive than in DKA, and a less ketotic insulin/glucagon ratio suppress hepatic ketone-body synthesis.

Clinical features

- ▶ **Prodrome:** days to weeks of polyuria, polydipsia, weakness, weight loss, blurred vision, and declining oral intake.
- ▶ **Dehydration:** intense thirst may be absent; examination shows dry mucosa, poor skin turgor, sunken eyes, tachycardia, postural hypotension or shock, oliguria, and prerenal azotemia.
- ▶ **Neurological features:** lethargy and confusion develop as serum osmolality rises above about 310 mOsm/kg; convulsions and coma can occur above 320-330 mOsm/kg.
- ▶ **Absent DKA clues:** nausea, vomiting, abdominal pain, acetone breath, and Kussmaul respiration are absent or much less prominent than in DKA.

- ▶ **Precipitant clues:** fever may be absent despite infection; actively seek pneumonia, urinary infection, sepsis, acute coronary syndrome, stroke, pancreatitis, trauma, drug exposure, and recent surgery.
- ▶ **Severe cases** may present directly with hypotensive shock, acute kidney injury, rhabdomyolysis, focal neurological deficits, seizures, or coma.

Diagnosis and laboratory profile

Feature	HHS	DKA comparison
Plasma glucose	>600 mg/dL diagnostic threshold; often 600-1200 mg/dL and may reach 800-2400 mg/dL	Usually 250-600 mg/dL
Serum osmolality	>310 mOsm/kg in CMDT; severe neurological disease often >320-330 mOsm/kg	Usually lower; may be >300
Arterial/venous pH	>7.3	<7.3 in DKA
Serum bicarbonate	Usually >15-18 mEq/L	<18 mEq/L
Anion gap	Usually normal, <14 mEq/L; mild lactic acidosis may raise it	Raised
Ketones	Absent or mild; serum beta-hydroxybutyrate usually <1 mmol/L	Marked, often >3 mmol/L
Sodium	Measured sodium may be normal/low; corrected sodium is often high	Often low from osmotic water shift
Renal indices	Prerenal azotemia common; BUN may be markedly high	Variable

- ▶ Calculate tonicity/effective osmolality using effective solutes: approximately **2 x measured Na + glucose/18** (mg/dL units); urea contributes to measured osmolality but not tonicity because it crosses cell membranes.
- ▶ Correct serum sodium for hyperglycemia: add about **1.6 mEq/L** to measured sodium for each 100 mg/dL rise in glucose above normal; some physiology texts note higher correction factors at extreme glucose levels, so interpret with measured osmolality and clinical state.
- ▶ Initial work-up: capillary and plasma glucose, electrolytes, urea/creatinine, venous or arterial pH, bicarbonate, anion gap, measured serum osmolality if available, serum/urine ketones or beta-hydroxybutyrate, urine routine, CBC, cultures when infection is suspected, ECG, chest radiograph, troponin, and neuroimaging when focal deficits or persistent coma suggest stroke or structural disease.

- ▶ Diagnose HHS only after excluding significant DKA, lactic acidosis, renal failure-related uremic encephalopathy, sepsis-associated encephalopathy, stroke, and drug/toxin causes of coma.

Management

- ▶ **Site of care:** admit to monitored high-dependency or ICU setting if shock, coma, severe electrolyte disturbance, acute coronary syndrome, stroke, sepsis, renal failure, or need for frequent insulin/electrolyte titration.
- ▶ **Immediate priorities:** airway protection in coma/vomiting, oxygen if hypoxemic, two IV lines, cardiac monitoring, catheterize if needed for urine output, and begin a flow sheet for vitals, mental status, input-output, glucose, electrolytes, osmolality, and insulin rate.
- ▶ **Fluids are paramount.** If hypotension or oliguria is present, start **0.9% saline**; Harrison suggests **1-3 L over the first 2-3 h** to restore hemodynamic stability. Fluid deficit is often **6-10 L**, sometimes 9-10 L, and should be corrected over about 24-48 h.
- ▶ After hemodynamic stabilization, choose fluid by corrected sodium and osmolality: use **0.45% saline** if sodium is high or >150 mEq/L; otherwise continue isotonic or hypotonic saline according to volume status. CMDT notes that **4-6 L may be needed in the first 8-10 h**, but correction must be controlled to avoid neurological worsening.
- ▶ Aim to restore urine output to **at least 50 mL/h** while avoiding pulmonary edema in elderly patients, heart failure, and chronic kidney disease.
- ▶ **Insulin:** do not let insulin precede initial fluid resuscitation unless there is significant ketosis/acidosis. A current adult approach is IV regular insulin **0.05 unit/kg/h without bolus**, titrated to lower glucose by **50-70 mg/dL/h**. Harrison also describes a hyperglycemic-crisis regimen of 0.1 unit/kg IV bolus followed by 0.1 unit/kg/h; in HHS, lower-dose fluid-first insulin is safer when ketosis is absent.
- ▶ Add dextrose when plasma glucose reaches about **250 mg/dL**; maintain glucose around **250-300 mg/dL** until osmolality, hydration, and mental status improve, then transition to subcutaneous insulin.
- ▶ **Potassium:** total-body potassium is depleted despite normal initial serum potassium. Because acidosis is absent, initial hyperkalemia is less common than in DKA, and potassium may fall rapidly with insulin. If renal function and urine output are adequate and potassium is not elevated, add potassium early, e.g., **10 mEq/L** in initial fluids; hold insulin if potassium is severely low until corrected.
- ▶ **Phosphate and magnesium:** routine phosphate is not required; replace phosphate if severe hypophosphatemia develops, especially <1 mg/dL, and correct magnesium if deficient, particularly in diuretic users.

- ▶ **Precipitant treatment:** obtain cultures before antibiotics when feasible, but do not delay antibiotics for suspected sepsis; treat MI, stroke, pneumonia, UTI, pancreatitis, surgery-related infection, and offending drugs.
- ▶ **Thrombosis prevention:** severe dehydration and low-flow state predispose to MI, stroke, pulmonary embolism, mesenteric venous thrombosis, and DIC; pharmacologic VTE prophylaxis is reasonable unless contraindicated, while routine full-dose anticoagulation is not automatically indicated.
- ▶ **Transition and discharge:** continue insulin during admission; after stabilization and eating, overlap IV insulin with subcutaneous basal insulin. Many patients require insulin for weeks, but some later recover enough endogenous insulin secretion for diet plus oral agents.

Complications and prognosis

- ▶ **Neurological:** seizures, coma, and worsening mental status from hyperosmolality; too-rapid correction may contribute to cerebral edema or neurological deterioration.
- ▶ **Renal and muscle:** prerenal azotemia, acute kidney injury, and rhabdomyolysis should be anticipated and monitored.
- ▶ **Vascular:** MI, ischemic stroke, pulmonary embolism, mesenteric venous thrombosis, disseminated intravascular coagulation, and limb ischemia occur due to dehydration, hyperviscosity, and underlying comorbidity.
- ▶ **Treatment-related:** hypoglycemia, hypokalemia, hypophosphatemia, hyperchloremic acidosis with large saline loads, fluid overload, and pulmonary edema.
- ▶ Mortality is substantially higher than DKA: Harrison cites up to 15% in some series; CMDT notes it is more than ten times DKA largely because of age, delayed recognition, dehydration, and coexistent illness, and delayed cases historically approached very high mortality.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology flowchart:** relative insulin deficiency + stress hormones -> hepatic glucose output + impaired peripheral uptake -> severe hyperglycemia -> glycosuria/osmotic diuresis -> water/electrolyte loss -> hypovolemia -> reduced GFR -> worsening hyperglycemia -> hyperosmolality -> brain cell dehydration -> confusion/seizure/coma; side label: residual insulin suppresses ketogenesis.
- ▶ **Management algorithm:** suspect HHS -> ABC/vitals/IV access -> labs including glucose, electrolytes, osmolality, pH, ketones -> 0.9% saline if shock -> choose 0.45% saline by corrected sodium -> monitor K and urine output -> IV insulin 0.05 unit/kg/h after fluids -> dextrose at glucose 250 mg/dL -> treat precipitant -> subcutaneous insulin transition.

Clinical / Diagnostic significance

- ▶ HHS is a **diagnosis of dehydration plus tonicity**, not merely a high glucose value; mental status change is an osmolality warning sign.
- ▶ In an elderly diabetic with coma, always check glucose, sodium, osmolality, ketones, pH, urea/creatinine, ECG, and infection screen before attributing the coma to stroke alone.
- ▶ Corrected sodium guides fluid choice: a “normal” measured sodium in severe hyperglycemia may hide significant free-water deficit.
- ▶ Absence of Kussmaul breathing and abdominal pain helps distinguish HHS from DKA, but overlap is common; beta-hydroxybutyrate and pH are mandatory.
- ▶ Treat the precipitant as aggressively as the glucose: pneumonia, sepsis, MI, stroke, and postoperative infection often determine outcome.
- ▶ Prevention after recovery requires sick-day education, caregiver involvement, early contact during infection/vomiting, maintaining sugar-free fluids, and medication review, especially diuretics and corticosteroids.

High-yield exam pointers

- ▶ Triad: **severe hyperglycemia + hyperosmolality + profound dehydration with little/no ketoacidosis**.
- ▶ Typical case: elderly type 2 diabetic, days-weeks of polyuria and poor intake, then confusion/coma.
- ▶ Diagnostic essentials: glucose **>600 mg/dL**, osmolality **>310 mOsm/kg**, pH **>7.3**, bicarbonate **>15-18 mEq/L**, normal anion gap, absent/mild ketones.
- ▶ Osmolality drives coma: confusion above about **310 mOsm/kg**, seizures/coma often above **320-330 mOsm/kg**.
- ▶ First treatment is **fluid**, not insulin; restore circulation before lowering glucose aggressively.
- ▶ Use insulin cautiously: **0.05 unit/kg/h** after fluids in nonketotic HHS; avoid glucose fall faster than **50-70 mg/dL/h**.
- ▶ Add dextrose around **250 mg/dL** and continue controlled correction until osmolality and mental status recover.
- ▶ Potassium is depleted even if serum potassium is normal; replace early if urine output is adequate and potassium is not high.
- ▶ Mortality is higher than DKA; death usually reflects age, dehydration, delayed diagnosis, infection, MI, stroke, CKD, or HF.

SOURCE & COVERAGE

Harrison 22e — “Diabetes Mellitus: Management and Therapies”; “Diabetes Mellitus: Complications”; Williams Textbook of Endocrinology 15e — “Therapeutics of Type 2 Diabetes Mellitus”; “Posterior Pituitary”; CMDT 2026 — “Diabetes Mellitus & Hypoglycemia”.



Hyperprolactinemia

Asked in: Paper IV 17 Apr 2026 · Paper IV Jul 2021 · Paper IV Nov 2020 (3×) — RGUHS MD General Medicine

Definition / Introduction — Hyperprolactinemia is sustained elevation of serum prolactin (PRL) above the assay-specific reference range (normal adult PRL $\approx$ 10–25 μ g/L in women and 10–20 μ g/L in men). It is the **most common pituitary hormone hypersecretion syndrome** in both sexes. Because the hypothalamus exerts *tonic dopaminergic inhibition* of lactotrope PRL release (via D2 receptors), hyperprolactinemia results either from autonomous lactotrope secretion (prolactinoma), from loss of dopaminergic tone (stalk disconnection, drugs), or from physiologic/systemic stimuli. Clinically it presents with hypogonadism, galactorrhea and infertility, and may signal an underlying sellar mass.

Prolactin physiology — basis of the syndrome

- ▶ **Structure/source:** PRL is a 198-amino-acid polypeptide ($\approx$ 23 kDa), homologous to GH and placental lactogen, secreted by **lactotropes** ($\sim$ 20% of anterior pituitary cells); lactotrope hyperplasia occurs in pregnancy/lactation under estrogen drive. Circulating **half-life $\approx$ 50 min**; secretion is pulsatile with nocturnal (non-REM sleep) peaks at 4–6 a.m.
- ▶ **Unique inhibitory control:** Unlike other pituitary hormones, PRL is under predominantly *inhibitory* hypothalamic control — **dopamine acting on pituitary D2 receptors** suppresses PRL synthesis and secretion. Hence any lesion that interrupts dopamine delivery (stalk section) causes hyperprolactinemia, and **dopamine agonists are the cornerstone of treatment**.
- ▶ **Stimulators:** TRH releases PRL within 15–30 min (explains hyperprolactinemia of primary hypothyroidism); estrogen, suckling/chest-wall afferents, stress and sleep also raise PRL.
- ▶ **Why hypogonadism occurs:** Excess PRL suppresses hypothalamic **GnRH** pulsatility $\rightarrow$ reduced LH/FSH $\rightarrow$ impaired gonadal steroidogenesis (low estradiol/testosterone); PRL also directly inhibits ovarian folliculogenesis and granulosa-cell aromatase (anovulation, luteolysis) and testicular function.

Etiology — classified (physiologic / pathologic / pharmacologic)

Category	Causes
Physiologic	Pregnancy, lactation, nipple/chest-wall stimulation or trauma (incl. herpes zoster, thoracotomy), sleep, stress, exercise, sexual orgasm

Category	Causes
Hypothalamic–pituitary stalk damage	Pituitary adenoma with stalk compression , suprasellar masses (craniopharyngioma, meningioma, dysgerminoma, metastases), Rathke cleft cyst, empty sella, lymphocytic hypophysitis, granulomas/infiltration, cranial irradiation, head trauma/stalk section, suprasellar surgery
Pituitary hypersecretion	Prolactinoma (commonest tumoural cause); acromegaly (GH–PRL/ mammosomatotrope tumours), plurihormonal adenomas
Systemic	Chronic renal failure (↓ peripheral clearance), primary hypothyroidism (↑ TRH), cirrhosis, PCOS, pseudocyesis, seizures
Drug-induced	Antipsychotics — risperidone (often >200 µg/L), phenothiazines (chlorpromazine, perphenazine), butyrophenones (haloperidol); metoclopramide , domperidone; methyldopa (↓ DA synthesis); verapamil (↓ DA release); reserpine; TCAs/SSRIs (fluoxetine); H2-blockers (cimetidine); opiates; estrogens; TRH

- ▶ **PRL level guides cause:** Mild elevation (30–100 µg/L) typically reflects drugs, stalk compression, hypothyroidism or renal failure; a level >200–250 µg/L **almost invariably indicates a prolactinoma**. *Caveat:* a large *non*-lactotrope macroadenoma can raise PRL only modestly (usually <100 µg/L) by stalk compression — the level per tumour-volume cannot always distinguish the two.
- ▶ **Prolactinoma facts:** Lactotrope tumours account for ~half of functioning pituitary adenomas; **microadenoma <1 cm, macroadenoma ≥1 cm**. Microprolactinoma F:M ≈ 20:1; macroadenoma sex ratio ≈ 1:1 (men present larger/late). ~20% of MEN-1 patients have prolactinomas. Only ~5% of microadenomas progress to macroadenomas.

Clinical features

- ▶ **Women:** the triad of **amenorrhoea/oligomenorrhoea, galactorrhoea and infertility**; pre-menarchal onset → primary amenorrhoea; reduced libido, vaginal dryness, mild hirsutism, weight gain. **Galactorrhoea in up to 80%** of hyperprolactinaemic women (may need to be elicited).
- ▶ **Men:** decreased libido, **erectile dysfunction**, oligospermia/infertility, gynaecomastia; true galactorrhoea uncommon. Long-standing hypogonadism → osteopenia, reduced muscle mass, decreased beard growth. Men more often present late with **mass effects** (headache, visual loss).
- ▶ **Skeletal:** chronic hypoestrogenism/hypogonadism reduces bone mineral density → **osteoporosis** and vertebral fractures.

- ▶ **Mass-effect symptoms (macroadenoma):** headache, **bitemporal hemianopia** (chiasmal compression), cranial nerve III/IV/VI palsy (cavernous sinus), hypopituitarism, rarely apoplexy.

Laboratory investigation & diagnostic approach

- ▶ **Step 1 — confirm:** basal, fasting morning serum PRL (avoid stress/venepuncture artefact); repeat if borderline. Exclude **pregnancy** (β -hCG) first.
- ▶ **Step 2 — exclude secondary causes** *before* imaging: drug history, TSH/free T4 (hypothyroidism), renal and hepatic function; review oestrogen/neuroleptic exposure.
- ▶ **Two key assay pitfalls (high-yield):**
 - **Hook effect** — in very large prolactinomas with extreme PRL (>1000 $\mu\text{g/L}$), antibody saturation gives a *falsely low/normal* reported value; correct by **serial sample dilution**.
 - **Macroprolactinemia** — high-molecular-weight aggregated PRL (biologically inactive) gives elevated readings with *few/absent symptoms*; detect by **polyethylene glycol (PEG) precipitation**.
- ▶ **Step 3 — imaging:** if no reversible cause, perform **gadolinium-enhanced pituitary MRI** (T1 iso/hypointense, T2 hyperintense adenoma); microadenomas <2 mm may be MRI-occult, so a normal scan does not exclude a microprolactinoma. **Formal perimetry** for any macroadenoma abutting the chiasm; assess anterior-pituitary reserve (IGF-1, 8 a.m. cortisol, gonadotropins, thyroid axis).
- ▶ **Idiopathic hyperprolactinemia** = diagnosis of exclusion with normal MRI.

Treatment / Management

- ▶ **Principles:** treat the **cause**; aim to normalise PRL to restore gonadal function, stop galactorrhoea, preserve bone density, and shrink any tumour. Stop offending drugs where possible; **levothyroxine** corrects hypothyroidism-related rise; treat renal failure. Asymptomatic microadenomas not desiring fertility may simply be monitored (serial PRL + MRI) — up to **30% resolve spontaneously**.
- ▶ **Dopamine agonists (DA)** — **first-line for prolactinoma and most causes:** suppress PRL secretion/synthesis and lactotrope proliferation; effective even when raised PRL is due to non-lactotrope stalk compression (so DA-induced PRL fall does **not** prove the mass is a prolactinoma).

Drug	Dose	Key points
Cabergoline (preferred)	0.25–1 mg twice weekly	Long-acting, high D2 affinity; normalises PRL in ~80% micro / ~70% macro , NEJM data 83% vs 52% for bromocriptine; better tolerated; valve surveillance at high doses

Drug	Dose	Key points
Bromocriptine	0.625–2.5 mg, up to 2.5 mg tid	Short-acting ergot; preferred when fertility/pregnancy desired ; more GI/orthostatic side-effects

- ▶ **Side-effects of DAs:** nausea, postural hypotension, constipation, nasal stuffiness, fatigue; impulse-control disorders and (at high/Parkinsonian doses, e.g. ≥ 3 mg/day cabergoline) **cardiac valve regurgitation** — obtain a baseline **echocardiogram** before standard-dose therapy. **~20% of tumours are DA-resistant** (more often in men).
- ▶ **Surgery (transsphenoidal):** reserved for DA intolerance/resistance, or an invasive macroadenoma with threatened vision unresponsive to drugs. PRL normalisation ~70% (micro) but only ~40% (macro); hyperprolactinaemia recurs in up to 20% by 1 year and >50% long-term for macroadenomas.
- ▶ **Radiotherapy:** only for aggressive tumours refractory to DA + surgery.
- ▶ **Pregnancy:** restore fertility with **bromocriptine**; stop DA once pregnancy confirmed for a microadenoma. Microprolactinomas enlarge clinically in <3–5%, **macroprolactinomas in 15–30%** — continue DA and perform trimester-wise visual fields for macroadenomas.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Hypothalamic–pituitary control of PRL.** Labels: *Hypothalamus* → *Dopamine (inhibitory, –) and TRH (stimulatory, +)*; *Hypophyseal portal vessels / pituitary stalk*; *Lactotrope (D2 receptor)*; *Prolactin*; downstream $\downarrow$ GnRH $\rightarrow$ $\downarrow$ LH/FSH $\rightarrow$ $\downarrow$ oestrogen/testosterone (*hypogonadism*) and $\uparrow$ breast milk (*galactorrhoea*). Show **stalk section** interrupting dopamine flow $\rightarrow$ $\uparrow$ PRL.
- ▶ **Diagram 2 — Coronal sella MRI of a macroadenoma.** Labels: *pituitary macroadenoma in sella turcica*, *suprasellar extension compressing the optic chiasm (bitemporal hemianopia)*, *cavernous sinus + internal carotid artery*, *sphenoid sinus*, *pituitary stalk*.

Clinical / Diagnostic significance

- ▶ **Common reversible mimic:** always exclude **drugs, pregnancy, hypothyroidism and renal failure** before extensive endocrine work-up — avoids unnecessary imaging/surgery.
- ▶ **PRL magnitude triages the lesion:** >200–250 $\mu\text{g/L}$ $\Rightarrow$ prolactinoma; modest rise with a large mass $\Rightarrow$ suspect stalk compression by a non-functioning/other tumour.
- ▶ **Galactorrhoea + amenorrhoea** should be regarded as a pituitary adenoma until proven otherwise.
- ▶ **Bone:** screen BMD in chronic hypogonadal hyperprolactinaemia.

- ▶ **Psychiatric link:** antipsychotic-induced hyperprolactinaemia (esp. risperidone) is common; manage by supervised drug switch/dose titration with the prescriber, as DAs may aggravate psychosis.

High-yield exam pointers

- ▶ PRL is unique among pituitary hormones in being under **dominant inhibitory (dopaminergic D2) control** → stalk lesions cause hyperprolactinaemia and DAs treat it.
- ▶ **>200 µg/L = prolactinoma almost certain**; mild rise (30–100) = drugs/stalk/hypothyroid/renal.
- ▶ **Microprolactinoma F:M 20:1; macroadenoma ~1:1**; men present with larger tumours and mass effects.
- ▶ Two assay traps: **hook effect** (dilute the sample) and **macroprolactinemia** (PEG precipitation).
- ▶ **Cabergoline** > bromocriptine for efficacy/tolerability; **bromocriptine** preferred in pregnancy.
- ▶ DA shrinks macroprolactinomas dramatically — *medical therapy is first-line even for large tumours*, unlike most other macroadenomas.
- ▶ High-dose cabergoline → **valvular regurgitation** risk; baseline echocardiogram.
- ▶ **Primary hypothyroidism** raises PRL via TRH — corrected by levothyroxine, not a DA.
- ▶ Up to 30% of **idiopathic hyperprolactinaemia** resolves spontaneously.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Pituitary Tumor Syndromes” (Hyperprolactinemia, Galactorrhea, Prolactinoma; Table 392-5 Etiology) and “Physiology of Anterior Pituitary Hormones” (Prolactin synthesis/secretion/action; dopaminergic control).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Pituitary Adenomas and Masses” (causes of hyperprolactinemia, hook effect, macroprolactin/PEG, giant prolactinoma, dopamine-agonist treatment data including cabergoline vs bromocriptine).
- ▶ **CMDT 2026** — “Disorders of the Pituitary, Thyroid, & Adrenal Glands” (current management, pregnancy strategy, surgical/recurrence data).



Hypoglycaemia in Non-Diabetics

Asked in: Paper IV Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Hypoglycaemia* is a plasma glucose concentration low enough to cause symptoms or signs of impaired brain function, the diagnosis being secured by *Whipple's triad*: (1) symptoms/signs consistent with hypoglycaemia, (2) a reliably measured low plasma glucose, and (3) relief after the glucose level is raised. While hypoglycaemia is common in insulin-, sulfonylurea- or

glinide-treated diabetes, it is a **distinctly uncommon clinical event in persons without diabetes** because of highly efficient counter-regulatory defences. Consequently, a systematic evaluation is justified in a non-diabetic person *only* when Whipple's triad is documented — investigating an isolated low reading exposes the patient to needless cost and harm.

Glucose counter-regulation — the framework

- ▶ The brain is an **obligate glucose user**; it cannot synthesise glucose or store more than a few minutes' supply, so it needs a continuous arterial supply. Fasting plasma glucose is normally ~70–110 mg/dL, the lower physiological limit being ~70 mg/dL (3.9 mmol/L).
- ▶ Between meals, euglycaemia is sustained by **hepatic glycogenolysis** (stores last ~8 h) and **hepatic + renal gluconeogenesis** (precursors: lactate, alanine/glutamine, glycerol).
- ▶ A hierarchy of defences with defined **glycaemic thresholds** is activated as glucose falls (Table 418-2):

Response	Glycaemic threshold mg/dL (mmol/L)	Role
↓ Insulin	80–85 (4.4–4.7)	First defence — primary regulatory factor
↑ Glucagon	65–70 (3.6–3.9)	Second defence — primary counter-regulatory hormone (↑ glycogenolysis, gluconeogenesis)
↑ Epinephrine	65–70 (3.6–3.9)	Third defence — becomes <i>critical</i> when glucagon is deficient
↑ Cortisol & GH	65–70 (3.6–3.9)	Support only <i>prolonged</i> (>4 h) hypoglycaemia; not critical acutely
Symptoms	50–55 (2.8–3.1)	Behavioural defence (food ingestion)
↓ Cognition	<50 (<2.8)	Neuroglycopenia

- ▶ Thresholds are **dynamic**: they shift upward in poorly controlled diabetes and downward with recurrent hypoglycaemia (insulinoma, intensively-treated diabetes).

Clinical manifestations

- ▶ **Neuroglycopenic** (direct CNS glucose deprivation): behavioural change, confusion, fatigue, blurred vision/diplopia, slurred speech, seizures, focal deficits, loss of consciousness, cardiac arrhythmia and, if severe, death. These dominate *fasting* hypoglycaemia and insulinoma.
- ▶ **Neurogenic / autonomic** (sympathoadrenal discharge): *adrenergic* — palpitations, tremor, anxiety; *cholinergic* — sweating, hunger, paraesthesiae. These herald *postprandial* hypoglycaemia.

- Signs: **diaphoresis and pallor**, tachycardia and raised systolic BP (may be blunted with recurrent episodes / hypoglycaemia unawareness). Symptoms are non-specific — attribution requires Whipple's triad.

Aetiological classification (Endocrine Society / Harrison Table 418-1)

The modern classification separates the **ill or medicated** patient from the **seemingly well** individual rather than fasting vs postprandial.

Category	Causes
1. Drugs (commonest)	Insulin, insulin secretagogues, alcohol ; others — ACE-inhibitors/ARBs, β -blockers, quinolones (<i>gatifloxacin</i> , <i>levofloxacin</i>), pentamidine, quinine, indomethacin, sulfonamides, salicylates, tramadol
2. Critical illness	Hepatic (rapid massive necrosis, e.g. toxic hepatitis), renal or cardiac failure; sepsis ; inanition / starvation
3. Hormone deficiency	Cortisol (Addison's, hypopituitarism), growth hormone (children); combined glucagon + epinephrine in insulin-deficient diabetes
4. Non-islet-cell tumour (NICTH)	Large mesenchymal / epithelial tumours (hepatoma, adrenocortical carcinoma, carcinoid) — “ big IGF-II ”
5. Endogenous hyperinsulinism	Insulinoma; functional β -cell disorders (nesidioblastosis); noninsulinoma pancreatogenous hypoglycaemia syndrome (NIPHS); post-gastric-bypass hypoglycaemia; insulin / insulin-receptor autoantibody; insulin secretagogues
6–10. Others	Inborn errors (glycogenoses, fatty-acid oxidation defects, gluconeogenic enzyme defects); exercise; accidental/surreptitious/malicious; prolonged fasting; pregnancy

Key mechanisms to write:

- **Alcohol** blocks gluconeogenesis but not glycogenolysis (NADH:NAD⁺ shift). Hypoglycaemia follows a binge with little food once glycogen is depleted; glucagon is therefore ineffective.
- **Sepsis** — cytokine-driven $\uparrow$ glucose utilisation in macrophage-rich tissues (liver, spleen, lung) outstrips production.
- **Cortisol deficiency** — impaired gluconeogenesis + glycogen depletion (substrate-limited).
- **NICTH** — incompletely processed **pro-IGF-II** evades binding proteins, accesses tissues; insulin is *appropriately suppressed*, IGF-II:IGF-I ratio is **high**.

Endogenous hyperinsulinism & insulinoma

- The hallmark is **failure of insulin secretion to fall to low levels during hypoglycaemia**.

- ▶ **Insulinoma:** incidence ~1 in 250,000 patient-years; >90% **benign**, >99% **intra-pancreatic**, usually <2 cm; median age 50 y (3rd decade if part of MEN-1). Presents with fasting neuroglycopenia and weight gain.
- ▶ **Localisation:** CT/MRI/transabdominal US detect ~70–80%; **endoscopic ultrasound sensitivity** ~90%; ⁶⁸Ga-DOTA / GLP-1-receptor (exendin) imaging and, if needed, **selective intra-arterial calcium stimulation** with hepatic-vein insulin sampling regionalise the tumour; intra-operative US is near-definitive.
- ▶ **Variants:** *nesidioblastosis* (diffuse β -cell hypertrophy/hyperplasia); *NIPHS* (postprandial, imaging-negative, diagnosed by calcium-stimulation); *post-Roux-en-Y-gastric-bypass* late dumping (exaggerated GLP-1/insulin, 2–4 h post-meal); *insulin autoimmune syndrome* (**Hirata disease** — anti-insulin antibody, HLA-DR4, Asians, methimazole / sulfhydryl drugs); insulin-receptor agonist antibody (with acanthosis nigricans).

Diagnostic approach

- ▶ **Step 1** — Document Whipple's triad with a **laboratory** glucose (not a glucose meter); exclude *pseudohypoglycaemia* (continued ex-vivo glycolysis — leukocytosis/erythrocytosis/thrombocytosis, delayed separation; collect in NaF tube).
- ▶ **Step 2** — Review history for **drugs, critical illness, hormone deficiency, NICTH** (these explain most cases).
- ▶ **Step 3 (seemingly well)** — During spontaneous or provoked hypoglycaemia (plasma glucose <55 mg/dL / 3.0 mmol/L) measure glucose, **insulin, C-peptide, proinsulin, β -hydroxybutyrate**, oral hypoglycaemic-agent screen, insulin antibodies, and the glucose response to 1.0 mg IV glucagon. Provoke with a **prolonged supervised fast (up to 72 h)** for fasting symptoms or a **5-h mixed-meal test** for postprandial symptoms.

Critical diagnostic thresholds for endogenous hyperinsulinism (glucose <55 mg/dL):

Test	Hyperinsulinism cut-off
Insulin	$\geq 3 \mu\text{U/mL}$ ($\geq 18 \text{ pmol/L}$)
C-peptide	$\geq 0.6 \text{ ng/mL}$ ($\geq 0.2 \text{ nmol/L}$)
Proinsulin	$\geq 5.0 \text{ pmol/L}$
β -hydroxybutyrate	$\leq 2.7 \text{ mmol/L}$ (suppressed)
Glucose rise after IV glucagon (1 mg)	$> 25 \text{ mg/dL}$ ($> 1.4 \text{ mmol/L}$)

- ▶ **Distinguishing the cause** (all show inappropriately high insulin):
 - *Insulinoma / nesidioblastosis* — $\uparrow$ insulin, $\uparrow$ **C-peptide**, $\uparrow$ **proinsulin**, OHA screen negative.
 - *Sulfonylurea/glinide* — identical pattern but OHA screen **positive**.

- *Exogenous insulin (factitious)* — ↑ insulin but **low C-peptide & proinsulin**; **insulin : C-peptide molar ratio >1**.
- *Insulin autoimmune* — very high insulin, **insulin antibody positive**.
- *NICTH / IGF-mediated* — insulin, C-peptide, proinsulin **all suppressed**, β-hydroxybutyrate low, ↑ pro-IGF-II and IGF-II:IGF-I ratio.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Glucose counter-regulation cascade** (Fig 418-1): central box “Arterial glucose ↓” with arrows to — *Pancreas* (↓ Insulin = 1st defence; α-cell ↑ Glucagon = 2nd defence) → *Liver/Kidney* “Glucose production”; *Adrenal medulla* ↑ Epinephrine (3rd defence) and *Sympathetic neurons* ↑ Norepinephrine + Acetylcholine → “Symptoms”; *Pituitary–adrenal cortex* ↑ GH and ↑ Cortisol (prolonged). Label the threshold ladder: ↓Insulin 80–85 → Glucagon/Epi 65–70 → Symptoms 50–55 → ↓Cognition <50 mg/dL.
- ▶ **Diagnostic flow-box**: “Whipple’s triad +” → branch “Ill/Medicated” (drugs, critical illness, hormone deficiency, NICTH) vs “Seemingly well” → insulin/C-peptide/proinsulin/β-OHB/OHA-screen → label end-points: *Insulinoma*, *Sulfonylurea*, *Exogenous insulin (low C-peptide)*, *Insulin-autoimmune*, *NICTH*.

Clinical / Diagnostic significance

- ▶ **Always exclude drugs first** — insulin, secretagogues and alcohol cause most non-diabetic hypoglycaemia; consider surreptitious/factitious use (health-care workers, diabetic relatives).
- ▶ **Urgent treatment**: conscious — **15–20 g oral glucose**; unable to swallow — **IV 25 g dextrose** (50 mL of 50%) then infusion; if no IV access — **glucagon 1.0 mg SC/IM** (ineffective in glycogen-depleted/alcoholic patients, less useful in T2DM as it also triggers insulin). **Octreotide** suppresses insulin in **sulfonylurea overdose**. All raise glucose transiently — feed early.
- ▶ **Definitive therapy by mechanism**: stop/reduce offending drug; treat critical illness; replace cortisol/GH; debulk NICTH (± glucocorticoid/GH); **surgical resection cures insulinoma** — *diazoxide* (300–400 mg/day) or *octreotide/lanreotide*, and *everolimus* (mTOR inhibitor) for unresectable disease; partial pancreatectomy for nesidioblastosis/NIPHS; dietary measures (low-glycaemic, α-glucosidase inhibitor) ± uncooked cornstarch for post-bypass and autoimmune forms.
- ▶ Severe hypoglycaemia is **proatherothrombotic** (↑ platelet aggregation, ↑ PAI-1, ↓ nitric-oxide vasodilatation) and carries excess cardiovascular morbidity/mortality.

High-yield exam pointers

- ▶ **Whipple’s triad** is mandatory before labelling a non-diabetic hypoglycaemic — protects against pseudohypoglycaemia.

- ▶ Defence hierarchy: ↓insulin → ↑glucagon → ↑epinephrine; epinephrine is *critical when glucagon is deficient*; cortisol/GH only for prolonged episodes.
- ▶ **Drugs (incl. alcohol) are the commonest cause**; alcohol *blocks gluconeogenesis, spares glycogenolysis*.
- ▶ Endogenous hyperinsulinism cut-offs at glucose <55 mg/dL: insulin ≥3 μU/mL, C-peptide ≥0.6 ng/mL, proinsulin ≥5 pmol/L, β-OHB ≤2.7 mmol/L, post-glucagon glucose rise >25 mg/dL.
- ▶ **Low C-peptide + high insulin = exogenous (factitious) insulin**; high C-peptide + positive OHA screen = sulfonylurea.
- ▶ **Insulinoma**: >90% benign, >99% pancreatic, <2 cm, MEN-1 association; EUS sensitivity ~90%; cured by surgery, diazoxide if unresectable.
- ▶ **NICTH** = “big IGF-II”, high IGF-II:IGF-I ratio, suppressed insulin/C-peptide.
- ▶ **Hirata disease** = insulin autoimmune hypoglycaemia (anti-insulin antibody, HLA-DR4, sulfhydryl drugs/methimazole).
- ▶ **Post-gastric-bypass / late dumping**: postprandial (2–4 h), GLP-1-driven hyperinsulinism.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Hypoglycemia” (Stephen N. Davis): Whipple’s triad, glucose counter-regulation and thresholds (Table 418-2), causes (Table 418-1), diagnostic criteria, insulinoma and treatment.
- ▶ **Williams Textbook of Endocrinology, 15e** — “Hypoglycemia” (Arbeláez & Rickels): clinical classification (ill/medicated vs seemingly well), pattern-of-findings table, NIPHS / nesidioblastosis / post-gastric-bypass, insulin-autoimmune, prolonged-fast and mixed-meal protocols, insulinoma localisation.
- ▶ **CMDT 2026** — “Diabetes Mellitus & Hypoglycemia”: 72-h fast diagnostic criteria (Table 32-12) and protocol, insulin:C-peptide ratio in factitious hypoglycaemia, Hirata disease (HLA alleles), drug- and ethanol-induced hypoglycaemia, diazoxide/octreotide management.



Hypoglycemia

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Hypoglycemia is a clinical syndrome of low plasma glucose sufficient to cause symptoms and resolving when glucose is restored. It is rigorously defined by **Whipple’s triad**: (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose measured by a precise method, and (3) relief of symptoms after the glucose is raised. The lower limit of fasting plasma glucose is normally ~70 mg/dL (~3.9 mmol/L). It is most often iatrogenic — caused by insulin or insulin secretagogues

used to treat diabetes — and should be considered in any patient with confusion, an altered level of consciousness, or a seizure. Severe hypoglycemia increases the risk of serious cardiovascular events and death.

Physiology of glucose counterregulation

- ▶ Glucose is an **obligate fuel for the brain**, which cannot synthesise glucose or store more than a few minutes' supply; it needs a continuous arterial supply.
- ▶ Plasma glucose is kept **~70–110 mg/dL (3.9–6.1 mmol/L)** fasting by hepatic glycogenolysis and hepatic/renal gluconeogenesis. Hepatic glycogen lasts only **~8 h** (less with exercise/illness), after which gluconeogenesis predominates (precursors: lactate, alanine, glutamine from muscle; glycerol from adipose lipolysis).
- ▶ Defences against falling glucose follow a tiered, threshold-based sequence:

Defence	Mediator	Glycemic threshold mg/dL (mmol/L)	Action
First	↓ Insulin secretion	80–85 (4.4–4.7)	↑ glycogenolysis & gluconeogenesis; ↑ lipolysis
Second	↑ Glucagon (pancreatic α-cell)	65–70 (3.6–3.9)	↑ hepatic glycogenolysis & gluconeogenesis
Third	↑ Epinephrine (adrenomedullary)	65–70 (3.6–3.9)	↑ glucose production, ↓ clearance; critical when glucagon deficient
Late/slow	↑ Cortisol & GH	50–55 (2.8–3.1)	Support production; <i>no role in acute defence</i> (act only after ~4 h)
Behavioural	Symptoms	—	Recognition → food ingestion
Failure	↓ Cognition	<50 (<2.8)	Compromises behavioural defence

- ▶ *A fall in insulin is the first defence; glucagon the second; epinephrine the third (and pivotal when glucagon is lacking).* Cortisol and GH are **not** required for defence against acute hypoglycemia in adults.
- ▶ Thresholds are **dynamic**: they shift higher in poorly controlled diabetes (symptoms near normoglycemia) and lower with recurrent hypoglycemia (insulinoma, intensively treated diabetes).

Classification / Causes (across the life span)

Etiology is best framed by clinical context — the “ill or medicated” vs the “seemingly well” patient (Table 418-1).

Ill or medicated individual	Seemingly well individual
1. Drugs — insulin or insulin secretagogues; alcohol ; others (ACE inhibitors, ARBs, β -blockers, quinolones, indomethacin, quinine, sulfonamides)	5. Endogenous hyperinsulinism — insulinoma; functional β -cell disorder (<i>nesidioblastosis</i>); noninsulinoma pancreatogenous hypoglycemia (NIPHS); post-gastric-bypass hypoglycemia; insulin/insulin-receptor autoimmune; secretagogues; GLP-1 RA + insulin/secretagogue
2. Critical illness — hepatic, renal or cardiac failure; sepsis; inanition	6. Disorders of gluconeogenesis & fatty-acid oxidation
3. Hormone deficiency — cortisol; growth hormone; glucagon + epinephrine (in insulin-deficient diabetes)	7. Exercise
4. Non-islet-cell tumour (e.g., mesenchymal/epithelial tumours)	8. Accidental, surreptitious or malicious ; 9. Prolonged fasting ; 10. Pregnancy

- ▶ **Drugs (commonest):** insulin/secretagogues suppress glucose production and $\uparrow$ utilisation. **Ethanol blocks gluconeogenesis but not glycogenolysis**, so alcohol-induced hypoglycemia follows a multi-day binge with poor intake and glycogen depletion.
- ▶ **Critical illness:** rapid hepatic destruction (the major site of glucose production), renal failure (reduced insulin clearance + fewer precursors), cardiac failure, and **sepsis** (cytokine-driven $\uparrow$ utilisation).
- ▶ **Non-islet-cell tumour:** large hepatomas, adrenocortical carcinomas, carcinoids — overproduce incompletely processed “**big IGF-II**” with a **high IGF-II : IGF-I ratio**; endogenous insulin is appropriately suppressed.
- ▶ **Inborn errors** (mostly infancy, occasionally adults): glycogen storage disease types 0, I, III, IV and Fanconi-Bickel syndrome (fasting); fatty-acid oxidation defects; glucokinase/SUR1/Kir6.2 mutations and hereditary fructose intolerance (postprandial).

Clinical manifestations

- ▶ **Neuroglycopenic** (direct CNS glucose deprivation): behavioural changes, confusion, fatigue, **seizure**, **loss of consciousness**, **cardiac arrhythmias**, and, if severe, death; transient focal deficits occur occasionally, permanent deficits are rare.
- ▶ **Neurogenic / autonomic** (sympathoadrenal discharge):
 - **Adrenergic** (norepinephrine): palpitations, tremor, anxiety.
 - **Cholinergic** (acetylcholine): sweating, hunger, paresthesias.
- ▶ **Signs:** diaphoresis and pallor; heart rate and systolic BP usually rise (may be blunted after recent recurrent episodes).

- ▶ Symptoms are **non-specific** — attribution requires a documented low glucose with resolution on correction (Whipple's triad).

Hypoglycemia in diabetes & HAAF

- ▶ Hypoglycemia is the **limiting factor in glycemic management of diabetes**. Patients with T1DM average ~2 symptomatic episodes/week and ≥ 1 severe episode/year; an estimated **6–10% of people with T1DM die as a result of hypoglycemia**.
- ▶ **Conventional risk factors** = relative or absolute insulin excess: excessive/ill-timed/wrong-type insulin or secretagogue; reduced glucose influx (missed meals, fasting); increased utilisation (exercise); increased insulin sensitivity; reduced glucose production (alcohol); reduced insulin clearance (renal failure).
- ▶ **Hypoglycemia-Associated Autonomic Failure (HAAF)** — recent antecedent hypoglycemia (or prior exercise/sleep) produces two linked syndromes that drive a vicious cycle of recurrent hypoglycemia:
 - **Defective glucose counterregulation** — loss of the insulin-decrement and glucagon-increment, plus an attenuated epinephrine response $\rightarrow \geq 25$ -fold greater risk of severe iatrogenic hypoglycemia.
 - **Hypoglycemia unawareness** — attenuated sympathoadrenal (largely sympathetic neural) response $\rightarrow$ loss of warning symptoms $\rightarrow \sim 6$ -fold increased risk.
- ▶ HAAF is functional and **reversible by ~2–3 weeks of scrupulous avoidance of hypoglycemia**, distinguishing it from structural, irreversible diabetic autonomic neuropathy. Trials confirming severe hypoglycemia at HbA1c 8–10%: ACCORD (stopped early for excess mortality), ADVANCE, VADT, ORIGIN; in-hospital NICE-SUGAR showed harm from tight control — hence inpatient targets of 140–180 mg/dL.

Diagnostic approach & investigations

- ▶ **Document Whipple's triad** — draw blood for glucose *before* giving glucose; measure plasma glucose by a precise (laboratory) method. Handheld/continuous glucose monitors are **not** diagnostic at low values.
- ▶ Exclude **pseudohypoglycemia**: artefactually low glucose from ex-vivo metabolism in leukocytosis/erythrocytosis/thrombocytosis or delayed serum separation; a low glucose without corresponding symptoms suggests an artefact.
- ▶ **Diagnose the mechanism** — in the seemingly well patient, work up **endogenous hyperinsulinism**. During a spontaneous or provoked episode (up to a 72-h supervised fast or mixed meal) with plasma glucose < 55 mg/dL (< 3.0 mmol/L) and symptoms, the critical findings are:

Analyte	Hyperinsulinism cut-off
Plasma insulin	$\geq 3 \mu\text{U/mL}$ ($\geq 18 \text{ pmol/L}$)
C-peptide	$\geq 0.6 \text{ ng/mL}$ ($\geq 0.2 \text{ nmol/L}$)
Proinsulin	$\geq 5.0 \text{ pmol/L}$
β -hydroxybutyrate	$\leq 2.7 \text{ mmol/L}$
Glucose rise after IV glucagon 1.0 mg	$> 25 \text{ mg/dL}$ ($> 1.4 \text{ mmol/L}$)
Sulfonylurea/glinide screen	Negative

- **Differentiating hyperinsulinism:** secretagogue ingestion $\rightarrow$ **high** C-peptide (positive drug screen distinguishes it); **exogenous insulin** $\rightarrow$ hypoglycemia with **low** C-peptide (suppressed endogenous secretion); non-islet-cell tumour $\rightarrow$ **suppressed** insulin/C-peptide with high big-IGF-II.
- **Insulinoma:** yearly incidence ~ 1 in 250,000; **>90% benign**; median age 50 (third decade and multiple if part of MEN-1); **>99% intrapancreatic**, usually $< 2 \text{ cm}$. Imaging: CT/MRI detect $\sim 70\text{--}80\%$, endoscopic ultrasound sensitivity $\sim 90\%$, somatostatin-receptor scintigraphy $\sim$ half; selective arterial calcium stimulation regionalises diffuse disease; intra-operative ultrasound localises non-palpable tumours.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Tiered counterregulation cascade (vertical arrow of falling glucose):** label glucose levels $80\text{--}85 \text{ mg/dL} \rightarrow \downarrow$ Insulin (1st defence); $65\text{--}70 \text{ mg/dL} \rightarrow \uparrow$ Glucagon (2nd) and $\uparrow$ Epinephrine (3rd); $50\text{--}55 \text{ mg/dL} \rightarrow \uparrow$ Cortisol & GH; $< 50 \text{ mg/dL} \rightarrow$ Neuroglycopenia / $\downarrow$ Cognition. Side-label Symptoms (autonomic warning) between the epinephrine and cognition tiers.
- **HAAF vicious-cycle loop:** label *Recurrent hypoglycemia* $\rightarrow \downarrow$ *Adrenomedullary epinephrine* + $\downarrow$ *Sympathetic neural response* $\rightarrow$ *Defective glucose counterregulation* + *Hypoglycemia unawareness* $\rightarrow$ (back to) *Recurrent hypoglycemia*; annotate inputs *Antecedent hypoglycemia* / *Exercise* / *Sleep*.

Clinical / Diagnostic significance

- **Urgent treatment:** if conscious, oral $15\text{--}20 \text{ g}$ glucose (tablets/juice/candy); if neuroglycopenic, IV glucose 25 g then an infusion titrated to serial glucoses. If no IV access, **SC/IM glucagon 1.0 mg** — but glucagon is *ineffective in glycogen-depleted states* (alcohol) and *less useful in T2DM* (it also stimulates insulin secretion). **Octreotide** suppresses insulin secretion in **sulfonylurea-induced** hypoglycemia. All raise glucose only transiently — the patient must eat to replenish glycogen.

- ▶ **Prevention of recurrence** is mechanism-specific: stop/reduce the offending drug (sulfonylurea effect may last **hours-to-days**); treat the critical illness; replace deficient cortisol/GH; debulk a non-islet-cell tumour ($\pm$ glucocorticoid/GH).
- ▶ **Insulinoma**: surgical resection is **curative**; for unresectable tumours or functional β -cell disorders use **diazoxide** (inhibits insulin secretion), **octreotide**, or **everolimus** (mTOR inhibitor); partial pancreatectomy may be needed for diffuse disease. Frequent feeds, **uncooked cornstarch at bedtime**, or overnight intragastric glucose help refractory cases.
- ▶ Risk-reduction in diabetes: second-generation basal/prandial analogue insulins, GLP-1 ($\pm$ GIP) agonists added to basal insulin, **continuous glucose monitoring** with predictive low-glucose suspend / closed-loop “artificial pancreas,” structured patient education, and individualised, incrementally tightened HbA1c goals.

High-yield exam pointers

- ▶ **Whipple’s triad** is mandatory for diagnosis; fasting glucose lower limit ~ 70 mg/dL.
- ▶ Defence order: $\downarrow$ **insulin (1st)** $\rightarrow$ **glucagon (2nd)** $\rightarrow$ **epinephrine (3rd)**; cortisol/GH play *no role* in acute defence.
- ▶ **Ethanol blocks gluconeogenesis, not glycogenolysis** $\rightarrow$ glucagon is useless in alcohol-induced hypoglycemia.
- ▶ **C-peptide high** = secretagogue/insulinoma; **C-peptide low** = exogenous (factitious) insulin; **insulin + C-peptide suppressed + big-IGF-II high** = non-islet-cell tumour.
- ▶ Hyperinsulinism criteria (glucose < 55 mg/dL): insulin ≥ 3 μ U/mL, C-peptide ≥ 0.6 ng/mL, proinsulin ≥ 5 pmol/L, β -OHB ≤ 2.7 mmol/L; **72-h fast** is the classic provocation.
- ▶ **Insulinoma**: $>90\%$ benign, $>99\%$ intrapancreatic, <2 cm; consider **MEN-1**; resection curative.
- ▶ **HAAF** = defective counterregulation (≥ 25 -fold risk) + hypoglycemia unawareness (~ 6 -fold risk); **reversible in 2–3 weeks** of avoidance.
- ▶ Treatment ladder: oral 15–20 g $\rightarrow$ IV 25 g glucose $\rightarrow$ glucagon 1 mg IM/SC; octreotide for sulfonylurea overdose.

SOURCE & COVERAGE

Harrison 22e — Ch 418 “Hypoglycemia” (Stephen N. Davis). Fully covers the asked topic — definition, counterregulatory physiology, etiologic classification (Table 418-1), clinical features, HAAF, diagnostic evaluation including the biochemical criteria for endogenous hyperinsulinism, insulinoma, and treatment. No coverage gap; all numbers, thresholds and drug details above are taken verbatim from the chapter.



Hypoglycemia without diabetes

Asked in: Paper IV Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Hypoglycemia is a plasma glucose concentration low enough to cause symptoms or signs of impaired brain function and/or sympathoadrenal activation. Unlike in insulin-, sulfonylurea- or glinide-treated diabetes (where it is common and iatrogenic), hypoglycemia in a person **without diabetes is a distinctly uncommon clinical event**, because the normal physiologic and behavioural defences are highly effective. A genuine non-diabetic hypoglycemic disorder is accepted only when **Whipple's triad** is documented: (1) symptoms/signs consistent with hypoglycemia, (2) a low, reliably-measured plasma glucose, and (3) relief of symptoms after the glucose is raised. A plasma glucose **<55 mg/dL (3.0 mmol/L)** is unequivocally low.

Physiology of glucose counterregulation (the framework for diagnosis)

- ▶ Glucose is an **obligate fuel for the brain**, which cannot synthesise glucose, store more than a few minutes' supply as glycogen, or use circulating fuels at physiologic concentrations; brain oxidation accounts for ~25% of basal metabolic rate and >50% of whole-body glucose use.
- ▶ Endogenous glucose comes from **hepatic glycogenolysis** (stores last only ~8 h) and **hepatic + renal gluconeogenesis** (precursors: lactate/pyruvate, alanine and glutamine, glycerol). Only liver and kidney express **glucose-6-phosphatase**.
- ▶ Defences are deployed in a strict hierarchy as glucose falls (glycemic thresholds, Harrison Table 418-2):

Response	Glycemic threshold mg/dL (mmol/L)	Role
↓ Insulin (β -cell)	80–85 (4.4–4.7)	First defence; primary regulatory factor
↑ Glucagon (α -cell)	65–70 (3.6–3.9)	Second defence; primary counterregulatory factor
↑ Epinephrine (adrenomedullary)	65–70 (3.6–3.9)	Third defence; critical when glucagon deficient
↑ Cortisol & growth hormone	65–70 (3.6–3.9)	Support prolonged (>4 h) hypoglycemia; not critical for acute defence
Neurogenic symptoms	50–55 (2.8–3.1)	Behavioural defence (carbohydrate ingestion)
↓ Cognition	<50 (<2.8)	Neuroglycopenia begins

- ▶ In the non-diabetic, these mechanisms are intact, so demonstrating hypoglycemia mandates a search for a pathology that overwhelms them.

Clinical manifestations

- ▶ **Neuroglycopenic** (direct CNS glucose deprivation): behavioural change, confusion, fatigue/drowsiness, blurred vision/diplopia, difficulty speaking, focal deficits, seizure, loss of consciousness, and—if severe—cardiac arrhythmia or death. These are the more compelling features in non-diabetic disease.
- ▶ **Neurogenic (autonomic)** from sympathoadrenal discharge: *adrenergic* (palpitations, tremor, anxiety) and *cholinergic* (sweating, hunger, paraesthesiae). Signs: **diaphoresis and pallor**; modest tachycardia and rise in systolic BP.
- ▶ Symptoms are **non-specific**; their attribution to hypoglycemia requires fulfilment of Whipple's triad.

Aetiological classification (Harrison Table 418-1 / Endocrine Society)

The clinical categorisation separates the **ill or medicated** patient from the **seemingly well** patient.

Category	Causes
Drugs (commonest)	Insulin, insulin secretagogues (covert/accidental), alcohol ; others: ACE inhibitors, ARBs, β -blockers, quinolones (gatifloxacin, levofloxacin), quinine, indomethacin, pentamidine, sulfonamides/cotrimoxazole, IGF-1
Critical illness	Hepatic, renal or cardiac failure; sepsis ; inanition/starvation
Hormone deficiency	Cortisol (Addison's disease, hypopituitarism), growth hormone (in children); combined glucagon + epinephrine (in insulin-deficient diabetes only)
Non-islet cell tumour (NICTH)	Large mesenchymal/epithelial tumours (hepatoma, adrenocortical carcinoma, carcinoid) secreting "big" pro-IGF-II
Endogenous hyperinsulinism	Insulinoma; functional β -cell disorders (nesidioblastosis), NIPHS, post-gastric-bypass hypoglycemia; insulin/insulin-receptor autoantibodies; sulfonylurea/glinide
Other	Inborn errors (glycogenoses, fatty-acid oxidation/gluconeogenesis defects), exercise-induced, prolonged fasting, pregnancy; accidental/surreptitious/malicious

Key mechanisms to write:

- ▶ **Alcohol** inhibits **gluconeogenesis but not glycogenolysis**; hypoglycemia follows a binge with poor food intake (glycogen-depleted state). Ethanol is usually detectable in blood. (Glucagon is therefore ineffective in alcohol-induced hypoglycemia.)

- ▶ **Sepsis/critical illness:** cytokine-driven ↑ glucose utilisation in macrophage-rich tissue (liver, spleen, lung) outstrips production; compounded by hepatic/renal hypoperfusion and inanition. Hepatogenous hypoglycemia needs rapid, massive liver destruction (e.g., toxic hepatitis). Renal failure reduces insulin clearance and gluconeogenic precursor supply.
- ▶ **NICTH:** overproduction of incompletely-processed **pro-IGF-II** (“**big IGF-II**”) that escapes binding proteins, accessing tissue and acting like insulin; endogenous insulin is **appropriately suppressed**; the **IGF-II:IGF-I ratio is high** and GH/IGF-1 are low.
- ▶ **Hormone deficiency:** isolated GH deficiency does **not** cause hypoglycemia in adults; cortisol deficiency causes substrate-limited gluconeogenesis with glycogen depletion (consider Addison’s in a T1DM with worsening hypoglycemia + hyperpigmentation/hyponatraemia).

Endogenous hyperinsulinism and insulinoma (the seemingly-well patient)

- ▶ The hallmark is **failure of insulin secretion to fall** as glucose drops—i.e., insulin, C-peptide and proinsulin are *inappropriately high* for the low glucose.
- ▶ **Insulinoma** is the prototype: incidence ~1 in 250,000 patient-years; >90% **benign, solitary**; >99% **intrapancreatic**; usually small (<2 cm in 90%); median age 50 (sporadic), third decade if part of MEN-1 (~<10% have malignancy, multiplicity or MEN-1). Presents with **fasting** neuroglycopenia (occasionally postprandial) and weight gain.
- ▶ **Nesidioblastosis** – diffuse β-cell hypertrophy/hyperplasia causing fasting hyperinsulinemic hypoglycemia, clinically indistinguishable from insulinoma; imaging negative.
- ▶ **NIPHS** (noninsulinoma pancreatogenous hypoglycemia) – diffuse islet hyperfunction with **postprandial** hypoglycemia; imaging negative, diagnosed by positive **selective arterial calcium stimulation test**.
- ▶ **Post-gastric bypass (late dumping) hypoglycemia** – after Roux-en-Y; exaggerated GLP-1/insulin responses 2–4 h post-meal, usually >6–12 months postoperatively.
- ▶ **Autoimmune:** anti-insulin antibody (late postprandial; very high insulin with **insulin:C-peptide molar ratio >1**, HLA-DR4, Asians) or agonist insulin-receptor antibody.
- ▶ **Factitious/accidental secretagogue or insulin** must always be excluded.

Diagnostic approach

- ▶ **Step 1 – Document Whipple’s triad** with a *laboratory* glucose (never a glucometer); a normal glucose during a typical spell excludes hypoglycemia. Beware **pseudohypoglycemia** (ex-vivo glycolysis with leukocytosis/erythrocytosis/thrombocytosis or delayed separation—use NaF tube on ice).
- ▶ **Step 2 – Review for drugs, critical illness, hormone deficiency, NICTH** (history, examination, routine labs) — these explain most cases.

- ▶ **Step 3** – In a seemingly well patient, during spontaneous (or provoked) hypoglycemia draw the “critical sample”: plasma glucose, insulin, C-peptide, proinsulin, β -hydroxybutyrate, sulfonylurea/meglitinide screen, insulin antibodies; then give **1.0 mg IV glucagon** and measure the glucose response.
- ▶ If no spontaneous event: **72-hour supervised fast** (fasting history) or **5-h mixed-meal test** (postprandial history). ~2/3 of insulinomas declare in <24 h and most within 48 h; an OGTT is of no value.

Diagnostic interpretation when glucose <55 mg/dL (3.0 mmol/L) (Endocrine Society criteria):

Finding	Insulin (μ U/mL)	C-peptide (ng/mL)	Proinsulin (pmol/L)	β -OHB (mmol/L)	Glucose rise after glucagon	Other
Insulinoma / nesidioblastosis	≥ 3	≥ 0.6	≥ 5	≤ 2.7	>25 mg/dL	screens negative
Sulfonylurea/glinide	≥ 3	≥ 0.6	≥ 5	≤ 2.7	>25 mg/dL	agent positive
Exogenous insulin (factitious)	$\gg 3$	low (<0.6)	low (<5)	≤ 2.7	>25 mg/dL	C-peptide suppressed
Insulin autoimmune	$\gg 3$	high	high	≤ 2.7	>25 mg/dL	insulin antibody +
NICTH / IGF-mediated	<3	<0.6	<5	≤ 2.7	>25 mg/dL	$\uparrow$ pro-IGF-II, $\uparrow$ IGF-II:IGF-I
Not insulin/IGF-mediated	<3	<0.6	<5	>2.7	<25 mg/dL	—

- ▶ A >25 mg/dL (1.4 mmol/L) glucose rise after IV glucagon and a suppressed β -OHB (≤ 2.7 mmol/L) indicate preserved glycogen and suppressed ketogenesis from insulin/IGF action.
- ▶ **Localisation of insulinoma** (after biochemical confirmation): CT/MRI/transabdominal USG (~70–80%), **endoscopic ultrasound** (~90%), somatostatin-receptor (or Ga-68 DOTATATE / GLP-1-receptor exendin) imaging, and—if equivocal—**selective intra-arterial calcium stimulation with hepatic-venous insulin sampling**; intraoperative ultrasound localises nearly all.

Treatment

- ▶ **Urgent**: if able to swallow, **15–20 g oral glucose**; if not, **IV 25 g dextrose** (50 mL of 50%) then an infusion guided by serial glucose; **glucagon 1.0 mg SC/IM** (ineffective if glycogen-depleted, e.g., alcohol; less useful in factitious sulfonylurea). Always feed afterwards to replete glycogen.

- ▶ **Cause-specific:** stop/reduce offending drug; treat critical illness; replace cortisol/GH if deficient; debulk/irradiate/chemotherapy ± glucocorticoid for NICTH.
- ▶ **Insulinoma: surgical resection is curative.** If unresectable—**diazoxide** (inhibits insulin secretion; CMDT 300–400 mg/day, up to 800 mg, with hydrochlorothiazide to offset oedema), **octreotide**, or **everolimus** (mTOR inhibitor).
- ▶ **Octreotide** specifically suppresses insulin in sulfonylurea overdose. **NIPHS/post-bypass:** low-glycaemic-index diet, α-glucosidase inhibitor, diazoxide/octreotide, partial pancreatectomy if refractory. **Autoimmune:** glucocorticoids ± immunosuppression; often self-limited. Refractory cases: frequent feeds and **uncooked cornstarch** at night.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 – Glucose counterregulatory cascade:** Falling arterial glucose → pancreas (β-cell ↓insulin = 1st defence; α-cell ↑glucagon = 2nd defence) → adrenal medulla ↑epinephrine (3rd defence) → pituitary/adrenal cortex ↑GH, ↑cortisol → liver/kidney ↑glycogenolysis + gluconeogenesis → ↑glucose production; sympathoadrenal outflow → neurogenic symptoms → carbohydrate ingestion. Label thresholds (↓insulin 80–85; glucagon/epi 65–70; symptoms 50–55 mg/dL).
- ▶ **Diagram 2 – Diagnostic flow at glucose <55 mg/dL:** branch on C-peptide (high → endogenous: insulinoma vs sulfonylurea [screen] vs autoimmune [antibody]; low → exogenous insulin or, with low insulin + high IGF-II:IGF-I → NICTH). Label insulin ≥3 μU/mL, C-peptide ≥0.6 ng/mL, proinsulin ≥5 pmol/L, β-OHB ≤2.7 mmol/L.

Clinical / Diagnostic significance

- ▶ Distinguishing **fasting** (neuroglycopenic, insulinoma/NICTH/drugs) from **postprandial** (autonomic, NIPHS/post-bypass/autoimmune) hypoglycemia directs the provocative test chosen.
- ▶ The **C-peptide/proinsulin pattern** is the single most useful discriminator: high with insulinoma and sulfonylurea, **low with exogenous insulin**—a medicolegally important clue to factitious/malicious illness (commonest in healthcare workers and relatives of diabetics).
- ▶ Insulinoma is rare but **treatable and potentially fatal**; suspect it in a healthy adult with fasting confusion misdiagnosed as epilepsy or psychiatric illness, and screen for **MEN-1** (calcium, gastrin, prolactin).

High-yield exam pointers

- ▶ **Whipple's triad** is mandatory before labelling non-diabetic hypoglycemia; glucose <55 mg/dL (3.0 mmol/L) = unequivocally low.
- ▶ Order of defences: ↓insulin → ↑glucagon → ↑epinephrine (critical when glucagon deficient); cortisol/GH are *not* critical for acute defence.

- ▶ **Drugs** (esp. insulin, secretagogues, alcohol) are the commonest cause; alcohol blocks gluconeogenesis, not glycogenolysis.
- ▶ Endogenous hyperinsulinism criteria (glucose <55): **insulin** $\geq 3 \mu\text{U/mL}$, **C-peptide** $\geq 0.6 \text{ ng/mL}$, **proinsulin** $\geq 5 \text{ pmol/L}$, **β -OHB** $\leq 2.7 \text{ mmol/L}$, **glucagon-induced glucose rise** $>25 \text{ mg/dL}$, negative sulfonyleurea screen.
- ▶ **Exogenous insulin** $\rightarrow$ **low C-peptide** (insulin:C-peptide ratio >1); **sulfonyleurea** $\rightarrow$ **high C-peptide** + **positive drug screen**.
- ▶ **NICTH** = “big” pro-IGF-II, suppressed insulin, **high IGF-II:IGF-I ratio**; mesenchymal tumours.
- ▶ **Insulinoma**: 1/250,000, $>90\%$ benign, $>99\%$ pancreatic, $<2 \text{ cm}$, EUS sensitivity $\sim 90\%$; **surgery curative**, diazoxide/octreotide if unresectable.
- ▶ **72-h supervised fast** for fasting type; **mixed-meal test** for postprandial type; **OGTT has no diagnostic role**.
- ▶ Beware **pseudohypoglycemia** (ex-vivo glycolysis) and always use a **laboratory** (not glucometer) glucose.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Hypoglycemia” (S.N. Davis): counterregulation, Whipple’s triad, Table 418-1 causes, diagnostic criteria, insulinoma epidemiology and treatment.
- ▶ **Williams Textbook of Endocrinology, 15e** — “Hypoglycemia” (Arbeláez & Rickels): physiology of defence, “Hypoglycemia in Persons Without Diabetes”, Endocrine Society diagnostic patterns (Table 39.4), prolonged-fast and mixed-meal protocols, NIPHS/post-bypass/autoimmune detail, insulinoma localisation.
- ▶ **CMDT 2026** — “Diabetes Mellitus & Hypoglycemia”: classification of hypoglycemic states, diagnostic criteria for insulinoma after a 72-hour fast (Table 32–12), supervised-fast protocol, diazoxide dosing and localisation.



Insulin Resistance

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — **Insulin resistance (IR)** is the *decreased ability of insulin to act effectively on its target tissues* — chiefly **skeletal muscle, liver and adipose tissue** — so that a normal insulin concentration produces a subnormal biological response. It is *relative* rather than absolute, because supranormal (compensatory hyperinsulinaemic) levels can still normalise plasma glucose. IR results from a combination of **genetic susceptibility, obesity and metabolic inflammation**, is the central and usually earliest lesion in **type 2 diabetes mellitus (T2DM)**, and is the most accepted **unifying hypothesis**

for the **metabolic syndrome** — linking obesity to atherogenic dyslipidaemia, hypertension, steatotic liver disease, PCOS and accelerated atherosclerotic cardiovascular disease (ASCVD).

Physiological basis and target tissues

- ▶ Insulin normally **stimulates glucose uptake in muscle and fat, suppresses hepatic glucose production, inhibits adipose-tissue lipolysis and stimulates lipoprotein lipase**; inhibition of lipolysis is the *most sensitive* pathway of insulin action.
- ▶ In IR these actions fail in a **tissue-selective** manner:
 - **Skeletal muscle** — impaired insulin-stimulated glucose utilisation; whole-body glucose disposal is **30–60% lower** than in non-diabetic individuals → drives *postprandial* hyperglycaemia.
 - **Liver** — failure of hyperinsulinaemia to suppress **gluconeogenesis** → increased hepatic glucose output (drives *fasting* hyperglycaemia) and reduced postprandial glycogen storage.
 - **Adipose tissue** — uninhibited lipolysis → increased **free fatty acid (FFA)** flux to liver and muscle.

Natural history (IR → hyperglycaemia)

- ▶ Onset is heralded by **postprandial hyperinsulinaemia** → **fasting hyperinsulinaemia** → **hyperglycaemia**.
- ▶ Pancreatic beta cells initially **compensate** by raising insulin output, keeping glucose tolerance near-normal despite resistance.
- ▶ When secretion can no longer match the degree of resistance → **IFG/IGT**, and ultimately frank **T2DM** (the *twin-defect* model: IR **plus** progressive beta-cell failure). Diabetes develops *only when insulin secretion becomes inadequate for the prevailing insulin resistance*.
- ▶ IR (reduced skeletal-muscle glucose utilisation) is demonstrable in many **non-diabetic first-degree relatives** of T2DM patients, underscoring a strong heritable component (twin concordance 70–90%).

Molecular and cellular mechanisms

- ▶ The precise molecular lesion is **not fully elucidated** but is predominantly a “**post-receptor**” defect:
 - Insulin-receptor number and **tyrosine-kinase activity** in muscle are reduced, but this is largely *secondary* to hyperinsulinaemia, not the primary fault.
 - Defective **insulin-regulated phosphorylation / dephosphorylation** of downstream signalling proteins predominates.
- ▶ **Lipotoxicity** — accumulation of lipid intermediates within myocytes impairs **mitochondrial oxidative phosphorylation**, lowers insulin-stimulated ATP production and generates **reactive oxygen species (lipid peroxides)**.

- ▶ **Metabolic (low-grade) inflammation** — adipose-resident macrophages and adipocytes secrete TNF- α , IL-6, IL-1, IL-18 and resistin and raise CRP; this feeds back and *directly worsens* IR.
- ▶ **Selective (pathway-specific) resistance** — the mitogenic MAP-kinase growth/differentiation pathway remains insulin-sensitive; compensatory hyperinsulinaemia therefore *over-drives* it, potentially **accelerating atherosclerosis**.

Adipose tissue, free fatty acids and adipokines

- ▶ **Central/visceral obesity** (high waist–hip ratio) is pivotal; $\geq 80\%$ of T2DM patients are obese. Visceral fat drains via the **portal vein**, delivering FFAs and adipokines directly to the liver and contributing to hepatic IR. Importantly, **normal-weight South-Asian, Southeast-Asian and Central-American individuals can be insulin-resistant** (“metabolically obese, normal weight”).
- ▶ Excess FFAs impair muscle glucose uptake, promote hepatic gluconeogenesis and **VLDL-triglyceride** synthesis, accumulate as intramuscular/intrahepatic triglyceride, and impair beta-cell function.
- ▶ **Adipokines** modulate sensitivity:
 - **Adiponectin** — insulin-sensitising and anti-inflammatory (activates AMP-kinase, $\uparrow$ fatty-acid oxidation, $\downarrow$ hepatic gluconeogenesis); **reduced** in obesity $\rightarrow$ contributes to hepatic IR.
 - **Leptin** — normally $\downarrow$ appetite, $\uparrow$ energy expenditure, $\uparrow$ insulin sensitivity; obesity produces **hyperleptinaemia with leptin resistance**.
 - Pro-resistance mediators — **resistin, retinol-binding protein-4, visfatin, fetuin-A, asprosin, PAI-1, TNF- α , IL-6**.

Consequences and clinical correlates of insulin resistance

Domain	Mechanism / effect of IR
Type 2 DM / IGT–IFG	Primary, earliest defect; $\sim 75\%$ of patients with T2DM or IGT have the metabolic syndrome
Atherogenic dyslipidaemia	$\uparrow$ Triglyceride/VLDL, $\downarrow$ HDL, small dense LDL , $\uparrow$ apoC-III (inhibits lipoprotein lipase)
Hypertension	Loss of insulin’s NO-mediated vasodilation with <i>preserved</i> renal Na^+ reabsorption; $\uparrow$ sympathetic activity; $\uparrow$ adipose angiotensinogen
Metabolic syndrome	IR is the unifying pathophysiological mechanism (syndrome X / insulin-resistance syndrome)
MASLD / MASH (NAFLD/NASH)	Hepatic triglyceride accumulation from $\uparrow$ FFA flux + VLDL synthesis
PCOS	IR present in 50–80% ; independently raises T2DM risk

Domain	Mechanism / effect of IR
Hyperuricaemia	↓Renal tubular uric-acid excretion; promotes endothelial dysfunction/hypertension
Prothrombotic / proinflammatory state	↑PAI-1, fibrinogen, CRP
ASCVD	Relative risk ~1.5–3×; MI/stroke risk threefold higher in metabolic syndrome

Severe insulin-resistance syndromes

Syndrome	Key features	Underlying defect
Type A insulin resistance	Young women; severe hyperinsulinaemia, obesity, hyperandrogenism, acanthosis nigricans	Undefined defect in the insulin-signalling pathway
Type B insulin resistance	Middle-aged women; severe hyperinsulinaemia, hyperandrogenism, autoimmune disease	Autoantibodies to the insulin receptor (block → hyperglycaemia; stimulate → intermittent hypoglycaemia)
Insulin-receptor mutations	Rare; features of T2DM/IGT	Impaired insulin binding or signal transduction
Leprechaunism (Donohue) / Rabson-Mendenhall	Severe congenital IR	Genetic defects in insulin action
Lipodystrophies	Selective loss of adipose tissue → severe IR + hypertriglyceridaemia	Inherited (Berardinelli-Seip congenital generalised; Dunnigan familial partial) or acquired (HIV-related)
PCOS	Chronic anovulation + hyperandrogenism	IR in a major subset; independent T2DM risk

- ▶ *Acanthosis nigricans* and signs of hyperandrogenism (hirsutism, acne, oligomenorrhoea) are the physical hallmarks of **severe IR**.
- ▶ Secondary IR also accompanies **endocrinopathies** (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma) and **drugs** (glucocorticoids, calcineurin/mTOR inhibitors, certain antiretrovirals, nicotinic acid, thiazides).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology of IR / metabolic syndrome (central-obesity hub)**: draw an expanded adipocyte at the centre releasing FFAs, TNF- α / IL-6 / **resistin** / PAI-1 and *reduced adiponectin*; arrows to **Liver** (↑gluconeogenesis, ↑VLDL-triglyceride → fasting hyperglycaemia + dyslipidaemia), **Muscle** (↓glucose uptake → postprandial

hyperglycaemia), **Pancreas** (compensatory **hyperinsulinaemia**), **Vessels** ($\downarrow$ NO, $\uparrow$ Na⁺ reabsorption, $\uparrow$ SNS $\rightarrow$ hypertension) and **Blood** ($\uparrow$ CRP/fibrinogen $\rightarrow$ prothrombotic state).
Labels: FFA, *adiponectin* $\downarrow$, *TNF- α* , *IL-6*, *PAI-1*, *VLDL/TG*, *small dense LDL*, *HDL* $\downarrow$, *hyperinsulinaemia*, *NO* $\downarrow$, *ASCVD*.

- **Beta-cell compensation curve (insulin secretion vs insulin sensitivity):** hyperbolic curve with points A (normal) $\rightarrow$ B (insulin-resistant, $\uparrow$ secretion) $\rightarrow$ C (IGT) $\rightarrow$ D (Type 2 DM).
Labels: *insulin sensitivity (M value)*, *insulin secretion*, *NGT*, *IGT*, *Type 2 DM*.

Clinical / Diagnostic significance

- **Clinical clues** — **acanthosis nigricans**, skin tags, central obesity ($\uparrow$ waist circumference), and hyperandrogenism (hirsutism, acne, oligomenorrhoea) flag significant IR.
- **Assessment of IR:**
 - *Surrogate indices* — fasting insulin and **HOMA-IR** (homeostasis model assessment) are the practical clinical surrogates; the chapter notes that fasting insulin / HOMA only *partially* capture IR.
 - *Quantitative gold standard* — the **hyperinsulinaemic-euglycaemic clamp**, expressing whole-body glucose disposal as the “M value” ($\mu\text{mol}/\text{min per kg}$) = insulin sensitivity.
 - *Clinical surrogate* — meeting **metabolic-syndrome criteria** (NCEP:ATP III 2001 / Harmonizing definition: central obesity + ≥ 2 of $\uparrow$ TG ≥ 150 mg/dL, HDL $< 40 / < 50$ mg/dL, BP $\geq 130 / 85$ mmHg, FPG ≥ 100 mg/dL).
- **Management — reduce/reverse IR (insulin sensitisation):**
 - **Lifestyle is first-line** — weight loss (target ≥ 5 –7% body weight), saturated-fat restriction and ≥ 150 min/week physical activity. The **Diabetes Prevention Program (DPP)** showed intensive lifestyle change reduced incident T2DM by **58%**.
 - **Metformin (biguanide)** — enhances hepatic insulin action and suppresses endogenous glucose production; DPP reduction **31%**; benefits IR in PCOS.
 - **Thiazolidinedione (pioglitazone)** — improves insulin-mediated glucose uptake in muscle/adipose tissue *and* hepatic action; a meta-analysis (9 trials, 12,026 participants) showed $\downarrow$ **ASCVD events**; caution — weight gain, oedema/CHF, fractures.
 - **GLP-1 receptor agonists / tirzepatide** — improve insulin sensitivity largely via weight loss.
 - Treat the clustered components — statins/fibrates for dyslipidaemia, antihypertensives, and urate-lowering where indicated.

High-yield exam pointers

- IR = **reduced insulin action on muscle, liver and fat**; *relative* (overcome by hyperinsulinaemia); central lesion of T2DM and **unifying mechanism of metabolic syndrome**.

- ▶ Sequence: **postprandial** → **fasting hyperinsulinaemia** → **hyperglycaemia**; T2DM only when **beta-cell compensation fails**.
- ▶ Predominantly a **post-receptor signalling defect**; lipotoxicity + ROS + metabolic inflammation; **MAP-kinase pathway spared** → hyperinsulinaemia promotes atherosclerosis.
- ▶ **FFA excess** and **low adiponectin / high resistin**, **TNF- α** , **IL-6**, **leptin resistance** drive IR.
- ▶ **Type A** = insulin-signalling defect (young women); **Type B** = **anti-insulin-receptor antibodies** (autoimmune, middle-aged women).
- ▶ **Acanthosis nigricans + hyperandrogenism** = clinical markers of severe IR; lipodystrophy (Berardinelli-Seip, Dunnigan) causes severe IR with hypertriglyceridaemia.
- ▶ **PCOS**: IR in 50–80%, independent T2DM risk.
- ▶ Best quantified by **hyperinsulinaemic-euglycaemic clamp**; HOMA-IR is the practical surrogate.
- ▶ Sensitisers = **metformin and pioglitazone**; lifestyle/weight loss is most effective (DPP 58% vs metformin 31%).

SOURCE & COVERAGE

Harrison 22e — Ch 415 “Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology” + Ch 420 “The Metabolic Syndrome”. Coverage note: The HOMA-IR formula (fasting insulin $\times$ fasting glucose $\div$ 22.5) and the use of the hyperinsulinaemic-euglycaemic clamp as the quantitative gold standard are universally accepted standard internal medicine; the provided chapters reference “homeostasis model assessment”, fasting insulin, and the clamp-derived “M value” (insulin sensitivity) but do not print the HOMA-IR formula explicitly. Drug doses are deliberately not stated, as the source chapters cite drug classes rather than specific doses (detailed dosing is in Ch 416, not provided).



Insulin Sensitizers

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — *Insulin sensitizers* are glucose-lowering agents that act by enhancing the responsiveness of target tissues (liver, skeletal muscle, adipose) to circulating insulin, thereby reducing insulin resistance, rather than by stimulating insulin secretion. Two oral classes form this group: the **biguanides** (metformin) and the **thiazolidinediones / glitazones** (pioglitazone, rosiglitazone). Because their action is insulin-dependent and does not augment β -cell secretion, they **do not cause hypoglycaemia as monotherapy** and are central to the management of type 2 diabetes mellitus (T2DM), where insulin resistance is a defining lesion.

Classification and rationale

- ▶ **Biguanides** — metformin (the only biguanide in current use; *phenformin* and *buformin* were withdrawn from most markets in the 1970s after deaths from lactic acidosis). Acts predominantly on the **liver** to lower hepatic glucose output.
- ▶ **Thiazolidinediones (TZDs)** — *pioglitazone* and *rosiglitazone*; the first agent, *troglitazone* (1997), was withdrawn in 2000 because of rare fatal hepatotoxicity. Act predominantly on **adipose tissue** (PPAR- γ) with secondary benefit at liver and muscle.
- ▶ Both classes lower glucose without directly raising insulin levels; circulating insulin actually **falls** with effective therapy, confirming improved sensitivity.
- ▶ They target the *insulin-resistance* arm of T2DM pathophysiology and so are complementary to secretagogues, incretins and SGLT-2 inhibitors in combination regimens.

Biguanides — Metformin

- ▶ **Mechanism (incompletely defined):** principally **reduces hepatic gluconeogenesis** and hepatic insulin resistance; less consistently improves peripheral (muscle) glucose uptake; influences gut function (alters microbiome, increases GLP-1 release). At the molecular level it **activates AMP-activated protein kinase (AMPK)** (a sensor of depleted cellular energy), and more recent work implicates **inhibition of mitochondrial glycerophosphate dehydrogenase** and a direct effect on the intestinal mucosa signalling to brain/liver.
- ▶ **Pharmacokinetics:** half-life ~1.5–3 h; **not protein-bound, not metabolised, excreted unchanged by the kidney** (hence the dependence of safety on renal function).
- ▶ **Efficacy:** lowers **HbA1c** by ~1–2%; reduces fasting plasma glucose and insulin; modestly improves the lipid profile ($\downarrow$ LDL, $\downarrow$ triglycerides) and procoagulant factors; **weight-neutral to modest weight loss**; no hypoglycaemia; inexpensive — hence the **first-line agent** in most T2DM algorithms (ADA/EASD, IDF, AACE).
- ▶ **Dosing:** start low (500 mg once–twice daily *with food*) and titrate every 1–2 weeks; maximally tolerated dose **2000 mg/day** (formal maximum 2550 mg, little extra benefit beyond 2000 mg). IR: 500 mg tid or 850–1000 mg bid; **extended-release (ER)** once daily has fewer upper-GI effects and better adherence.
- ▶ **Adverse effects:** GI intolerance (nausea, anorexia, abdominal cramps, diarrhoea, metallic taste) in up to 20–30%, often transient and dose-related; **vitamin B12 deficiency** (interferes with calcium-dependent absorption of the B12–intrinsic-factor complex in the terminal ileum — monitor periodically, especially if neuropathy or macrocytosis); **lactic acidosis** — the major but *very rare* toxicity (incidence <10/10,000 patient-years), almost confined to patients with predisposing illness.
- ▶ **Contraindications / cautions:** **eGFR <30 mL/min/1.73 m² (contraindicated)**; do not *initiate* if eGFR <45, and halve the dose ($\approx$ 1000 mg/day) if eGFR 30–45; hepatic insufficiency, excess alcohol intake, unstable/decompensated CHF, any acidosis, severe hypoxaemia. **Withhold for**

iodinated radiographic contrast (halt on the day in patients with eGFR 30–60, restart after 48 h once renal function is confirmed stable) and in hospitalised/NPO/acutely ill patients (substitute insulin).

- ▶ **Cardiovascular / outcome data:** in overweight patients in the UKPDS (UKPDS 34), metformin reduced *any diabetes-related endpoint* by 32%, *myocardial infarction* by 39% and *all-cause mortality* by 36%; benefit persisted at 10-year post-trial follow-up (a “legacy”/metabolic-memory effect). Metformin also **reduces progression from prediabetes to diabetes** (Diabetes Prevention Program). It is the insulin sensitiser with the best long-term outcome record.

Thiazolidinediones (Glitazones)

- ▶ **Mechanism:** bind and activate the nuclear transcription factor **peroxisome proliferator-activated receptor- γ (PPAR- γ)**, which forms a **heterodimer with the retinoid X receptor (RXR)**. PPAR- γ is expressed at highest levels in **adipocytes**. Activation regulates many genes $\rightarrow$ promotes **adipocyte differentiation**, **redistributes fat from central/visceral to peripheral/subcutaneous depots**, reduces hepatic fat, promotes fatty-acid storage and **lowers circulating free fatty acids**, thereby improving whole-body insulin sensitivity. Onset is **slow (weeks–months)**.
- ▶ **Efficacy:** HbA1c reduction **~ 0.5 – 1.4%** (up to 1–2%); effective as monotherapy or with metformin/sulfonylurea/insulin. When combined with insulin they **lower insulin requirement by 30–50%**. **No hypoglycaemia** as monotherapy. **Preserve β -cell function** — in ADOPT, rosiglitazone gave the slowest rate of secondary glycaemic failure vs metformin and glyburide.
- ▶ **Pioglitazone (preferred TZD):** dose 15–45 mg once daily (start 15 mg; 30 mg $\approx$ 80% of maximal glucose-lowering; 45 mg least well tolerated); **favourable lipid effect** — $\downarrow$ triglycerides (~ 9 –20%), $\uparrow$ HDL, neutral/ $\downarrow$ LDL; reduces hepatic fat and can **reverse hepatic fibrosis (benefit in NASH/MASH)**; lowers blood pressure and urinary albumin. Metabolised by CYP2C8 / CYP3A4.
- ▶ **Rosiglitazone:** raises LDL and triglycerides; embroiled in a still-unresolved controversy over possible increased myocardial-infarction risk (meta-analyses), leading to a **shift away from its use worldwide** (RECORD trial showed no excess CV death/hospitalisation but did not settle the dispute).
- ▶ **Cardiovascular data (pioglitazone):** PROactive (5238 T2DM with macrovascular disease) — the broad primary endpoint was negative but a tighter secondary composite (death/MI/stroke) fell by **16%**; the IRIS study showed pioglitazone reduced recurrent **stroke or MI** in insulin-resistant, non-diabetic patients after stroke/TIA. Overall, **pioglitazone appears to reduce recurrent cardiovascular events**, partly offset by fluid retention/heart failure.
- ▶ **Adverse effects:** **weight gain (2–4 kg)** — from both fluid retention and an increase in subcutaneous fat; **fluid retention / peripheral oedema** (~ 5 –10%, rising to 10–15% with concomitant insulin or sulfonylurea) which may precipitate **congestive heart failure** — TZDs are **contraindicated in NYHA class III/IV heart failure**; **bone fractures** (especially distal long bones in postmenopausal women — PPAR- γ diverts mesenchymal stem cells from osteoblastic to

adipocytic lineage and reduces lumbar BMD); **macular oedema**; mild **anaemia** (dilutional, small fall in haematocrit); **hepatotoxicity** caution (check LFTs; contraindicated if ALT >2.5× ULN); possible **bladder-cancer** association with pioglitazone (conflicting data — avoid with active or prior bladder cancer). TZDs **induce ovulation in PCOS** — counsel premenopausal women on contraception as safety in pregnancy is unestablished.

Biguanide vs Thiazolidinedione — comparison

Feature	Biguanide (Metformin)	Thiazolidinedione (Pioglitazone)
Primary site / target	Liver; activates AMPK	Adipose tissue; PPAR-γ-RXR heterodimer
Dominant action	↓ Hepatic gluconeogenesis	↑ Peripheral insulin sensitivity, fat redistribution
HbA1c reduction	~1–2%	~0.5–1.4% (up to 2%)
Onset	Days	Weeks–months
Effect on weight	Neutral / slight loss	Gain (2–4 kg)
Hypoglycaemia (mono)	No	No
Key adverse effects	GI upset, B12 deficiency, lactic acidosis	Oedema/CHF, fractures, macular oedema, ?bladder Ca
Major contraindication	eGFR <30, acidosis, hypoxia	NYHA class III/IV heart failure, hepatic disease
Outcome highlight	UKPDS 34 ↓ MI & mortality	PROactive/IRIS ↓ recurrent CV events; benefit in NASH

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- “**Sites of action of insulin sensitizers**”: a central panel with three organs labelled — **Liver** (arrow “Metformin → AMPK → ↓ gluconeogenesis / ↓ hepatic glucose output”), **Skeletal muscle** (“↑ insulin-stimulated glucose uptake”), and **Adipose tissue** (“Pioglitazone → PPAR-γ → adipocyte differentiation, fat redistributed visceral → subcutaneous, ↓ free fatty acids”). Add a peripheral box: “Net result = ↓ insulin resistance, ↓ circulating insulin, no hypoglycaemia.” Labels: *Metformin*, *AMPK*, *hepatic gluconeogenesis*, *PPAR-γ*, *FFA*, *insulin resistance*.
- “**TZD molecular mechanism**”: *TZD* → binds **PPAR-γ**, which dimerises with **RXR**; the **PPAR-γ-RXR heterodimer** binds the **PPRE (PPAR response element)** on **DNA** → gene transcription → adipocyte differentiation / insulin-sensitising genes. Labels: *TZD*, *PPAR-γ*, *RXR*, *PPRE*, *DNA*, *target genes*.

Clinical / Diagnostic significance

- ▶ **Metformin** is the recommended **first-line drug** for T2DM (efficacy, safety, weight neutrality, cardiovascular benefit, low cost) and is continued through combination therapy even after HbA1c falls below target.
- ▶ Check **eGFR before starting and at least annually** for metformin; obtain **vitamin B12** periodically, particularly when peripheral neuropathy or macrocytosis appears (do not misattribute to diabetic neuropathy).
- ▶ **Pioglitazone** is especially useful where insulin resistance, **NASH/MASH**, or hepatic steatosis coexist, and as an inexpensive generic add-on; screen for and avoid in **heart failure** and assess **fracture risk** (BMD) before prescribing, particularly in postmenopausal women.
- ▶ Neither agent causes hypoglycaemia alone, but **dose reduction of insulin/sulfonylurea** is needed when either is added to those drugs.
- ▶ In current ADA/EASD practice, when **ASCVD, heart failure or CKD** dominate, a GLP-1 RA or SGLT-2 inhibitor is layered onto metformin; pioglitazone is favoured for the MASH/ASCVD-risk phenotype provided heart failure is absent.

High-yield exam pointers

- ▶ Two insulin-sensitiser classes: **biguanides (metformin)** and **thiazolidinediones (pioglitazone, rosiglitazone)** — improve sensitivity, **no hypoglycaemia** as monotherapy.
- ▶ **Metformin**: ↓ hepatic gluconeogenesis via **AMPK**; renally excreted unchanged; **B12 deficiency** and **lactic acidosis**; stop if **eGFR <30** and hold for **contrast/surgery**.
- ▶ **UKPDS 34**: metformin ↓ MI 39% and all-cause mortality 36% in overweight T2DM (legacy effect).
- ▶ **TZDs**: activate **PPAR-γ-RXR** heterodimer in adipocytes → fat redistribution and ↓ FFA.
- ▶ **Pioglitazone** ↓ triglycerides, ↑ HDL, benefits **NASH/MASH**; **PROactive/IRIS** suggest reduced recurrent CV/stroke events.
- ▶ **TZD red flags**: fluid retention → **CHF (contraindicated NYHA III/IV)**, **fractures** in postmenopausal women, macular oedema, possible **bladder cancer** (pioglitazone).
- ▶ **Troglitazone** withdrawn (hepatotoxicity); **phenformin** withdrawn (lactic acidosis) — historical safety landmarks.
- ▶ TZDs **preserve β-cell function** (slowest secondary failure in ADOPT) and **induce ovulation** in PCOS.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Diabetes Mellitus: Management and Therapies" (Biguanides, Thiazolidinediones; Table of agents used for type 1/type 2 diabetes).

- **Williams Textbook of Endocrinology, 15e** — “Therapeutics of Type 2 Diabetes Mellitus” (mechanisms of metformin/AMPK and mitochondrial glycerophosphate dehydrogenase; PPAR pharmacology; UKPDS 34 outcomes; PROactive/RECORD/ADOPT/IRIS).
- **CMDT 2026** — “Diabetes Mellitus & Hypoglycaemia” (current dosing, renal thresholds, TZD safety profile, treatment algorithm).



Investigations and Treatment of Diabetes Insipidus

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Diabetes insipidus (DI) is a hypotonic polyuria–polydipsia syndrome caused by a deficiency of **arginine vasopressin (AVP / antidiuretic hormone)** secretion or by renal resistance to its action, leading to excretion of abnormally large volumes of dilute urine (24-h urine volume >40–50 mL/kg body weight, usually >3 L/day) with compensatory polydipsia. Harrison 22e adopts the revised nomenclature: *AVP deficiency* (formerly central / neurogenic / cranial / pituitary DI) and *AVP resistance* (formerly nephrogenic DI). The core clinical task is to **confirm hypotonic polyuria, exclude osmotic diuresis, and differentiate the three look-alike disorders** — AVP deficiency, AVP resistance, and primary polydipsia — because their treatment differs fundamentally.

Classification and etiology (basis for investigation)

The differential of the polyuria–polydipsia syndrome has four mechanistic groups; investigations are designed to separate them.

Disorder (new term / old term)	Basic defect	Representative causes
AVP deficiency (central DI)	Deficient AVP synthesis/secretion	Trauma/surgery, tumours (craniopharyngioma, germinoma, meningioma, metastases), granulomatous (histiocytosis, sarcoidosis), infective (TB, meningitis), lymphocytic/IgG4 infundibuloneurohypophysitis, idiopathic; genetic — autosomal dominant <i>AVP–neurophysin II</i> mutations, <i>WFS1</i> (Wolfram)
AVP resistance (nephrogenic DI)	Reduced renal sensitivity to AVP	Drugs (lithium , demeclocycline, cisplatin), hypercalcemia , hypokalemia , infiltration (amyloid, myeloma), sickle cell, obstruction/PKD; genetic — X-

Disorder (new term / old term)	Basic defect	Representative causes
		linked <i>AVPR2</i> , autosomal <i>AQP2</i> mutations
Primary polydipsia	Excess fluid intake (low thirst set-point)	Dipsogenic, psychogenic (chronic schizophrenia), compulsive/"health-enthusiast" water drinking
Gestational AVP deficiency	Placental vasopressinase (N-terminal aminopeptidase) degrades AVP	Pregnancy; remits weeks after delivery

Step 1 — Initial clinical and biochemical evaluation

- ▶ **Document true polyuria:** collect a 24-h urine on unrestricted fluid intake. Volume >40–50 mL/kg per day and/or >3 L/day with **urine osmolality** <800 mosm/kg confirms hypotonic polyuria and warrants further work-up. Urine volume <50 mL/kg/24 h points to a genitourinary cause instead.
- ▶ **Exclude osmotic diuresis first:** absence of **glucosuria** (rule out diabetes mellitus); also exclude high solute load.
- ▶ **Measure serum sodium / plasma osmolality** — this triages the patient:
 - Serum Na <135 mmol/L → favours **primary polydipsia** (patients can “drink themselves into” hyponatremia).
 - Serum Na >147 mmol/L (hypernatremia) → favours **AVP deficiency or AVP resistance** (true DI).
 - Normal Na (136–146 mmol/L) — the commonest situation — mandates **provocative testing** (below).
- ▶ A bedside discriminator when Na is high: give **desmopressin 2 µg SC** and repeat urine osmolality — a brisk rise indicates **AVP deficiency**, while failure to concentrate indicates **AVP resistance**. (Done as an inpatient to allow serial osmolality checks.)

Step 2 — Confirmatory tests: water deprivation and desmopressin

The **indirect water deprivation test** (Miller–Moses principle) was the long-standing gold standard — it indirectly assesses AVP activity by measuring urine-concentrating capacity during supervised dehydration, then after a dose of desmopressin. *Limitation flagged by Harrison:* its published criteria gave an overall diagnostic accuracy of only ~70%, and just 41% in **primary polydipsia**, hence the move to copeptin.

Interpretation (per the diagnostic algorithm, Fig. 393-4):

Test result	Interpretation
Water deprivation → urine osmolality >800 mosm/kg	Mild primary polydipsia
Urine osmolality 300–800 mosm/kg, then desmopressin → >9% further rise	Partial central DI (AVP deficiency)
Urine osmolality 300–800, then desmopressin → <9% rise	Primary polydipsia
Urine osmolality <300 mosm/kg, then desmopressin → >50% rise	Complete central DI
Urine osmolality <300, then desmopressin → <50% rise	Nephrogenic DI (AVP resistance)

- ▶ Direct plasma AVP assay was proposed but is **not in routine use** because of technical instability of the AVP assay.

Step 3 — Copeptin-based diagnosis (current preferred approach)

Copeptin is the C-terminal glycopeptide of the AVP prohormone, co-secreted stoichiometrically with AVP but far more **stable ex vivo**, making it a reliable AVP surrogate.

- ▶ **Baseline copeptin >21.4 pmol/L** (without prior water deprivation) **unequivocally identifies AVP resistance (nephrogenic DI)**.
- ▶ For the harder split between AVP deficiency and primary polydipsia, perform a **hypertonic saline infusion test**: a **stimulated copeptin >4.9 pmol/L at a plasma sodium ≥150 mmol/L** diagnoses **AVP deficiency** with an overall accuracy of **96.5–97%** (values <4.9 pmol/L indicate primary polydipsia). Requires **close monitoring of sodium**.
- ▶ **Arginine-stimulated copeptin** is a gentler alternative but with lower diagnostic accuracy. Copeptin assays are commercially available in Europe, Australia, **India**, and Mexico.

Step 4 — Localisation / imaging

- ▶ Once AVP deficiency is confirmed, obtain **MRI of the sella and suprasellar region** to find the underlying lesion (tumour, infiltration, stalk thickening) and assess the posterior pituitary and stalk.
- ▶ The normal **posterior pituitary “bright spot”** (T1 hyperintensity reflecting AVP-laden neurosecretory vesicles) is typically **absent in AVP deficiency**; however, its absence alone is **not diagnostic** (it may persist early in disease or be absent in normal elderly people).
- ▶ Stalk thickening prompts evaluation for infiltrative/inflammatory disease (sarcoid, histiocytosis, IgG4, germinoma) and screening of anterior pituitary function.

Treatment

A. AVP deficiency (central DI) — desmopressin (DDAVP):

- ▶ **DDAVP**, a synthetic AVP analogue, acts **selectively on V2 receptors** to concentrate urine in a dose-dependent fashion; it is **more resistant to degradation** than AVP with a 3- to 4-fold longer **duration of action**.
- ▶ **Adult doses (route-dependent)**: 1–2 µg once or twice daily SC/IV; 10–20 µg twice or thrice daily intranasal spray; 100–400 µg twice or thrice daily orally (tablet/melt). Onset of antidiuresis is rapid — ~15 min after injection to ~60 min after oral dosing.
- ▶ **Main complication — hyponatremia**: mild dilutional fall (Na 131–134 mmol/L) in ~25% of patients with intact thirst; more severe (<130 mmol/L) in ~15%. **Desmopressin escape** — intentionally delaying a DDAVP dose for a few hours to permit a transient aquaresis — reduces this risk.
- ▶ Because DDAVP resists placental vasopressinase, it is the agent of choice for gestational AVP deficiency.

B. AVP resistance (nephrogenic DI) — difficult to treat:

- ▶ **Remove the cause** where possible (most commonly stop **lithium**); correct hypercalcemia/hypokalemia.
- ▶ Partial resistance may respond to **high-dose desmopressin**.
- ▶ Mainstay: **thiazide diuretic and/or amiloride + low-sodium diet + an NSAID** (e.g., indomethacin) — this paradoxically reduces polyuria, but the combination is **nephrotoxic** and demands **renal-function monitoring**.
- ▶ Persistent **lithium-induced** resistance is treated with **hydrochlorothiazide + amiloride**. *Caution*: thiazide-induced volume contraction **reduces lithium excretion and can precipitate lithium toxicity**.

C. Primary polydipsia: graded reduction of fluid intake; relieve mouth dryness with **ice chips / hard candy** to stimulate salivary flow. Drug therapy has been inconsistent; a recent study suggests **GLP-1 analogues** reduce fluid intake, urine output, and thirst. (Desmopressin is *avoided* — it precipitates water intoxication.)

D. Adipsic AVP deficiency and acute hypernatremia:

- ▶ Replace AVP with DDAVP, then **regulate intake by body weight/serum sodium** rather than thirst — monitor input/output as an inpatient to reach **eunatremia**, record the eunatremic weight, prescribe ~1.5–2 L **fluid/day**, weigh daily, and replace deficits when below eunatremic weight (Table 393-2).
- ▶ For established **hypertonic hypernatremia**, estimate the **free-water deficit** from body weight and serum sodium; replace with **hypotonic fluid** (0.45% saline or 5% dextrose) plus ongoing losses over **24–48 h**, ensuring sodium does **not fall too rapidly**; monitor urea/creatinine for rhabdomyolysis-related acute kidney injury.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm of the polyuria–polydipsia syndrome.** Labels: *Confirm polyuria* ($>40\text{--}50\text{ mL/kg/24 h}$) $\rightarrow$ *Measure serum Na / plasma osmolality* $\rightarrow$ branches: Na $<135 \rightarrow$ **primary polydipsia**, Na $>147 \rightarrow$ **central or nephrogenic DI**, Na $136\text{--}146 \rightarrow$ **provocative testing**; under testing — **Water deprivation test** (urine osm >800 = mild primary polydipsia; $300\text{--}800 / <300 \rightarrow$ **Desmopressin test**: $>9\%$ = partial central DI, $<9\%$ = primary polydipsia, $>50\%$ = complete central DI, $<50\%$ = nephrogenic DI) and **Baseline copeptin** ($>21.4\text{ pmol/L}$ = nephrogenic DI; $\leq 21.4 \rightarrow$ **hypertonic saline** $\rightarrow$ **stimulated copeptin** $>4.9\text{ pmol/L}$ at Na ≥ 150 = **AVP deficiency**, <4.9 = primary polydipsia).
- ▶ **AVP–neurophysin II–copeptin prohormone schematic.** Labels: *signal peptide*, *AVP* (*nonapeptide*), *neurophysin II*, *copeptin*; arrow showing co-secretion of copeptin as the stable AVP surrogate.

Clinical / Diagnostic significance

- ▶ The three disorders are clinically indistinguishable on history alone — **biochemistry** (Na, plasma/urine osmolality) and a **provocative test** (**copeptin preferred**) are decisive; misclassification risks dangerous mistreatment (e.g., DDAVP in primary polydipsia $\rightarrow$ water intoxication).
- ▶ **Copeptin** has largely supplanted the inaccurate water-deprivation test and removes the need for an unreliable AVP assay.
- ▶ **MRI** is essential after diagnosing central DI to detect tumour/infiltrative/inflammatory causes and to screen for combined anterior pituitary failure.
- ▶ **Adipsic DI** carries the highest morbidity (rhabdomyolysis, thromboembolism, AKI) because the protective thirst response is lost — these patients need weight/sodium-guided fluid prescriptions.

High-yield exam pointers

- ▶ **DI = hypotonic polyuria** $>40\text{--}50\text{ mL/kg/day}$ ($>3\text{ L/day}$), urine osmolality $<800\text{ mosm/kg}$, glucosuria absent.
- ▶ New terms: **AVP deficiency** (central) and **AVP resistance** (nephrogenic).
- ▶ Na low $\rightarrow$ **primary polydipsia**; Na high $\rightarrow$ **true DI**.
- ▶ **Copeptin** $>21.4\text{ pmol/L}$ baseline = **nephrogenic DI**; stimulated $>4.9\text{ pmol/L}$ (Na ≥ 150) after hypertonic saline = **central DI** ($\approx 97\%$ accuracy).
- ▶ Water deprivation + desmopressin: $>50\%$ rise = **complete central**, $<50\%$ = **nephrogenic**, $<9\%$ = **primary polydipsia**.
- ▶ Posterior pituitary **bright spot absent** in central DI (not fully specific).

- ▶ **DDAVP** = selective **V2 agonist**; oral 100–400 µg, intranasal 10–20 µg, parenteral 1–2 µg; **hyponatremia** is the key adverse effect; use **desmopressin escape**.
- ▶ **Nephrogenic DI**: stop lithium; **thiazide ± amiloride + low-salt diet + NSAID** (nephrotoxic combo); thiazide can cause **lithium toxicity**.
- ▶ **Gestational DI** responds to **DDAVP** (resists placental vasopressinase).

SOURCE & COVERAGE

Harrison 22e — Ch 393 “Disorders of the Neurohypophysis” (Christ-Crain & Sherlock), including Tables 393-1, 393-2 and the differential-diagnosis algorithm (Fig. 393-4). SIAD/hyponatremia management is cross-referenced to Ch 56 in the source but is outside this answer’s scope. No coverage gap for the asked topic — investigations and treatment of DI are fully supported by the provided chapter.



Maturity-Onset Diabetes of the Young (MODY)

Asked in: Paper IV Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — MODY is a clinically and genetically heterogeneous group of **monogenic** (single-gene) forms of diabetes characterised by **autosomal-dominant inheritance**, **young age at onset** (typically diagnosed before 30 years, often ≤ 25 years), a **primary β -cell secretory defect** (impaired glucose-induced insulin secretion) rather than insulin resistance, **absence of obesity**, and **absence of islet autoimmunity and ketosis**. It belongs to the “other specific types” category of the ADA classification and accounts for roughly **1–2% of all diabetes**. It is the prototype of **precision (genotype-directed) diabetes medicine** — accurate molecular diagnosis changes treatment, prognosis and family screening.

Historical note & nomenclature

- ▶ The term was coined by **Fajans and Tattersall (1974)** after study of the multigenerational Michigan “**R-W pedigree**” (Fajans, from 1958) and Tattersall’s description of *mild familial diabetes with dominant inheritance*, distinguishing it from classic juvenile-onset (type 1) diabetes.
- ▶ “MODY” historically refers to autosomal-dominant β -cell diabetes; with **>30 causative genes** now known, the older numerical “**MODY-X**” nomenclature (MODY 1–14) is being replaced by **gene-based names** (e.g., *HNF1A*-MODY rather than MODY 3).
- ▶ *Monogenic diabetes* is the umbrella term encompassing both **MODY** and **neonatal diabetes** (onset generally <6 months), plus rarer **syndromic** forms.

When to suspect MODY — clinical clues

MODY is frequently **misclassified as type 1 or type 2 diabetes**; suspect it when atypical features are present.

- ▶ **Atypical for type 1 DM:** absence of pancreatic islet autoantibodies; persistent endogenous insulin production **beyond the honeymoon period**; **measurable C-peptide** (≥ 0.60 ng/mL [≥ 0.2 nmol/L]) in the presence of hyperglycaemia; low insulin requirement; **no ketoacidosis when insulin is withheld**.
- ▶ **Atypical for type 2 DM:** onset **<45 years**; **lack of significant obesity**; absence of acanthosis nigricans; normal triglycerides and/or normal-to-high HDL cholesterol.
- ▶ **Strong multigenerational family history** of diabetes (parent affected; 2–3 generations) with an autosomal-dominant pattern.
- ▶ The **Exeter MODY probability calculator** (uses age at diagnosis, sex, BMI, HbA1c, treatment, family history; valid for diagnosis <35 years) and **type 1 genetic risk scores (T1D-GRS)** help select patients for genetic testing.

Classification of the main MODY subtypes

The four classic genes — GCK, HNF1A, HNF4A, HNF1B — account for the great majority of cases (relative frequencies vary geographically: *HNF1A* predominates in many UK/European registries, while *GCK* predominates in others and in paediatric/incidental cohorts).

Gene (locus) — old name	Protein / defect	Approx. share*	Hallmark clinical features	Precision treatment
GCK (7p) — MODY 2	Glucokinase = β -cell “glucose sensor”; glucose-sensing defect	>70% (of suspected)	Mild, stable, non-progressive fasting hyperglycaemia (≈ 99 –144 mg/dL) present from birth; small OGTT rise (< 90 mg/dL); HbA1c usually $< 7.5\%$; essentially no micro-/macrovascular complications	None — diet only; oral agents/insulin not recommended (contraindicated) ; treat only in pregnancy if fetus unaffected
HNF1A (12q24.2) — MODY 3	Hepatocyte nuclear factor-1 α ; transcription factor $\rightarrow$ progressive β -cell dysfunction	20–30%	Progressive hyperglycaemia; glycosuria at low renal threshold (reduced SGLT2 expression); hepatic adenomas; increased	Low-dose sulfonylurea (markedly sensitive — can cause hypoglycaemia); insulin later as β -cells fail

Gene (locus) — old name	Protein / defect	Approx. share*	Hallmark clinical features	Precision treatment
			cardiovascular mortality	
HNF4A (20q12–13.1) — MODY 1	Hepatocyte nuclear factor-4 α ; transcription factor	~5%	Fetal macrosomia + transient neonatal hyperinsulinaemic hypoglycaemia; progressive hyperglycaemia; low HDL/apoA2	Low-dose sulfonylurea, insulin later
HNF1B (17q12) — MODY 5	Hepatocyte nuclear factor-1 β ; transcription factor	<2%	Renal cysts and diabetes (RCAD) syndrome; pancreatic hypoplasia + exocrine insufficiency; hypomagnesaemia, hyperuricaemia, genital-tract anomalies, abnormal LFTs; 50–60% de novo (17q12 deletions)	Insulin (sulfonylurea-unresponsive)

*Relative incidence among patients suspected to have MODY (Williams Table 37.3).

- **Rarer / disputed subtypes (<1% each):** *IPF1/PDX1* (MODY 4), *NEUROD1* (MODY 6), *INS*, *CEL* (MODY 8), *ABCC8*, *KCNJ11*, *APPL1*; refuted/disputed: *KLF11* (MODY 7), *PAX4* (MODY 9), *BLK* (MODY 11).

Pathophysiology in brief

- All classic MODY genes converge on **defective glucose-stimulated insulin secretion** by the pancreatic β -cell.
- **GCK** raises the glucose threshold for insulin release (a regulatory “reset”), giving lifelong **mild, stable** hyperglycaemia.
- **HNF1A**, **HNF4A**, **HNF1B** are interacting **transcription factors** controlling β -cell development and gene expression; haploinsufficiency causes **progressive** β -cell failure (hence the deteriorating course and eventual insulin need in *HNF1A/HNF4A*).
- *HNF1A* also drives renal **SGLT2** expression — its loss explains glycosuria at a low renal threshold, often **preceding** frank hyperglycaemia.

Diagnostic approach (biomarker-led pathway to genetic testing)

A stepwise strategy avoids unnecessary, costly sequencing:

- ▶ **Endogenous insulin secretion** — serum C-peptide or urinary C-peptide/creatinine ratio (UCPCR).
- ▶ If C-peptide ≥ 0.60 ng/mL (0.2 nmol/L) or UCPCR ≥ 0.2 nmol/mmol $\rightarrow$ measure islet autoantibodies (GAD-65 and IA-2).
- ▶ If autoantibody-negative $\rightarrow$ proceed to **molecular genetic testing** (targeted next-generation sequencing gene panel including GCK, HNF1A, HNF4A, HNF1B $\pm$ others).
- ▶ **GCK-MODY** has a distinctive, near-pathognomonic biochemical signature (mild stable fasting hyperglycaemia, tiny OGTT increment) and can often be recognised clinically before sequencing.
- ▶ Confirming the variant enables **cascade (predictive) genetic screening of first-degree relatives**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Diagnostic algorithm for monogenic diabetes:** boxes labelled “Diabetes” $\rightarrow$ branch on autoantibodies +/- and C-peptide; left arm *autoantibody-positive / low C-peptide* $\rightarrow$ Type 1 DM; *high BMI, acanthosis nigricans, metabolic syndrome* $\rightarrow$ Type 2 DM; right arm *autoantibody-negative, C-peptide ≥ 0.2 nmol/L, family history* $\rightarrow$ MODY testing, splitting to **GCK** (mild fasting hyperglycaemia, HbA1c $< 8\%$, no microvascular complications), **HNF1A** (glycosuria, high HDL), **HNF4A** (low HDL, neonatal hypoglycaemia/macrosomia history), **HNF1B** (renal cysts, hypomagnesaemia, pancreatic/genital anomalies). Add a side box: *diagnosis < 6 months $\rightarrow$ test neonatal-diabetes genes *KCNJ11, ABCC8, INS.**
- ▶ **Diagram 2 — β -cell glucose-stimulated insulin secretion:** label GLUT2 (SLC2A2) glucose entry $\rightarrow$ glucokinase (GCK) $\rightarrow$ glycolysis/Krebs $\rightarrow$ $\uparrow$ ATP $\rightarrow$ closure of K-ATP channel (KCNJ11/ABCC8 subunits) $\rightarrow$ membrane depolarisation $\rightarrow$ opening of voltage-gated Ca^{2+} channel $\rightarrow$ Ca^{2+} influx $\rightarrow$ insulin granule exocytosis; nucleus labelled with transcription factors HNF1A, HNF4A, HNF1B, NEUROD1, PDX1.

Clinical / Diagnostic significance

- ▶ **Treatment is genotype-specific:** GCK-MODY needs **no pharmacotherapy** (and is harmed by it); HNF1A/HNF4A-MODY respond dramatically to **low-dose sulfonylureas** (often allowing patients on insulin to be switched off it); HNF1B-MODY requires **insulin**.
- ▶ **Avoids lifelong mislabelling** — many MODY patients are wrongly on insulin as “type 1,” or chased with intensifying type 2 regimens; a molecular diagnosis can de-escalate therapy.
- ▶ **Prognostic / surveillance value:** HNF1A carries excess **cardiovascular mortality** (warrants statin) and risk of **hepatic adenomas**; HNF1B mandates renal, electrolyte (magnesium), hepatic, urogenital and (in 17q12 deletions) neurodevelopmental surveillance — multidisciplinary care.

- ▶ **Pregnancy** is a special situation: in **GCK-MODY**, management depends on whether the fetus inherited the mutation — if the fetus is **unaffected**, maternal hyperglycaemia drives fetal hyperinsulinism and **macrosomia**, so **insulin** is given (often >1 IU/kg/day) with delivery considered at ~38 weeks; if the fetus is affected, no treatment is needed. *HNF1A/HNF4A* carriers are usually switched from sulfonylurea to **insulin** during pregnancy (glyburide crosses the placenta); *HNF4A* fetuses need monitoring for macrosomia and **neonatal hypoglycaemia**.
- ▶ **GCK-MODY** is a frequent cause of apparent “gestational diabetes” that fails to resolve postpartum (~2% of GDM).

High-yield exam pointers

- ▶ MODY = **autosomal-dominant, young-onset (<25–30 yr), non-obese, autoantibody-negative, ketosis-resistant, C-peptide-positive** diabetes; ~1–2% of all diabetes.
- ▶ **Four classic genes**: GCK, HNF1A, HNF4A, HNF1B — know each gene’s phenotype and treatment.
- ▶ **GCK (MODY 2)** = mild **stable** fasting hyperglycaemia from birth, **no complications, no treatment** (except pregnancy).
- ▶ **HNF1A (MODY 3)** = commonest *symptomatic* MODY in many populations; **glycosuria, sulfonylurea-sensitive**, hepatic adenomas, ↑CV risk.
- ▶ **HNF4A (MODY 1)** = **macrosomia + neonatal hypoglycaemia**, sulfonylurea-responsive.
- ▶ **HNF1B (MODY 5)** = **renal cysts and diabetes (RCAD)**, hypomagnesaemia, pancreatic/genital anomalies, **insulin-requiring**, often **de novo**.
- ▶ Diagnostic gateway: **C-peptide/UCPCR** → **islet autoantibodies** → **gene panel**; use the **Exeter MODY calculator** to triage.
- ▶ It is the **flagship example of precision medicine** in diabetes; molecular diagnosis enables **cascade family screening**.
- ▶ Do not confuse with **neonatal diabetes** (<6 months; *KCNJ11/ABCC8* K-ATP channel mutations → high-dose sulfonylureas; *INS* mutations → insulin) or **MIDD** (m.3243A>G, maternally inherited diabetes + deafness; avoid metformin).

SOURCE & COVERAGE

- ▶ **Williams Textbook of Endocrinology (15e)** — “**Monogenic Diabetes**” (dedicated chapter; subtype classification, biomarker pathway, gene/phenotype/treatment table, pregnancy management — primary source for depth).
- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “**Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology**” (ADA aetiologic classification of monogenic/MODY).

- CMTD 2026 — “Diabetes Mellitus & Hypoglycemia” (definition, autosomal-dominant onset ≤ 25 yr, genetic-screening candidacy, current management framing).



Metabolic Syndrome

Asked in: Paper IV 17 Apr 2026 · Paper I Nov 2021 (2×) — RGUHS MD General Medicine

Definition / Introduction — The **metabolic syndrome** (*syndrome X*, *insulin-resistance syndrome*) is a constellation of inter-related metabolic abnormalities — **central (visceral) obesity**, **atherogenic dyslipidaemia** (high triglycerides, low HDL-cholesterol), **raised blood pressure** and **hyperglycaemia** — that together confer a markedly increased risk of **atherosclerotic cardiovascular disease (ASCVD)** and **type 2 diabetes mellitus**. The unifying pathophysiological substrate is **insulin resistance** driven by an expanded, dysfunctional visceral adipose mass. It is a clustering construct, not a single disease, and is diagnosed by meeting an agreed set of cut-point criteria.

Definitions and diagnostic criteria (evolution)

- The criteria have evolved since the first **WHO definition (1998)**, which required *demonstrable insulin resistance* (type 2 diabetes, impaired glucose tolerance/fasting glucose, or low insulin-mediated glucose uptake) as an obligatory anchor plus additional components.
- The **NCEP:ATP III (2001)** definition popularised a simple, non-glucose-clamp, “any 3 of 5” approach. The **IDF (2005)** definition made *central obesity (ethnicity-specific waist)* mandatory plus 2 others. The **2009 Harmonized joint statement** (IDF, AHA/NHLBI, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity) requires *any 3 of 5* components with **population/ethnicity-specific waist thresholds**.

Component	NCEP:ATP III 2001 (any 3 of 5)	Harmonized / IDF (any 3 of 5; ethnicity-specific waist)
Central obesity (waist)	>102 cm men, >88 cm women	Europid / sub-Saharan African / Eastern & Middle Eastern: ≥ 94 men, ≥ 80 women · South Asian, Chinese, ethnic South & Central American: ≥ 90 men, ≥ 80 women · Japanese: ≥ 85 men, ≥ 90 women
Triglycerides	≥ 150 mg/dL (or on Rx)	>150 mg/dL (or on specific Rx)
HDL cholesterol	<40 mg/dL (men), <50 mg/dL (women), or on Rx	<40 mg/dL (men), <50 mg/dL (women), or on Rx
Blood pressure	≥ 130 systolic or ≥ 85 diastolic (or on Rx)	>130 systolic or >85 diastolic, or prior Dx / specific Rx

Component	NCEP:ATP III 2001 (any 3 of 5)	Harmonized / IDF (any 3 of 5; ethnicity-specific waist)
Fasting glucose	≥100 mg/dL (or on Rx / known T2DM)	≥100 mg/dL (or drug Rx of raised glucose)

- ▶ The AHA/NHLBI (2005) statement is essentially identical (3 of 5), applying Asian waist cut-points of ≥35 in. (men) / ≥32 in. (women) versus ≥40 in. / ≥35 in. for other groups — important because *normal-weight individuals from India, South-East Asia and Central America may be insulin-resistant* with metabolic syndrome at lower waist values.

Epidemiology and risk factors

- ▶ **Prevalence** ~33–35% of US adults (NCEP:ATP III); NHANES 1999–2018 (n = 28,049) showed 33.4%, rising with age from 19.5% (20–39 y) to 48.6% (≥60 y); nearly 50% of those >60 y are affected, with women predominating beyond 60.
- ▶ **Overweight/obesity** (especially central adiposity) is the principal driver; the global obesity epidemic underlies its rising recognition, including in children (~12–30% of obese/overweight children show features).
- ▶ **Sedentary lifestyle / low cardiorespiratory fitness** — >4 h/day of screen time carries a *twofold* increased risk versus <1 h/day.
- ▶ **Genetics** — no single gene; polygenic, with heritability of individual metabolic traits exceeding 50%.
- ▶ **Diabetes / impaired glucose tolerance** — ~75% of patients with type 2 DM or IGT have metabolic syndrome.
- ▶ **Lipodystrophy** — both genetic (*Berardinelli-Seip congenital*, *Dunnigan familial partial*) and acquired (HIV / antiretroviral-related) forms cause severe insulin resistance and the syndrome.

Etiology and pathophysiology

- ▶ **Insulin resistance** is the central, unifying hypothesis. It is heralded by postprandial then fasting **hyperinsulinaemia**, culminating in hyperglycaemia once β-cell compensation fails.
- ▶ **Free fatty acid (FFA) excess** — an expanded adipose mass releases abundant albumin-bound FFAs (lipolysis is the most insulin-sensitive pathway, so resistance amplifies lipolysis). FFAs flood the liver → ↑gluconeogenesis, ↑triglyceride and **VLDL (apoB)** production; in muscle they impair insulin-mediated glucose uptake and cause intramyocellular triglyceride accumulation.
- ▶ **Atherogenic dyslipidaemia** — ↑triglyceride-rich VLDL with elevated **apoC-III** (inhibits lipoprotein lipase, impairs remnant clearance); ↓HDL-cholesterol (cholesteryl-ester depletion via CETP making HDL small, dense, rapidly cleared); predominance of **small dense LDL** (when fasting TG >~180 mg/dL).

- ▶ **Hypertension** — in insulin resistance the vasodilator (nitric-oxide) action of insulin is lost while renal **sodium reabsorption** and **sympathetic** activation are preserved; ↑adipose **angiotensinogen** → **angiotensin II**; perivascular adipose ROS (NADPH oxidase) and **hyperuricaemia** (impaired NO synthase, RAAS stimulation) contribute.
- ▶ **Adipokines and inflammation** — adipose-tissue macrophages oversecrete **TNF-α, IL-6, IL-1, IL-18, resistin**, raising **CRP, fibrinogen and PAI-1** (a *pro-thrombotic state*); **adiponectin** (anti-inflammatory, insulin-sensitising; activates AMP-kinase) is **reduced**. Leptin resistance, mitochondrial/oxidative-stress dysfunction and an altered **gut microbiome** (↑Firmicutes/Bacteroidetes ratio) are additional contributors.

Clinical features and associated conditions

- ▶ Usually **asymptomatic**; examination shows **increased waist circumference and raised blood pressure**; less often **acanthosis nigricans** or lipoatrophy (markers of severe insulin resistance).
- ▶ **Cardiovascular disease** — patients are *twice as likely to die of CVD* and have a *threefold* higher risk of acute MI or stroke; relative risk for new-onset CVD $\approx 1.5\text{--}3\times$. Metabolic syndrome is present in up to **60%** of CHD patients >75 y and ~35% with premature CAD (≤ 45 y). In INTERHEART (26,903 subjects, 52 countries) diabetes (OR 2.72) and hypertension (OR 2.60) were the strongest components.
- ▶ **Type 2 diabetes** — risk increased **three- to fivefold**; in the Framingham Offspring Study the population-attributable risk was **62% (men)** and **47% (women)**, largely explained by rising fasting glucose.
- ▶ **Other associations** — **metabolic-(dysfunction)-associated fatty liver disease (MAFLD/MASLD)** and its progressive form **MASH/NASH** (affects ~10% of non-obese but up to **65%** of metabolic-syndrome patients; a route to cirrhosis and hepatocellular carcinoma); **polycystic ovary syndrome** (insulin resistance in 50–80%); **obstructive sleep apnoea**; hyperuricaemia/gout; microalbuminuria; raised homocysteine, apoB and viscosity.

Diagnosis and investigations

- ▶ Apply **Table criteria** at bedside + laboratory: measure **waist circumference and blood pressure**; **fasting lipid profile and fasting plasma glucose** are essential.
- ▶ Individualise additional tests: **apoB, hsCRP, fibrinogen, uric acid, urine albumin/creatinine ratio, liver function**; a **sleep study** if OSA is suspected; **testosterone, LH, FSH** if PCOS is suspected; assess MAFLD by the **FIB-4 fibrosis score or elastography**.
- ▶ Family history guides cardiovascular and diabetes risk; a **coronary artery calcium score** and the **10-year ASCVD risk estimator** refine primary-prevention decisions.

Management (target each component; weight loss is primary)

- **Lifestyle is first-line.** Weight reduction of **at least 5% (ideally $\geq 10\%$)** improves insulin sensitivity and most components. Caloric restriction is the key element (~ 3500 kcal ≈ 1 lb fat; a ~ 500 -kcal/day deficit ≈ 1 lb/week); diet adherence matters more than macronutrient type, favouring fruit, vegetables, whole grains, lean poultry and fish. **Physical activity** 30 min/day minimum (60–90 min for weight loss) plus behaviour modification for maintenance.

Component	Preferred therapy (after lifestyle)
Obesity	Anti-obesity drugs — semaglutide 2.4 mg ($\sim 14.9\%$ loss/68 wk), tirzepatide (GIP/GLP-1; ~ 15 – 20.9%), liraglutide 3.0 mg ($\sim 6\%$), phentermine/topiramate ($\sim 8\%$ in half), naltrexone/bupropion ($\geq 10\%$ in $\sim 20\%$), orlistat (blocks $\sim 30\%$ fat absorption). Bariatric/metabolic surgery if BMI >40 (or >35 with comorbidity; ≥ 30 with T2DM)
LDL-cholesterol	Statins first-line (lower LDL 15–60%); add ezetimibe (15–20%), bempedoic acid (combo up to 35%); PCSK9 inhibitors (45–60%) if FH or insufficient response
Triglycerides	Fibrates (fenofibrate/gemfibrozil, $\downarrow 30$ – 45%); high-dose EPA omega-3 (REDUCE-IT, JELIS); treat TG >500 mg/dL to prevent pancreatitis
Blood pressure	ACE inhibitor or ARB first choice; add diuretic / CCB / β -blocker / finerenone
Impaired fasting glucose	Lifestyle $\pm$ metformin to prevent progression to T2DM
Insulin resistance	Metformin and pioglitazone (TZD) — a meta-analysis (9 trials, 12,026 participants) showed pioglitazone reduced ASCVD events; GLP-1 RAs also improve insulin sensitivity

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology flow diagram (central diagram):** Centre box = *Expanded visceral adipose tissue / Insulin resistance*. Arrows to: **Liver** ($\uparrow$ FFA $\rightarrow$ $\uparrow$ glucose, $\uparrow$ VLDL-TG, $\uparrow$ apoB, $\uparrow$ CRP, $\uparrow$ fibrinogen); **Muscle** ($\downarrow$ insulin-mediated glucose uptake, $\uparrow$ intramuscular triglyceride); **Pancreas** (hyperinsulinaemia $\rightarrow$ β -cell failure $\rightarrow$ hyperglycaemia); **Blood vessel** ($\uparrow$ Na reabsorption, $\uparrow$ SNS, $\uparrow$ angiotensin II $\rightarrow$ hypertension); **Adipokines** ($\uparrow$ TNF- α , $\uparrow$ IL-6, $\uparrow$ PAI-1, $\downarrow$ adiponectin). Output boxes: *small dense LDL, low HDL, pro-thrombotic state, ASCVD, type 2 diabetes*. Labels to include: FFA, VLDL, apoC-III, PAI-1, adiponectin, IL-6, TNF- α , CRP, SNS.

Component	Preferred therapy (after lifestyle)
▶ The “five-pointed star” of diagnostic criteria: a central pentagon labelled <i>Metabolic syndrome</i> (<i>need</i> ≥ 3) with the five arms labelled Central obesity (waist), ↑Triglycerides ≥ 150, ↓HDL (<40 M/<50 F), BP $\geq 130/85$, Fasting glucose ≥ 100.	

Clinical / Diagnostic significance

- ▶ Identifies, beyond LDL-cholesterol, a **high cardiometabolic-risk phenotype** warranting aggressive global risk-factor modification.
- ▶ Fasting glucose within the cluster is the **best predictor of incident type 2 diabetes**; the syndrome flags the need for diabetes screening and prevention.
- ▶ Mandates screening for MAFLD/MASH, OSA and PCOS, each of which both reflects and aggravates insulin resistance.
- ▶ Treatment is **component-directed**: weight loss is the highest-yield single intervention because it improves all five components simultaneously.

High-yield exam pointers

- ▶ Synonyms: **syndrome X** / **insulin-resistance syndrome**; core defect = **insulin resistance** + **visceral adiposity**.
- ▶ **Diagnosis** = any 3 of 5 (NCEP:ATP III / Harmonized); **IDF makes central obesity mandatory**; waist cut-points are **ethnicity-specific** (lower for South Asians: ≥ 90 cm men / ≥ 80 cm women).
- ▶ Five components: **waist**, **TG** ≥ 150 , **HDL** <40 (M)/ <50 (F), **BP** $\geq 130/85$, **FPG** ≥ 100 mg/dL.
- ▶ Confers $\sim 2\times$ CVD mortality, $\sim 3\times$ MI/stroke, $3\text{--}5\times$ type 2 diabetes.
- ▶ Key biochemical signature: **high TG**, **low HDL**, **small dense LDL**, **↑apoB/apoC-III**, **↑CRP/PAI-1/fibrinogen**, **↓adiponectin**.
- ▶ **Acanthosis nigricans** = clinical clue to severe insulin resistance.
- ▶ First-line management = $\geq 5\text{--}10\%$ **weight loss**; antihypertensive of choice = **ACEi/ARB**; insulin sensitisers = **metformin**, **pioglitazone**.
- ▶ Strongly associated with MAFLD/MASH, PCOS, OSA, hyperuricaemia.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “The Metabolic Syndrome” (primary source: definitions, epidemiology, etiology/pathophysiology, associated conditions, component-directed treatment); cross-referenced chapters on Disorders of Lipoprotein Metabolism, Diabetes Mellitus, and Obesity.
- ▶ **Williams Textbook of Endocrinology, 15e** — “Disorders of Lipoprotein Metabolism” (AHA/NHLBI 2005 diagnostic criteria table, Asian waist cut-points, atherogenic

dyslipidaemia) and “Pathophysiology of Type 2 Diabetes Mellitus” (insulin-resistance/adipokine and gut-microbiome mechanisms).

- ▶ **CMDT 2026** — current-management context for the component disorders (lipids, diabetes/obesity, hypertension).

Coverage note: Harrison Ch 420 provides full, dedicated coverage of this topic. The detailed WHO 1998 and IDF-2005 obligatory criteria (e.g., microalbuminuria) are summarised from universally accepted standard internal medicine, as Harrison and Williams give only the NCEP:ATP III, Harmonized and AHA/NHLBI cut-point tables verbatim.



Myxedema coma

Asked in: Paper IV May 2022 — RGUHS MD General Medicine

Definition / Introduction — Myxedema coma is the extreme, decompensated, life-threatening end-stage of severe, long-standing **hypothyroidism**, listed in Harrison’s among the rare neurologic complications of thyroid hormone deficiency (alongside reversible cerebellar ataxia, dementia, and psychosis). It is a misnomer because frank coma is often absent; the syndrome is better understood as **decompensated hypothyroidism** characterised by a depressed sensorium, **hypothermia**, and progressive multiorgan slowing, usually unmasked by a precipitating stress in an elderly, undiagnosed or non-adherent hypothyroid patient. It is an **endocrine emergency** with a high mortality, demanding empirical thyroid hormone plus glucocorticoid and intensive supportive care before biochemical confirmation returns.

Predisposing background and precipitating factors

- ▶ **Underlying substrate:** chronic untreated or under-treated hypothyroidism — most commonly **autoimmune (Hashimoto’s) hypothyroidism** (TPO and Tg antibodies positive in >95%), atrophic thyroiditis, post-radioiodine or post-thyroidectomy states, and drug-induced disease (amiodarone, lithium). Onset of hypothyroidism is insidious, so many patients present already decompensated.
- ▶ **Typical patient:** elderly woman in the **winter months**; the mean age at diagnosis of autoimmune hypothyroidism is ~60 years, and prevalence rises with age.
- ▶ **Common precipitants** (these tip compensated hypothyroidism into coma):
 - **Infection / sepsis** — pneumonia, urinary sepsis (most frequent trigger).
 - **Cold exposure** — exploits the already-impaired thermogenesis.
 - **Cardiovascular events** — myocardial infarction, congestive cardiac failure.
 - **Cerebrovascular accident, trauma, surgery, GI bleeding.**

- **CNS-depressant drugs** — sedatives, opioids, anaesthetics, antipsychotics.
- **Abrupt cessation of levothyroxine** (patients feel no immediate difference after missing doses, predisposing to self-discontinuation, per Harrison).
- ▶ **Coexisting adrenal insufficiency** must always be anticipated — autoimmune hypothyroidism associates with **Addison's disease (Schmidt's syndrome)** and **autoimmune polyendocrine syndrome type 2** (Addison's in 40–50%).

Pathophysiology and clinical features

The picture is one of “hypo-everything” — generalised slowing of metabolism with reduced thermogenesis, blunted respiratory drive, and reduced cardiac output, plus tissue **myxedema** (glycosaminoglycan deposition that traps water → non-pitting swelling).

- ▶ **Decreased mental status:** lethargy, obtundation, stupor, frank coma; **seizures** may occur. Memory and concentration are impaired; psychosis (“myxedema madness”) may precede coma.
- ▶ **Hypothermia:** core temperature may fall below 34°C; its degree correlates with prognosis, and a “normal” temperature in a hypothyroid septic patient is a red flag.
- ▶ **Hypoventilation / respiratory failure:** from **diminished ventilatory drive**, impaired respiratory muscle function, pleural effusion, and obstructive sleep apnoea (all named in the chapter) → **CO₂ retention (hypercapnia), hypoxia, and CO₂ narcosis** that deepen the coma.
- ▶ **Cardiovascular:** **bradycardia**, reduced myocardial contractility, reduced stroke volume and cardiac output, increased peripheral resistance with **diastolic hypertension**, and blood diverted from skin → **cool extremities**. **Pericardial effusions occur in up to 30%** (rarely tamponade); cardiomyopathy is rare. Late hypotension and shock supervene.
- ▶ **Renal / metabolic:** **hyponatremia** (impaired free-water excretion / SIADH-like), **hypoglycemia** (especially if concurrent adrenal failure), and free-water retention.
- ▶ **General myxedematous facies:** puffy face with **edematous eyelids**, macroglossia, non-pitting **pretibial edema**, dry coarse skin with carotene-yellow tinge, diffuse alopecia with loss of the outer third of eyebrows, hoarse voice, and **delayed relaxation of tendon reflexes** (hung-up reflexes).
- ▶ **GI:** constipation progressing to ileus / megacolon; ascites from serous cavity effusions.

Laboratory and diagnostic evaluation

- ▶ **Thyroid function:** in primary hypothyroidism, **TSH is markedly elevated** with a **low free T₄**; a normal TSH essentially excludes primary disease. In **secondary (central) hypothyroidism**, TSH may be low, normal, or only slightly raised, so a **low free T₄** is the confirmatory finding — do not be falsely reassured by a non-elevated TSH.
- ▶ **Supportive abnormalities** (per chapter): elevated creatine phosphokinase (CPK), raised cholesterol and triglycerides, and normocytic or macrocytic anemia.

- **Other:** hyponatremia, hypoglycemia, arterial blood gas showing hypoxia + hypercapnia + respiratory acidosis; ECG — sinus bradycardia, low-voltage complexes, prolonged QT, flattened/inverted T waves.
- **Always send a paired cortisol** (and ACTH) before steroids to detect concurrent adrenal insufficiency, and a septic screen (cultures, CXR) for the precipitant.
- **Diagnosis is clinical** — treatment must not await laboratory confirmation.

Management

Myxedema coma is treated in the ICU; therapy is empirical and combines thyroid hormone replacement, stress-dose glucocorticoid, and aggressive supportive care directed at the precipitant.

Component	Action / regimen	Rationale & cautions
Thyroid hormone (T4)	Levothyroxine IV loading 200–400 µg, then maintenance ~1.6 µg/kg/day reduced to ~75% when given IV	Rapidly restores a hormone pool; lower loading dose in the elderly / cardiac disease to avoid precipitating ischaemia or arrhythmia
+/- Liothyronine (T3)	May add IV T3 5–20 µg bolus then 2.5–10 µg every 8 h until stable	Peripheral T4→T3 conversion is impaired in critical illness; T3 acts faster but risks ischaemia — use lower doses in cardiac patients
Glucocorticoid	IV hydrocortisone 50–100 mg every 8 h	Covers coexisting adrenal insufficiency (Schmidt's syndrome / APS-2); give <i>before or with</i> thyroid hormone, as T4 can precipitate adrenal crisis
Ventilation	Airway protection, mechanical ventilation for hypercapnic/hypoxic respiratory failure	Hypoventilation + CO ₂ narcosis are leading causes of death
Rewarming	Passive external rewarming (blankets); avoid vigorous active rewarming	Active surface rewarming causes peripheral vasodilatation → hypotension and circulatory collapse
Hyponatremia	Fluid restriction; hypertonic saline only if severe/symptomatic	Correct slowly to avoid osmotic demyelination
Hypoglycemia	IV dextrose	Common, especially with adrenal failure
Hypotension	Cautious IV fluids; vasopressors often poorly effective until thyroid hormone given	Pressors of limited benefit in hypothyroid myocardium

Component	Action / regimen	Rationale & cautions
Precipitant	Empirical broad-spectrum antibiotics, treat MI/CHF, withdraw sedatives	Infection is the commonest trigger and is often occult (no fever)

- ▶ **General measures:** continuous cardiac monitoring, avoid all CNS depressants, slow careful warming, monitor electrolytes and glucose, and treat the precipitating illness aggressively.
- ▶ **Monitoring response:** clinical (mental status, temperature, respiration, heart rate) and serial TSH/free T4.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology spider diagram of myxedema coma** — central box “Severe long-standing hypothyroidism + Precipitant (infection / cold / sedatives / MI / stopping LT4)” with radiating labelled arms: Hypothermia, Hypoventilation → hypercapnia / hypoxia (CO₂ narcosis), Bradycardia / low cardiac output / pericardial effusion, Hyponatremia, Hypoglycemia, Altered sensorium → coma / seizures, Non-pitting myxedema / puffy facies.
- ▶ **Management flow box** — vertical labels: ICU + airway/ventilation → send cortisol → IV hydrocortisone 50–100 mg q8h → IV levothyroxine load 200–400 µg then 1.6 µg/kg/d → passive rewarming → correct Na⁺ / glucose → empirical antibiotics → treat precipitant.

Clinical / Diagnostic significance

- ▶ Suspect myxedema coma in any **elderly patient with unexplained hypothermia, hyponatremia and depressed consciousness**, especially with a thyroidectomy scar, myxedematous facies, or hung-up reflexes.
- ▶ It is a **clinical diagnosis and a medical emergency** — empirical thyroid hormone + glucocorticoid must begin before TSH/T4 return; delay increases mortality.
- ▶ **Never give thyroid hormone alone** when adrenal reserve is uncertain — it can accelerate cortisol clearance and trigger an Addisonian crisis; hence hydrocortisone first.
- ▶ **Mortality remains high (~20–40%)**; outcome correlates with depth of hypothermia, hypotension, and the severity of the precipitating illness — early recognition is the main determinant of survival.
- ▶ Distinguish from non-thyroidal illness (“sick euthyroid”), sedative overdose, hypothermia of other cause, and CO₂ narcosis from primary lung disease.

High-yield exam pointers

- ▶ Triad to write first: **hypothermia + altered sensorium + precipitating stress** in a known/occult hypothyroid patient.

- ▶ Commonest precipitant = infection (pneumonia/UTI); commonest season = winter; commonest patient = elderly woman.
- ▶ TSH high + free T4 low = primary; free T4 low with non-elevated TSH = central — do not miss it.
- ▶ Classic biochemistry: hyponatremia, hypoglycemia, raised CPK, hypercapnia/hypoxia on ABG; ECG bradycardia + low voltage + prolonged QT.
- ▶ Pericardial effusion in up to 30% of hypothyroid patients (chapter figure).
- ▶ Hydrocortisone before/with levothyroxine — anticipate Schmidt's syndrome (hypothyroidism + Addison's).
- ▶ Passive (not active) rewarming — active rewarming → vasodilatation and shock.
- ▶ High mortality — treat empirically in the ICU; do not wait for thyroid assays.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 395 “Hypothyroidism” (clinical manifestations Table 395-3; cardiovascular and respiratory features; laboratory evaluation; LT4 dosing; autoimmune/Schmidt's and APS-2 associations; myxedema coma listed among rare neurologic complications).

Coverage note: The provided ch395 text grounds the definition, predisposing causes, clinical features, cardiovascular/respiratory/renal derangements, and laboratory profile, but the file is **truncated and does not contain Harrison's dedicated myxedema-coma management paragraph** (it explicitly names myxedema coma only as a rare neurologic complication, line 259). The specific emergency **management details** — IV levothyroxine loading dose 200–400 µg then ~1.6 µg/kg/d, optional liothyronine 5–20 µg, hydrocortisone 50–100 mg q8h, passive rewarming, ventilatory support, and the ~20–40% mortality figure — are therefore drawn from **universally accepted standard internal medicine** (Harrison's myxedema-coma section / CMDT, flagged here per spec cmdt: true) rather than verbatim from the supplied chapter text. All such figures are standard and accurate; the candidate should treat the management table as textbook-standard rather than quoted from the provided excerpt.



Newer Hypoglycemic agents for management of Type II Diabetes Mellitus

Asked in: Paper IV 17 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — “Newer” glucose-lowering agents are the classes that have entered type 2 diabetes (T2DM) management after the traditional triad of **metformin**, **sulfonylureas** and **thiazolidinediones** (TZDs), and which target previously untapped pathophysiologic pathways — the

incretin axis and renal glucose handling. The four key groups are the DPP-4 inhibitors, the GLP-1 receptor agonists (GLP-1RAs), the dual GIP/GLP-1 receptor agonist (tirzepatide) and the SGLT-2 inhibitors. Their importance lies less in raw glucose lowering (modest HbA1c reduction of ~0.5–1%) than in their proven **cardiovascular, heart-failure and renal protection**, weight loss, and freedom from hypoglycaemia — which have moved them from “add-on” to **organ-protective first-line agents** in T2DM with comorbidity.

Classification of glucose-lowering agents (mechanistic)

Class	Site/Mechanism	Examples
Biguanide (context)	↓ Hepatic glucose output, ↑ insulin sensitivity	Metformin
Insulin secretagogues (older)	Close ATP-sensitive K ⁺ channel on β-cell	Sulfonylureas; glinides (repaglinide, nateglinide)
TZD (older)	PPAR-γ agonist → ↓ insulin resistance	Pioglitazone
DPP-4 inhibitors (<i>newer</i>)	Block GLP-1/GIP degradation (incretin <i>enhancers</i>)	Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin
GLP-1RAs (<i>newer</i>)	Incretin-mimetic; ↑ glucose-dependent insulin, ↓ glucagon, slows gastric emptying, satiety	Liraglutide, dulaglutide, semaglutide, lixisenatide, exenatide
GIP/GLP-1 dual agonist (<i>newest</i>)	Co-agonism at GIP + GLP-1 receptors	Tirzepatide
SGLT-2 inhibitors (<i>newer</i>)	Block proximal-tubule glucose reabsorption → glycosuria (insulin-independent)	Empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, bexagliflozin
Amylin analogue	Slows gastric emptying, ↓ glucagon	Pramlintide (injectable, with insulin)

Incretin-based therapies: DPP-4 inhibitors, GLP-1RAs and tirzepatide

- **The incretin effect:** oral glucose evokes a larger insulin response than IV glucose because intestinal L-cell GLP-1 (and K-cell GIP) amplify *glucose-dependent* insulin secretion, suppress glucagon, slow gastric emptying and increase satiety. Native GLP-1 is degraded within 1–2 minutes by dipeptidyl peptidase-4 (DPP-4).
- **DPP-4 inhibitors** (incretin *enhancers*) block this enzyme, roughly doubling endogenous GLP-1/GIP. They lower HbA1c by 0.5–0.8%, act mainly on fasting glucose, are **weight-neutral**, oral, and do **not** cause hypoglycaemia alone or with metformin. They are very well tolerated; rare adverse effects include **pancreatitis, severe arthralgia, angioedema and Stevens-Johnson syndrome**. They must **not** be combined with a GLP-1RA (redundant mechanism).

- ▶ **GLP-1RAs** are DPP-4-resistant peptide agonists giving *pharmacologic* GLP-1 levels — far greater incretin action than DPP-4 inhibitors. They produce **HbA1c ↓ 0.5–1.5%**, substantial **weight loss**, and **cardiovascular + renoprotective** benefit. Long-acting once-weekly agents (dulaglutide, extended-release exenatide, semaglutide) are preferred over short-acting twice-daily exenatide/lixisenatide. **Oral semaglutide** (co-formulated with the absorption enhancer **SNAC**) is the first oral GLP-1RA. Liraglutide 3 mg and semaglutide 2.4 mg are separately licensed for **obesity**.
- ▶ **Tirzepatide** — a once-weekly **dual GIP/GLP-1 receptor agonist** — is the most potent agent yet: in head-to-head trial vs semaglutide 1 mg, HbA1c fell **2.3%** (from 8.3% baseline) with **>10% weight loss in 57%** of patients. CMDT quotes HbA1c reductions of **1.9–2.6%** and weight loss of **6–13 kg**.

Agent	Route / frequency	Typical dose (titrated)	HbA1c ↓
Sitagliptin	Oral OD	100 mg (50 if eGFR 30–50; 25 if <30)	0.5–0.8%
Linagliptin	Oral OD	5 mg — <i>no renal adjustment</i> (biliary excretion)	0.5–0.8%
Alogliptin	Oral OD	25 mg (12.5 if eGFR 30–60; 6.25 if <30)	0.5–0.8%
Liraglutide	SC once daily	0.6 → 1.2 → 1.8 mg	0.6–1.5%
Dulaglutide	SC once weekly	0.75 → 1.5 → 4.5 mg	~1.5–1.8%
Semaglutide	SC once weekly	0.25 → 0.5 → 1 → 2 mg	1.5–2.1%
Oral semaglutide	Oral OD, fasting	3 → 7 → 14 mg	—
Tirzepatide	SC once weekly	2.5 → 5 → up to 15 mg	1.9–2.6%

SGLT-2 inhibitors

- ▶ **Mechanism:** SGLT-2 in the proximal convoluted tubule mediates ~90% of filtered glucose reabsorption. Inhibition **lowers the renal threshold for glucose**, producing glycosuria and an **insulin-independent** fall in plasma glucose (so efficacy is *eGFR-dependent* — weaker as CKD advances). Associated **natriuresis** gives a mild diuretic effect and a **3–6 mmHg fall in systolic BP**; caloric loss yields **2–5 kg weight loss**.
- ▶ **Efficacy:** HbA1c ↓ 0.5–1.0%; no intrinsic hypoglycaemia.
- ▶ **Cardiorenal benefit** is the defining feature: reduced **heart-failure hospitalisation** (most consistent effect), reduced MACE/CV mortality in established ASCVD, and **slowed progression of diabetic kidney disease**. Per KDIGO, may be initiated for renoprotection down to **eGFR ~20**

mL/min/1.73 m² and continued until dialysis, even though the *glucose-lowering* effect is lost below eGFR 45.

- **Adverse effects:** genital mycotic infections and UTIs (~8–9%); euglycemic DKA (insulin-deficient states, fasting, surgery, acute illness); volume depletion / transient creatinine rise; necrotizing fasciitis of the perineum (Fournier gangrene); canagliflozin specifically — ↑ amputations (CANVAS, HR ~1.97), ↓ bone mineral density and ↑ fractures; small (3–8%) rise in LDL. Withhold 3 days before major surgery and during acute illness.

Agent	Glycaemic dose	eGFR caution (glycaemic)
Empagliflozin	10 mg OD (max 25)	Avoid <30
Dapagliflozin	10 mg OD (5 mg if liver failure)	Avoid <45 (renoprotection to eGFR 25)
Canagliflozin	100 mg OD (up to 300)	100 mg if eGFR 30–60; avoid <30
Ertugliflozin	5 → 15 mg OD	Avoid <45

Cardiorenal outcome trials (high-yield)

Trial	Drug	Key result
EMPA-REG OUTCOME	Empagliflozin	↓ all-cause mortality 32%, CV death 38%, HF hospitalisation 35%
CANVAS	Canagliflozin	↓ MACE & HF; ↑ amputation (HR 1.97), ↑ fracture
DECLARE-TIMI 58	Dapagliflozin	↓ CV death / HF hospitalisation (incl. primary-prevention cohort)
CREDENCE	Canagliflozin	Renal-outcomes trial — ↓ progression of diabetic nephropathy
LEADER	Liraglutide	↓ MACE 13%, CV death 22%, all-cause mortality 15%, albuminuria 26%
SUSTAIN-6	Semaglutide	↓ MACE 26%; ↓ renal events; retinopathy signal ; no mortality benefit
REWIND	Dulaglutide	↓ MACE and composite microvascular (retinopathy + nephropathy)
SAVOR-TIMI 53 / EXAMINE	Saxagliptin / Alogliptin	↑ heart-failure hospitalisation (DPP-4 class caution)

Trial	Drug	Key result
TECOS / CAROLINA	Sitagliptin / Linagliptin	CV-neutral (CAROLINA: neutral vs glimepiride)

Choice of agent — ADA/EASD-style algorithm (Harrison Fig 416-3)

- ▶ **Metformin + lifestyle** remains the foundation when there is no cardiorenal disease (efficacious, cheap, weight-favourable).
- ▶ **Comorbidity now drives selection, independent of HbA1c:**
 - ASCVD or high CV risk → GLP-1RA or SGLT-2 inhibitor with proven benefit.
 - Heart failure (HFrEF or HFpEF) → SGLT-2 inhibitor.
 - Chronic kidney disease / albuminuria → SGLT-2 inhibitor (GLP-1RA if SGLT-2i not tolerated).
 - Weight loss a priority → GLP-1RA or tirzepatide (greatest effect).
- ▶ These agents may be **combined with metformin or each other** (e.g. metformin + SGLT-2i + GLP-1RA) for additive effect — but GLP-1RA + DPP-4 inhibitor is irrational. Reassess HbA1c every 3 months; add basal insulin if targets unmet.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Sites of action of glucose-lowering agents** (label: *intestine/L-cell* → GLP-1, *DPP-4 inhibitor*, *GLP-1RA*, *pancreatic β -cell (insulin) & α -cell (glucagon)*, *liver — hepatic glucose output / metformin*, *muscle & fat — insulin sensitivity / TZD*, *kidney proximal tubule — SGLT-2 inhibitor* → glycosuria).
- ▶ **Diagram 2 — Comorbidity-driven treatment algorithm** (boxes: *T2DM + metformin/lifestyle* → branch to *ASCVD/high risk* → GLP-1RA or SGLT-2i, *Heart failure* → SGLT-2i, *CKD* → SGLT-2i, *Weight loss* → GLP-1RA / tirzepatide).

Clinical / Diagnostic significance

- ▶ **Cardiorenal first:** in T2DM with ASCVD, HF or CKD, start an **SGLT-2 inhibitor and/or GLP-1RA early** regardless of baseline HbA1c — they reduce hard outcomes (CV death, HF hospitalisation, ESKD).
- ▶ **Hypoglycaemia avoidance:** incretin agents and SGLT-2i do not cause hypoglycaemia alone; reduce the dose of a co-prescribed **sulfonylurea or insulin** to prevent it.
- ▶ **Euglycemic DKA:** a “normal glucose” does **not** exclude DKA in a patient on an SGLT-2 inhibitor — check ketones in any unwell SGLT-2i user; hold the drug during fasting, acute illness and perioperatively.
- ▶ **GLP-1RA / tirzepatide safety:** contraindicated with **personal/family history of medullary thyroid carcinoma or MEN-2** (rodent C-cell tumours); avoid in prior **pancreatitis**; warn re

nausea/vomiting and stop if persistent abdominal pain; SUSTAIN-6 flagged worsening **retinopathy** with rapid glucose lowering.

- ▶ **Renal dosing:** linagliptin needs no adjustment (biliary); liraglutide/semaglutide/dulaglutide are safe in renal failure; exenatide is contraindicated below eGFR 30.

High-yield exam pointers

- ▶ “Newer” = DPP-4 inhibitors, GLP-1RAs, GIP/GLP-1 dual agonist (tirzepatide), SGLT-2 inhibitors.
- ▶ DPP-4i = incretin enhancer (weak, weight-neutral, oral); GLP-1RA = incretin mimetic (strong, weight loss, CV/renal benefit).
- ▶ EMPA-REG = first CVOT to show CV/HF benefit of an SGLT-2 inhibitor; LEADER = first for a GLP-1RA.
- ▶ SGLT-2i triad of harm: **genital mycotic infection, euglycemic DKA, Fournier gangrene**; canagliflozin → **amputation + fracture**.
- ▶ **Tirzepatide** (dual GIP/GLP-1) gives the greatest HbA1c ($\approx 2\text{--}2.6\%$) and weight reduction.
- ▶ **Linagliptin** = the DPP-4 inhibitor needing **no renal dose adjustment**.
- ▶ Never combine GLP-1RA with a DPP-4 inhibitor.
- ▶ Metformin: max ~ 2000 mg/day; reduce at eGFR 30–45; **stop if eGFR < 30** (lactic-acidosis risk).
- ▶ Comorbidity, not HbA1c alone, now selects the second agent.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Diabetes Mellitus: Management and Therapies” (glucose-lowering agent classes, mechanisms, Table of agents, glycaemic-management algorithm Fig 416-3).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Therapeutics of Type 2 Diabetes Mellitus” (incretin physiology, DPP-4 inhibitors, GLP-1RAs, tirzepatide, SGLT-2 inhibitors, and the cardiovascular/renal outcome trials EMPA-REG, CANVAS, DECLARE-TIMI 58, CREDENCE, LEADER, SUSTAIN-6, REWIND, CAROLINA).
- ▶ **CMDT 2026** — “Diabetes Mellitus & Hypoglycemia” (current drug doses, eGFR thresholds, KDIGO renoprotection cut-off, Fournier gangrene, euglycemic DKA, peri-operative discontinuation).



Newer Insulins

Asked in: Paper IV 17 Apr 2026 · Paper II May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — “Newer insulins” denotes the **insulin analogues** — insulin molecules whose amino-acid sequence is deliberately altered by recombinant DNA technology to modify absorption kinetics (onset, peak, duration) while preserving full biologic activity. They comprise **rapid-acting** and **ultra-rapid** prandial analogues, **long-acting / ultra-long-acting** basal analogues (including the **once-weekly** insulin), their **concentrated**, **biosimilar**, **premixed** and **fixed-ratio GLP-1RA combination** forms, and **inhaled** insulin. They were developed to mimic physiologic basal–bolus secretion more closely than the older human (regular, NPH) insulins.

Rationale — limitations of conventional human insulins

- ▶ **Regular (soluble) insulin** self-aggregates into hexamers in solution, giving a slow onset (~30–60 min, so it must be injected 20–30 min pre-meal), a delayed peak (2–3 h) and a long tail (6–8 h) that causes **late post-prandial hypoglycaemia**.
- ▶ **NPH (isophane)** has a pronounced peak (4–10 h) and a duration (10–20 h) too short for true 24-h basal cover, mandating twice-daily dosing and producing **nocturnal hypoglycaemia**; its action is variable within and between patients.
- ▶ Goal of analogue design: rapid analogues that match the post-prandial glucose excursion and decay with it, plus **peakless, reproducible, ~24-h (or longer) basal** insulin — together permitting flexible basal–bolus therapy with less hypoglycaemia.

Classification and pharmacokinetics

Category	Members (analogue)	Onset	Peak	Effective duration
Rapid-acting	Lispro, Aspart, Glulisine	<15 min	0.5–1.5 h	3–5 h
Ultra-rapid	Faster aspart (Fiasp), Lispro-aabc (Lyumjev)	~10–11 min faster than parent	—	shorter tail
Inhaled	Technosphere human insulin (Afrezza)	<15 min	~1 h	~3 h
Long-acting	Glargine U-100, Detemir	2–4 h	flat / minimal	20–24 h (detemir 12–24 h)
Ultra-long-acting	Degludec, Glargine U-300	1–9 h	flat	>42 h (degludec); >24 h (U-300)
Once-weekly	Insulin icodec	basal	flat	~1 week

(Standard human insulins for comparison: regular onset 0.5–1 h, peak 2–3 h, duration 6–8 h; NPH onset 2–4 h, peak 6–10 h, duration 12–20 h.)

Rapid-acting and ultra-rapid (prandial) analogues

- ▶ **Mechanism** — single/dual amino-acid changes abolish self-aggregation, so the insulin is absorbed as monomers → **faster onset, lower/earlier peak, shorter duration** than regular insulin. This entrains insulin action to the post-meal glucose rise and, because action decays as glucose falls, **reduces hypoglycaemia**.
- ▶ **Lispro** — proline and lysine at positions **B28/B29 are reversed** (Lys-B28, Pro-B29).
- ▶ **Aspart** — proline at **B28 replaced by aspartic acid**.
- ▶ **Glulisine** — asparagine-B3 → lysine and lysine-B29 → glutamic acid.
- ▶ Injected **just before (<10 min)** a meal; may be given **after** a meal in gastroparesis or unpredictable intake. Preferred over regular insulin for prandial coverage and are the insulins used in CSII pumps.
- ▶ **Ultra-rapid formulations** — *Fiasp* = aspart + **niacinamide (vitamin B3)** (onset ~10 min faster); *Lyumjev* (lispro-aabc) = lispro + **treprostinil + citrate** (local vasodilation + increased vascular permeability; onset ~11 min faster, lower 1–2 h post-prandial excursions). A **biosimilar lispro** (*Admelog*) is available.

Long-acting, ultra-long-acting and once-weekly (basal) analogues

- ▶ **Glargine** — asparagine at A21 replaced by glycine and two arginines added to the C-terminus of the B chain; this raises the isoelectric point so it is soluble at acidic pH but forms **microprecipitates at neutral subcutaneous pH**, releasing slowly → **peakless ~24-h action** with **less nocturnal hypoglycaemia than NPH**. Must **not be mixed** with other insulins (acidic pH). Biosimilars: *Basaglar*, *Semglee*, *Rezvoglar*.
- ▶ **Detemir** — fatty-acid (myristic acid) acylation at Lys-B29 promotes **reversible albumin binding**, prolonging action (12–24 h); being **phased out** of the market.
- ▶ **Degludec** — extension/modification of the B-chain carboxy-terminus causes formation of **soluble multihexamer chains in subcutaneous tissue plus albumin binding** → half-life ~25 h, duration >42 h. Gives glycaemic control similar to glargine but with **less nocturnal and severe hypoglycaemia**, and its long, flat profile allows **flexible (varying) injection timing**. Available U-100 and U-200.
- ▶ **Insulin icodec (once-weekly)** — Lys-B29 conjugated to a C20 fatty diacid (1,20-icosanedioic acid) with three substitutions (**A14E, B16H, B25H**); the diacid gives **strong reversible albumin binding** while the substitutions **attenuate receptor affinity and resist degradation**, yielding a ~1-week duration. Approved in Europe, Canada, Australia, China and Japan.

Concentrated, premixed, biosimilar and combination forms

- ▶ **Concentrated insulins** (smaller injection volume for high requirements / insulin resistance):
 - **U-300 glargine (Toujeo)** — one-third the volume, flatter and longer action, **less hypoglycaemia than U-100 glargine**.

- U-200 degludec, U-200 lispro, and U-500 regular (for severe insulin resistance / total daily dose >200 U; *not bioequivalent* to U-100 — switch with care).
- ▶ **Analogue premixes** — Humalog Mix 75/25 and 50/50 (NPL + lispro), NovoLog Mix 70/30 (aspart protamine/aspart); Ryzodeg 70/30 = degludec/aspart (can be given once or twice daily). Convenient (2 injections) but **not suitable for type 1 DM** as basal and prandial components cannot be titrated independently.
- ▶ **Fixed-ratio basal-insulin + GLP-1RA combinations** — degludec + liraglutide (IDegLira, Xultophy) and glargine + lixisenatide (iGlarLixi, Soliqua) — effective with **less weight gain**.
- ▶ **Biosimilars** lower cost (lispro and glargine biosimilars available).

Inhaled insulin

- ▶ **Technosphere insulin (Afrezza)** — dry-powder **regular human** insulin inhaled pre-meal; rapidly absorbed (peak insulin 12–15 min, baseline by ~3 h), effect comparable to rapid analogues when combined with basal insulin.
- ▶ Supplied as colour-coded 4-, 8-, 12-unit single-use cartridges.
- ▶ **Adverse effects / cautions** — cough (~27%), small early fall in FEV1; **contraindicated in smokers and in asthma/COPD**; perform **spirometry (FEV1)** before and periodically during therapy. A lung-cancer signal was noted (all in ever-smokers); the earlier inhaled insulin Exubera was withdrawn.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pharmacokinetic (action-profile) graph** — x-axis *Time (h)* 0–42, y-axis *Plasma insulin / glucose-lowering effect*; overlay labelled curves: **Rapid** (aspart/lispro/glulisine) sharp early peak; **Regular** broader peak; **NPH** intermediate dome; **Glargine U-100 / Detemir** flat ~24 h; **Degludec / Glargine U-300** flat >24–42 h; **Inhaled** narrow early spike. Label *onset*, *peak*, *duration* on the rapid and NPH curves.
- ▶ **Insulin molecule schematic** — A-chain and B-chain with labelled modification sites: B28/B29 reversal (lispro), B28 Asp (aspart), A21 Gly + B-chain di-arginine (glargine), B29 fatty-acid acylation (detemir/degludec/icodec).

Clinical / Diagnostic significance

- ▶ **Basal-bolus (MDI) regimen** — basal glargine/degludec once daily + rapid analogue (lispro/aspart/glulisine) at each meal; total **0.4–1.0 U/kg/day**, ~30–50% as basal. Prandial dose set by an **insulin-to-carbohydrate ratio** (commonly 1 U / 10–15 g) plus a **correction factor** ($\approx 1500 \div \text{total daily dose for mg/dL drop per unit}$).
- ▶ **Hypoglycaemia reduction** — flat, reproducible basal analogues markedly lower **nocturnal/severe hypoglycaemia** versus NPH; rapid analogues lower late post-prandial hypoglycaemia.

- ▶ **Flexibility** — degludec and U-300 glargine allow varied daily injection times; note degludec's long washout (~42 h) when a patient fasts for procedures or is switched to another basal insulin.
- ▶ **Special situations** — concentrated insulins for severe insulin resistance; ultra-rapid/inhaled insulin for unpredictable intake or needle-averse patients; fixed-ratio GLP-1RA combos when weight gain is a concern; biosimilars to reduce cost.
- ▶ Delivered by **pens (including Bluetooth “smart” pens)**, **vial/syringe**, or **CSII pumps / automated insulin-delivery (hybrid closed-loop) systems** using rapid analogues.

High-yield exam pointers

- ▶ Rapid analogues (lispro/aspart/glulisine): inject **<10–15 min pre-meal**; onset <15 min, duration 3–5 h; **do not self-aggregate**.
- ▶ **Glargine** = A21 Asn→Gly + 2 Arg on B-chain → microprecipitates; **peakless ~24 h**; never mix.
- ▶ **Degludec** = multihexamer + albumin binding; half-life ~25 h, duration **>42 h**; flexible timing.
- ▶ **Icodec** = once-weekly basal (C20 diacid → albumin binding; A14E/B16H/B25H substitutions).
- ▶ **Fiasp** = aspart + niacinamide; **Lyumjev** = lispro + treprostinil + citrate (ultra-rapid).
- ▶ **U-300 glargine / U-200 degludec / U-200 lispro / U-500 regular** = concentrated; U-500 for resistance >200 U/day.
- ▶ **Fixed-ratio combos**: IDegLira (Xultophy), iGlarLixi (Soliqua).
- ▶ **Inhaled (Afrezza)**: 4/8/12-U cartridges; cough ~27%, falls FEV₁; **contraindicated in smokers/asthma/COPD**; spirometry first.
- ▶ Only **regular and aspart** insulin may be given IV.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Diabetes Mellitus: Management and Therapies” (insulin preparations, mechanisms of lispro/glargine/degludec, Table 416-5, basal-bolus regimens).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Type 1 Diabetes Mellitus” (insulin types and action profiles, Table 35.6; ultra-rapid analogues; concentrated insulins; MDI/CSII dosing).
- ▶ **CMDT 2026** — “Diabetes Mellitus & Hypoglycemia” (analogue characteristics, ultra-rapid Fiasp/Lyumjev, glargine/degludec/**icodec** details, concentrated and premixed insulins, inhaled Technosphere insulin and its cautions).

Coverage note: The corpus richly covers all analogue classes including once-weekly icodec; insulin **detemir**'s specific fatty-acid (myristoyl) acylation mechanism is stated here as universally accepted standard pharmacology (the corpus notes detemir is being phased out but does not detail its structure).



Osteoporosis

Asked in: Paper IV Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Osteoporosis is a condition characterised by a **reduction in the strength of bone leading to skeletal fragility and an increased risk of fractures**. Although bone mineral density (BMD) is used to define it, bone strength also depends on **bone quality** — microarchitecture, remodelling rate, mineralisation and the accumulation of microdamage. It is operationally defined by the WHO as a BMD that is ≥ 2.5 standard deviations below the young-adult mean (T-score ≤ -2.5). It is the commonest metabolic bone disease, affecting >10 million individuals in the United States, predominantly **postmenopausal women**, though **30% of fragility fractures occur in men**. The clinically important fractures are **vertebral, hip and wrist (Colles') fractures**.

Densitometric classification (WHO) and key definitions

- ▶ T-score compares an individual's BMD with the mean of a **young-adult (age 30), sex- and race-matched** population (1 T-score unit = 1 SD); the **Z-score** compares with an **age- and sex-matched** reference population.

Category	T-score (lumbar spine / femoral neck / total hip)
Normal	> -1.0
Low bone density / osteopenia	-1.0 to -2.5
Osteoporosis	≤ -2.5
Severe (established) osteoporosis	≤ -2.5 with a fragility fracture

- ▶ **Fragility (low-trauma) fracture** = fracture following a fall from standing height or less; in adults aged >50, any fracture **except those of fingers, toes, face and skull** is regarded as fragility. Any fracture in a **woman >50 or a man >60** should trigger investigation for osteoporosis.
- ▶ Because **>50% of fractures occur in individuals with osteopenia** (T-score -1.0 to -2.5), emphasis has shifted to **absolute fracture risk** (e.g., FRAX) rather than BMD threshold alone.

Pathophysiology — bone remodelling

- ▶ In adults the principal skeletal process is **remodelling** (not modelling), performed by the **basic multicellular unit (BMU)**: osteoclasts (monocyte-macrophage lineage) resorb a cavity, then osteoblasts (mesenchymal lineage) lay down osteoid that mineralises; **osteocytes** are terminally differentiated osteoblasts that orchestrate the process.
- ▶ **Peak bone mass** is achieved by early adulthood and is largely **genetically determined** (heritability 50–80%); after age 30–45 years **resorption exceeds formation**, producing slow bone loss, exaggerated in women by oestrogen deficiency.

- ▶ **RANK–RANKL–OPG axis:** RANKL (a TNF-family cytokine from osteoblasts, osteocytes, T cells) binds **RANK** on osteoclast precursors → osteoclast formation, activation and survival. **Osteoprotegerin (OPG)** is a decoy receptor that neutralises RANKL. The balance of these three determines bone resorption.
- ▶ **Wnt–sclerostin pathway:** Wnt signalling (stimulated by mechanical loading and PTH) promotes osteoblastic bone formation and lowers RANKL; **sclerostin**, an osteocyte protein, inhibits Wnt and bone formation. Both RANKL and Wnt pathways are major drug targets.
- ▶ **Oestrogen deficiency** (chiefly menopause, mean age 51 y) drives loss by **increasing RANKL and decreasing OPG**, increasing remodelling activation frequency and prolonging osteoclast (while shortening osteoblast) lifespan. **Trabecular bone** (80% of surface area) is affected first — hence **vertebral fractures are the earliest consequence**.
- ▶ **Calcium/vitamin D:** inadequate intake → **secondary hyperparathyroidism** → increased remodelling and bone loss. **LRP5** activating mutations cause high bone mass; inactivating mutations cause osteoporosis–pseudoglioma syndrome.

Aetiology — primary and secondary causes

- ▶ **Primary:** postmenopausal (type I, oestrogen-related, trabecular/vertebral) and age-related/senile (type II); idiopathic (including in men and pre-menopausal women).
- ▶ **Secondary** — suggested by very low Z-scores, fractures in younger patients, or atypical features.

Group	Risk factors / causes
Non-modifiable	Personal history of adult fracture, family history of hip fracture, advanced age, female sex, white race, dementia
Modifiable	Current smoking, oestrogen deficiency, early menopause (<45 y) / oophorectomy , prolonged amenorrhoea (>1 y), low calcium/vitamin D intake, alcoholism, impaired vision, recurrent falls, inadequate physical activity, low BMI
Endocrine	Cushing's syndrome, hyperparathyroidism , thyrotoxicosis, diabetes mellitus (type 1 and 2) , acromegaly, adrenal insufficiency, hypogonadism (Turner's, Klinefelter's, anorexia nervosa, hyperprolactinaemia)
GI / nutritional	Malabsorption, coeliac disease , gastrectomy, primary biliary cirrhosis, malnutrition
Marrow / malignancy	Multiple myeloma , lymphoma/leukaemia, mastocytosis, thalassaemia
Inherited / other	Osteogenesis imperfecta, Marfan's, Ehlers–Danlos, homocystinuria, hypophosphatasia; rheumatoid

Group	Risk factors / causes
	arthritis, ankylosing spondylitis, immobilisation, COPD, multiple sclerosis
Drugs (Table 423-3)	Glucocorticoids (commonest medication-induced; risk if ≥ 5 mg prednisone/day for >3 months), aromatase inhibitors, androgen-deprivation therapy , GnRH agonists, excess thyroxine, anticonvulsants, SSRIs, proton-pump inhibitors, thiazolidinediones, heparin, lithium, cyclosporine, cytotoxics

Clinical features

- ▶ Osteoporosis itself is **asymptomatic until fracture** (“silent disease”).
- ▶ **Vertebral fractures**: ~70% are clinically silent; present with acute back pain (only ~30% are symptomatic), progressive **height loss** (>4 cm), **dorsal kyphosis**, restrictive lung disease (thoracic) or abdominal distension/early satiety (lumbar). Chronic pain is largely myofasciogenic, not bony.
- ▶ **Hip fracture**: almost always needs surgery; carries **20–25% mortality in the first year** and ~30% of survivors require long-term care.
- ▶ **Wrist (Colles’) fractures** rise after menopause; a first fracture markedly increases further-fracture risk, especially in the next **12–24 months** (“**imminent fracture risk**”).

Diagnosis and investigations

- ▶ **DXA (dual-energy x-ray absorptiometry)** of lumbar spine and hip is the **standard** for BMD; the **total hip** best predicts hip-fracture risk. Serial scans should use the same machine. (QCT, HR-pQCT, peripheral QCT and ultrasound are alternatives; **trabecular bone score [TBS]** adds microarchitectural information to spinal DXA.)
- ▶ **Indications for BMD testing**: all women ≥ 65 and men ≥ 70 ; younger post-menopausal women / men 50–69 with risk factors; any adult with a fracture at/after age 50; adults on a high-risk drug (e.g., glucocorticoids) or disease.
- ▶ **FRAX®**: integrates age, sex, BMI, prior fracture, parental hip fracture, smoking, alcohol, glucocorticoids, rheumatoid arthritis and secondary causes ($\pm$ femoral-neck BMD) to give the **10-year probability of major osteoporotic (hip, clinical spine, wrist, humerus) and of hip fracture**. US intervention threshold: **10-year major osteoporotic risk $\geq 20\%$ and/or hip risk $\geq 3\%$** .
- ▶ **Vertebral fracture assessment (VFA)/lateral spine imaging** detects silent vertebral fractures.
- ▶ **Laboratory screen for secondary causes**: CBC, serum & 24-h urine calcium, renal and liver function, serum 25(OH)D, TSH, PTH (if hypercalcaemic), **serum/urine electrophoresis and free light chains** (myeloma), **testosterone in men**, 24-h urinary free cortisol/overnight

dexamethasone (Cushing's), tissue transglutaminase IgA (coeliac), tryptase/urinary histamine (mastocytosis).

- ▶ **Biochemical bone-turnover markers** — formation: bone-specific alkaline phosphatase, osteocalcin, P1NP (preferred); resorption: urine/serum NTX, **serum CTX** (preferred, fasting 9 a.m.). Chiefly used to **monitor treatment response** (change earlier than BMD); a meaningful change is $\geq 30\text{--}40\%$.

Management

Non-pharmacological / universal measures

- ▶ Adequate **calcium** (RDA 1000–1200 mg/day; dietary preferred; supplement doses ≤ 600 mg) and **vitamin D** (target 25(OH)D > 30 ng/mL; 800–2000 IU/day, up to 4000 IU/day safe). Calcium + vitamin D reduces fractures mainly in the **deficient, institutionalised elderly**.
- ▶ **Weight-bearing and progressive resistance exercise** (small 3–4% BMD gains); **balance training/tai chi** reduces falls by $\sim 25\%$.
- ▶ **Risk-factor reduction**: smoking cessation, limit alcohol, treat impaired vision, minimise sedating drugs, **home/fall-proofing**, hip protectors in nursing-home residents.

Pharmacological agents — antiresorptive (slow resorption) versus anabolic (build bone). Anabolics are first-line in **very-high-risk/imminent-risk** patients; the ideal sequence is **anabolic followed by an antiresorptive**.

Agent	Class / mechanism	Dose & route	Fracture reduction
Alendronate	N-bisphosphonate (inhibits farnesyl-PP synthase $\rightarrow$ osteoclast apoptosis)	70 mg PO weekly	Vertebral $\sim 50\%$, hip up to 50%
Risedronate	N-bisphosphonate	35 mg PO weekly	Vertebral 40–50%, hip 40%
Ibandronate	N-bisphosphonate	150 mg PO monthly / 3 mg IV q3-monthly	Vertebral $\sim 40\%$, no overall non-vertebral benefit
Zoledronic acid	N-bisphosphonate	5 mg IV annually (30-min infusion)	Vertebral 70%, hip 40%, non-vertebral 25%
Denosumab	Human anti-RANKL monoclonal antibody	60 mg SC every 6 months	Vertebral 68%, hip 40%, non-vertebral 20%
Raloxifene	SERM (oestrogen agonist on bone)	60 mg PO daily	Vertebral 30–50%; also $\downarrow$ ER+ breast cancer

Agent	Class / mechanism	Dose & route	Fracture reduction
Teriparatide	PTH(1–34), anabolic (Wnt/osteoblast)	20 µg SC daily	Vertebral 65%, non-vertebral 53%
Abaloparatide	PTHrP analogue, anabolic	SC daily	Vertebral 86%, non-vertebral 43% (ACTIVE)
Romosozumab	Anti-sclerostin antibody (↑formation, ↓resorption)	210 mg SC monthly ×12	Vertebral 73% (FRAME)
Calcitonin	Hormone (osteoclast inhibition)	200 IU/day intranasal	Weak; analgesic in acute vertebral fracture

- **Oestrogen/hormone therapy** reduces hip & spine fracture (WHI: –34%) but raises MI, stroke, VTE and breast cancer; **not recommended for disease prevention** — reserved for menopausal symptoms.
- **Key adverse effects/precautions:** oral bisphosphonates cause **oesophagitis** (take fasting with a full glass of water, remain upright ≥30 min) and are **contraindicated if eGFR <30–35 mL/min**; class effects include **medication-related osteonecrosis of the jaw (MRONJ)** and **atypical femoral (subtrochanteric) fractures** (lateral thigh/groin pain warning), hypocalcaemia, and an **acute-phase reaction** with IV zoledronate. **Denosumab** has a **rebound increase in bone turnover with multiple vertebral fractures on discontinuation** — never give a drug holiday; bridge with a bisphosphonate. **Teriparatide** carried a (rodent) osteosarcoma signal. **Romosozumab** carries a **cardiovascular warning** — **avoid after recent MI/stroke** (ARCH trial).
- **Glucocorticoid-induced osteoporosis (GCIOP):** commonest cause of drug-induced osteoporosis; use lowest steroid dose, ensure calcium/vitamin D, and treat with bisphosphonates (alendronate, risedronate, zoledronate), denosumab or teriparatide.
- **Monitoring:** repeat DXA ~every 2 years; a significant change must exceed ~3% at **spine**, ~6% at **hip**; turnover markers detect response earlier (~3 months). “**Drug holidays**” apply to bisphosphonates only (long skeletal half-life) — avoided with denosumab and anabolic agents.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **RANK–RANKL–OPG and Wnt–sclerostin remodelling unit:** label *osteoblast/osteocyte*, *RANKL*, *RANK* (on preosteoclast), *osteoprotegerin (OPG, decoy)*, *multinucleated osteoclast resorbing bone*, *Wnt signal → bone formation*, *sclerostin (inhibits Wnt)*; mark drug targets — *denosumab → RANKL*, *romosozumab → sclerostin*, *bisphosphonates → osteoclast*.
- **T-score normal distribution curve:** label *young-adult mean (T = 0)*, *normal (> –1.0)*, *osteopenia (–1.0 to –2.5)*, *osteoporosis (≤ –2.5)*, with a marker at **T = –2.5**.

Clinical / Diagnostic significance

- ▶ Osteoporosis is a **silent disease diagnosed only after fracture or screening** — hence proactive DXA + FRAX in at-risk groups.
- ▶ A **first fragility fracture predicts imminent further fractures**; **fracture liaison services** improve secondary-fracture prevention (~20% fall in hip-fracture rate in the Kaiser system).
- ▶ Distinguish from **osteomalacia** (defective mineralisation, low/normal calcium and phosphate, raised ALP, looser zones) and **multiple myeloma** (punched-out lytic lesions, paraproteinaemia).
- ▶ Always exclude **secondary causes** before labelling primary osteoporosis, especially in men, premenopausal women and unexpectedly low Z-scores.

High-yield exam pointers

- ▶ WHO T-score ≤ -2.5 = **osteoporosis**; -1.0 to -2.5 = **osteopenia**; T = young-adult reference, Z = age-matched.
- ▶ **>50% of fractures occur in osteopenic patients** → use **absolute risk (FRAX)**; US thresholds $\geq 20\%$ major / $\geq 3\%$ hip.
- ▶ RANKL–RANK–OPG and Wnt–sclerostin are the central pathways and the basis for **denosumab** and **romosozumab**.
- ▶ **Zoledronic acid** (annual IV) gives the largest bisphosphonate fracture reduction (vertebral 70%, hip 40%).
- ▶ **Denosumab** — never stop abruptly (rebound vertebral fractures); bridge with bisphosphonate.
- ▶ **Romosozumab** — anabolic + antiresorptive but **cardiovascular boxed warning**.
- ▶ **Anabolic-first then antiresorptive** in very-high/imminent-risk patients.
- ▶ **Glucocorticoids** = commonest drug cause (risk ≥ 5 mg prednisone/day > 3 months).
- ▶ Oral bisphosphonate rules: **fasting, full glass of water, upright ≥ 30 min; avoid if eGFR < 30** ; watch for **MRONJ** and **atypical femoral fracture**.
- ▶ Hip fracture carries **20–25% one-year mortality**.

SOURCE & COVERAGE

Harrison 22e — Ch 423 “Osteoporosis” (P.R. Ebeling). Standard definitions (normal/osteopenia/osteoporosis T-score bands, “severe/established osteoporosis”, type I/II classification) and the osteomalacia/myeloma differential are universally accepted internal-medicine teaching used to round out the answer; all drug doses, fracture-reduction figures, trial names and thresholds are taken verbatim from the chapter. No coverage gap.



Pituitary hormones

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — The pituitary gland (~600 mg, lying within the sella turcica ventral to the diaphragma sella) is the “master gland” that, with the hypothalamus, orchestrates most endocrine function. It has two embryologically and functionally distinct lobes: the **anterior pituitary (adenohypophysis)**, derived from *Rathke’s pouch*, which secretes **six major hormones** — prolactin (PRL), growth hormone (GH), adrenocorticotrophic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH); and the **posterior pituitary (neurohypophysis)**, a neural extension storing **arginine vasopressin (AVP/ADH)** and **oxytocin**. All are secreted in a pulsatile manner under hypothalamic and feedback control.

Anatomy, development and regulatory principles

- ▶ **Vascular supply:** superior and inferior hypophyseal arteries. The **hypothalamic-pituitary portal plexus** carries hypothalamic releasing/inhibiting peptides to the anterior lobe in high concentration *without systemic dilution*, so anterior cells receive discrete hypothalamic pulses.
- ▶ The **posterior lobe** is supplied by the inferior hypophyseal arteries and is *directly innervated* by hypothalamic neurons via the supraopticohypophyseal and tuberohypophyseal tracts — hence AVP/oxytocin output is sensitive to stalk or hypothalamic damage.
- ▶ **Development from Rathke’s pouch** is governed by lineage-specific transcription factors: *Prop-1* and *Pit-1* (GH, PRL, TSH lineages), *SF-1* and *DAX-1* (gonadotropes), and *T-Pit* (corticotropes/POMC). Their mutations cause selective or combined pituitary hormone deficiency.
- ▶ **Three regulatory layers:** (1) hypothalamic releasing/inhibiting factors via the portal system; (2) **negative feedback** by peripheral target-gland hormones (e.g., cortisol on ACTH, T3/T4 on TSH); (3) **hormonal rhythms** — most pituitary hormones are entrained to sleep/circadian cycle (e.g., ACTH–cortisol peak ~6 a.m., nadir ~midnight; GH and PRL peak in non-REM/early sleep).

Anterior pituitary hormones — summary

Hormone	Cell (% of anterior cells)	Chemical nature	Hypothalamic stimulator	Inhibitor	Target	Principal action
PRL	Lactotrope (~20%)	Polypeptide, 198 aa	TRH, VIP, estrogen	Dopamine (tonic, D2 receptor)	Breast	Lactation; suppresses GnRH/gonadotropins
GH	Somatotrope (up to 50%)	Polypeptide, 191 aa (22 kDa)	GHRH, ghrelin	Somatostatin (SRIF), IGF-1	Liver, bone, tissues	IGF-1 generation, linear growth, insulin antagonism, lipolysis

Hormone	Cell (% of anterior cells)	Chemical nature	Hypothalamic stimulator	Inhibitor	Target	Principal action
ACTH	Corticotrope (~20%)	Polypeptide, 39 aa (from POMC, 266 aa)	CRH, AVP, cytokines (IL-6)	Glucocorticoids	Adrenal cortex	Cortisol/adrenal steroidogenesis
LH	Gonadotrope (~10%)	Glycoprotein ($\alpha + \beta$)	GnRH	Sex steroids (feedback)	Ovary/testis	Ovulation, corpus luteum; Leydig cell testosterone
FSH	Gonadotrope (~10%)	Glycoprotein ($\alpha + \beta$)	GnRH, activin	Inhibin	Ovary/testis	Folliculogenesis, ovarian estrogen; spermatogenesis
TSH	Thyrotrope (~5%)	Glycoprotein ($\alpha + \beta$)	TRH	T3/T4, dopamine, somatostatin, glucocorticoids	Thyroid	T4 synthesis and secretion

The glycoprotein hormones (LH, FSH, TSH; also hCG) share a common α subunit; biologic specificity resides in the hormone-specific β subunit.

Individual anterior hormones — key mechanisms

- **Prolactin:** 198 aa, weakly homologous to GH and human placental lactogen; half-life ~50 min. Uniquely, its predominant hypothalamic control is **inhibitory** (tonic dopamine via **D2 receptors**) — so stalk section (trauma, compressive lesions) *raises* PRL. The PRL receptor is a **type I cytokine receptor** signalling through JAK/STAT. PRL induces and maintains lactation and **suppresses reproductive function** by inhibiting hypothalamic GnRH and pituitary gonadotropins → hypogonadism (this underlies amenorrhoea-galactorrhoea and male hypogonadism in hyperprolactinaemia). PRL rises ~10-fold in pregnancy.
- **Growth hormone / IGF-1:** Most abundant anterior hormone. Stimulated by **GHRH** (44-aa peptide) and **ghrelin**; inhibited by **somatostatin (SRIF)** and by IGF-1 feedback. Of the five somatostatin receptor subtypes (SST1–SST5), **SST2 and SST5** suppress GH (and TSH). GH receptor belongs to the cytokine/haematopoietic family (JAK/STAT). GH causes protein synthesis/nitrogen retention, **insulin antagonism** (impaired glucose tolerance), lipolysis, and Na⁺/K⁺/water retention; much of its growth action is mediated by **IGF-1** (chiefly hepatic, carried by IGFBP3). *Pegvisomant*, a GH-receptor antagonist, treats acromegaly.
- **ACTH:** A 39-aa peptide cleaved from the **proopiomelanocortin (POMC, 266 aa)** precursor, which also yields β -lipotropin, β -endorphin, met-enkephalin, α -MSH and CLIP. POMC is

stimulated by **CRH** (41-aa, paraventricular nucleus), AVP and cytokines, and suppressed by glucocorticoids. ACTH acts via the **melanocortin-2 receptor** (GPCR) to drive adrenal cortisol synthesis; it shows a marked circadian rhythm and mediates the neuroendocrine stress response.

- ▶ **Gonadotropins (LH, FSH):** Controlled by **GnRH** (10-aa peptide) released in **pulses every 60–120 min**, itself regulated by **kisspeptin** (KISS1 gene). *Pulsatile* GnRH is essential; *continuous* exposure desensitises gonadotropes — the basis for long-acting **GnRH agonists** in precocious puberty and prostate cancer. **Inhibin** selectively suppresses FSH while **activin** stimulates it. Estrogen is normally inhibitory, but the rising preovulatory estrogen exerts **positive feedback** to trigger the mid-cycle LH surge.
- ▶ **TSH:** Stimulated by **TRH** (a hypothalamic tripeptide, pyroglutamyl-histidyl-prolinamide) and suppressed by thyroid hormone (the predominant negative regulator), dopamine, somatostatin and glucocorticoids. Long half-life and low pulse amplitude mean a single TSH level reliably reflects status. It acts on a thyroid follicular-cell GPCR.

Posterior pituitary (neurohypophysis) hormones

- ▶ The neurohypophysis is the distal axons of **magnocellular neurons** whose cell bodies lie in the **paraventricular and supraoptic nuclei**.
- ▶ **Arginine vasopressin (AVP/ADH):** a **nonapeptide** (six-member disulfide ring + tripeptide tail) synthesised as a precursor yielding AVP, **neurophysin II** and **copeptin** (single gene, chromosome 20). Secretion is governed mainly by **osmoreceptors** in the anteromedial hypothalamus; the osmotic set point is **~275 mosmol/L** (plasma Na⁺ ~135 meq/L), with a 2–4% rise giving maximal antidiuresis. AVP is also released by a fall in BP or volume loss **>10–20%** (baroregulated), and potently by nausea/emesis. **Action:** via renal **V2 receptors** → cAMP → insertion of **aquaporin-2 (AQP2)** channels into principal-cell apical membrane → water reabsorption (urine osmolarity up to **1200 mOsmol/L** at AVP 1–3 pg/mL). **V1a/V1b** receptors mediate vasoconstriction, hepatic glycogenolysis and ACTH potentiation. Half-life 10–30 min; *desmopressin (DDAVP)* resists vasopressinase and acts longer.
- ▶ **Oxytocin:** also a nonapeptide, differing from AVP at **positions 3 and 8**; little antidiuretic effect. It stimulates **milk letdown** (suckling reflex) and uterine smooth-muscle contraction in labour, and centrally regulates socioemotional behaviour (bonding, empathy).
- ▶ **Thirst** is regulated by a hypothalamic osmostat set **~3% higher** than the AVP osmostat, ensuring fluid intake before plasma tonicity exceeds the antidiuretic defence.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hypothalamic-pituitary axes (Fig. 390-1):** Hypothalamus (label releasing factors: *CRH, GnRH, TRH, GHRH, somatostatin/SRIF, dopamine*) → portal vessels → anterior pituitary (label cells: *corticotrope-ACTH, gonadotrope-LH/FSH, thyrotrope-TSH, somatotrope-GH, lactotrope-PRL*) → target glands (*adrenal-cortisol, gonads-sex steroids/inhibin, thyroid-*

T4/T3, liver-IGF-1, breast); draw **negative-feedback arrows** from target hormones back to hypothalamus/pituitary.

- ▶ **Posterior pituitary / AVP pathway** (Fig. 393-1/2): Label *supraoptic + paraventricular nuclei* → *magnocellular axons* → *posterior pituitary* → *AVP release*; and renal collecting-duct cell with labels *V2 receptor*, *Gs-cAMP*, *AQP2 (apical)*, *AQP3/AQP4 (basolateral)*, *water reabsorption*.

Clinical / Diagnostic significance

- ▶ **Hormone-excess syndromes from adenomas**: prolactinoma (amenorrhoea-galactorrhoea, hypogonadism), GH excess (gigantism/acromegaly; treat with somatostatin analogues, pegvisomant), ACTH excess (Cushing disease), TSH-secreting adenoma (central hyperthyroidism with inappropriately normal/high TSH).
- ▶ **Hypopituitarism** may be inherited (Pit-1/Prop-1 mutations) or acquired (tumour, surgery, irradiation, apoplexy, Sheehan syndrome); mass effect adds headache and **bitemporal hemianopia** (optic chiasm).
- ▶ **Stalk compression** raises PRL (loss of dopamine inhibition) — a useful localising clue.
- ▶ **Pulsatility matters**: pulsatile GnRH stimulates but continuous GnRH suppresses gonadotropins (therapeutic GnRH agonists).
- ▶ **Posterior pituitary disorders**: **AVP deficiency** (central DI) vs **AVP resistance** (nephrogenic DI) cause hypotonic polyuria (>40–50 mL/kg/24 h); differentiate with serum Na⁺, the desmopressin test and **copeptin** (baseline >21.4 pmol/L = AVP resistance; stimulated >4.9 pmol/L at Na⁺ ≥150 mmol/L diagnoses AVP deficiency, ~96.5% accuracy). The **pituitary “bright spot”** on T1 MRI marks AVP-containing vesicles and may be lost in AVP deficiency. Excess/inappropriate AVP causes **SIAD/hyponatraemia**.

High-yield exam pointers

- ▶ Six anterior hormones: **PRL, GH, ACTH, LH, FSH, TSH**; posterior stores **AVP and oxytocin** (made in hypothalamus, not the posterior lobe).
- ▶ Cell proportions: **GH ~50%**, **PRL ~20%**, **ACTH ~20%**, **LH/FSH ~10%**, **TSH ~5%**.
- ▶ **Prolactin is the only anterior hormone under tonic inhibitory (dopaminergic D2) control** → stalk section causes hyperprolactinaemia.
- ▶ Glycoprotein hormones (LH, FSH, TSH, hCG) share a **common α subunit**; β subunit confers specificity.
- ▶ ACTH derives from **POMC** (also yields α-MSH, β-endorphin, β-lipotropin); receptor = **melanocortin-2**.
- ▶ GH actions are largely mediated by **IGF-1**; GH itself is **diabetogenic** (insulin antagonist).

- ▶ GnRH pulses every **60–120 min**; kisspeptin is the upstream gatekeeper; continuous GnRH desensitises.
- ▶ AVP is a **nonapeptide** acting via **V2 receptors–AQP2**; osmotic set point **~275 mosmol/L**; copeptin is its stable surrogate.
- ▶ **Inhibin** ↓FSH, **activin** ↑FSH; rising estrogen gives positive feedback → LH surge.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 390 "Physiology of Anterior Pituitary Hormones" (anterior lobe, synthesis/secretion/action of PRL, GH, ACTH, LH/FSH, TSH; anatomy, development, regulation) and Ch 393 "Disorders of the Neurohypophysis" (AVP and oxytocin physiology, osmoregulation, DI/copeptin). Coverage note: the topic is fully supported by the two provided chapters; specific adenoma-syndrome management details (e.g., bromocriptine/cabergoline doses) are clinical add-ons drawn from standard internal medicine and are summarised, not source-detailed.



Regulation of Energy Balance in Human Adult

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Energy balance* is the state in which **energy intake** (calories from food) equals **total energy expenditure** (TEE), so that body energy stores (chiefly adipose triglyceride) and body weight remain stable over long periods. It is not a matter of conscious choice alone but a tightly **homeostatically regulated** process: the amount of stored energy is defended by fundamental physiologic mechanisms essential to survival. The **hypothalamus** is the master integrator, receiving adiposity signals (leptin, insulin) and gut signals (ghrelin, GLP-1, PYY, CCK, etc.) and translating them, via the **leptin–melanocortin pathway**, into adjustments of hunger, satiety and energy expenditure. Chronic imbalance (intake > expenditure) of as little as **~7 kcal/day** sustained over years produces obesity.

The energy balance equation and components of energy expenditure

- ▶ **Fundamental equation:** Change in energy stores = Energy intake – Total energy expenditure. Positive balance → fat storage (as triacylglycerol, which yields >2× the energy/gram of carbohydrate and needs no accompanying water); negative balance → mobilisation of free fatty acids and glycerol.
- ▶ **Macronutrient fuel value:** carbohydrate **4 kcal/g**, protein **4 kcal/g**, fat **9 kcal/g**, alcohol **7 kcal/g** (alcohol is a fuel but not a nutrient).
- ▶ **Total energy expenditure (TEE)** has three quantitatively important parts plus a minor one:

Component	Approx. share of TEE	Nature / regulation
Resting energy expenditure (REE / BMR)	~70%	Energy for basal cellular and organ function; chiefly regulated by thyroid hormone (thyrotoxicosis ↑ REE → weight loss)
Physical activity (exercise + NEAT)	~20%	Voluntary exercise + non-exercise activity thermogenesis (posture, fidgeting); most variable component
Thermic effect of food (TEF / specific dynamic action)	~10%	Energy of chewing, digestion, absorption and post-prandial sympathetic activation
Cold-induced (shivering) thermogenesis	minor	Thermoregulatory

- ▶ **Estimating requirements (Harrison/DRI):** the Estimated Energy Requirement (EER) = REE × physical activity level (PAL). In weight-stable adults, REE = 900 + 10m (males) and REE = 700 + 7m (females), where *m* = mass in kg. PAL multipliers: 1.4 (inactive), 1.6 (low active), 1.75 (active), 2.05 (very active). Average intake ≈ 2600 kcal/d (US men), 1800 kcal/d (US women).

The hypothalamus — the integrating centre

- ▶ The hypothalamus is **partially outside the blood–brain barrier**, allowing it to sample circulating hormones and combine them with neural, sensory and cognitive inputs.
- ▶ **First-order (primary) neurons** lie in the **arcuate nucleus** and fall into two antagonistic, leptin-responsive populations:

Neuronal population (arcuate n.)	Peptides released	Effect on appetite	Response to leptin
POMC neurons (anorexigenic)	Pro-opiomelanocortin → α-/β-MSH	↓ Food intake, ↑ energy expenditure	Stimulated by leptin
NPY/AGRP neurons (orexigenic)	NPY, AGRP, inhibitory GABA	↑ Food intake	Inhibited by leptin

- ▶ α-/β-MSH act on the **melanocortin-4 receptor (MC4R)** on **second-order neurons** in the **paraventricular nucleus (PVN)** → reduced intake and ↑ sympathetically-driven energy expenditure. AGRP is an endogenous antagonist that actively *switches off* melanocortin receptors. γ-MSH (**MC3 receptor**) influences linear growth and nutrient partitioning (lean vs fat).
- ▶ **Downstream effectors:** BDNF (ventromedial nucleus) and its receptor TrkB, and SIM1 (acts downstream of MC4R) — disruption causes hyperphagia and severe obesity.

- ▶ Lateral hypothalamus harbours orexigenic peptides **melanin-concentrating hormone (MCH)** and **orexin** (orexin loss → narcolepsy). The **endocannabinoid system** (CB1 receptors; ligands **anandamide** and **2-arachidonoylglycerol**) also promotes feeding.

Peripheral signals: adiposity (long-term) and gut (short-term)

- ▶ **Adiposity (long-term tonic) signals** report the *size of energy stores*: **leptin** (from adipocytes) and **insulin** (β -cells) rise with fat mass and act centrally to suppress intake.
- ▶ **Gut (short-term episodic) signals** report *the meal*: ghrelin drives hunger before meals; the post-prandial incretin/satiety peptides terminate the meal, often acting via **vagal afferents** → **brainstem** → **hypothalamus**.

Hormone	Source	Action on energy balance
Leptin	Adipocytes	Anorexigenic ; rises with fat stores; stimulates POMC, inhibits NPY/AGRP; falls <i>faster than fat</i> during caloric restriction
Insulin	Pancreatic β -cells	Central anorexigenic adiposity signal
Ghrelin	Stomach	Orexigenic ; rises in the unfed state/pre-meal, falls after eating — the only known circulating appetite <i>stimulant</i>
CCK	Duodenal I cells	Satiety via vagal CCK-A receptors → brainstem
GLP-1	L cells, small intestine	Satiety + incretin (glucose-dependent insulin release)
GIP	K cells, duodenum/proximal jejunum	Incretin; modulates adipocyte metabolism
PYY (PYY3-36)	L cells, large intestine	Satiety via Y2 receptor (NPY2R)
Oxyntomodulin	L cells, large intestine	Satiety
Amylin	Pancreatic β -cells (co-secreted with insulin)	Slows gastric emptying, hindbrain-mediated satiety, restores leptin sensitivity
GDF15	Many tissues under stress	Anorexia via brainstem GFRAL receptor

- ▶ Diets richer in **protein and fat** induce earlier satiation, partly because the appetite-suppressing gut hormones rise more in response to protein than to carbohydrate.

Set-point, adaptive thermogenesis and leptin resistance

- ▶ **Set-point / homeostatic defence:** classic 1940s rodent experiments showed animals *defend* a fixed body-fat level — after forced over- or under-feeding they return to baseline. In humans, body weight is similarly defended: weight loss triggers a *fall* in energy expenditure and a powerful *rise* in hunger that drive regain.
- ▶ **Adaptive (metabolic) thermogenesis:** hypocaloric feeding reduces energy expenditure by ~8 kcal/kg lean body mass in obese and ~6 kcal/kg in normal-weight individuals (a 15–20% daily fall) — beyond what the loss of body mass alone explains. This makes the dieter transiently more “energy-efficient” and promotes weight regain. (REE rebounds once weight stabilises.)
- ▶ **Asymmetry of leptin action explains “why leptin doesn’t prevent obesity”:** a *fall* in leptin below the habitual level is a **strong** stimulus to eat, whereas *raises* above normal have a **weak** suppressive effect — and at high levels extra leptin has little effect (**leptin resistance**). Evolution wired the system to defend against starvation, not against surfeit. Even “leptin-resistant” obese people retain *some* leptin action — otherwise they would be as hyperphagic as a congenitally leptin-deficient child.
- ▶ **Genes vs environment:** twin/adoption studies confirm a strong genetic basis for adiposity; the predisposition is exerted **mainly through the brain’s control of food intake** (predisposed individuals eat more and are less readily satiated), not through a measurably lower metabolic rate (severe hypothyroidism is the main “low-REE” exception). The recent epidemic, however, reflects an **obesogenic environment** (cheap, energy-dense, ubiquitous palatable food + mechanisation + thermoneutral living) acting on susceptible genotypes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Hypothalamic leptin–melanocortin circuit (sagittal/box scheme).** Labels: *Adipose tissue* → *Leptin*; *Arcuate nucleus*; *POMC neuron (LEPR)*; *NPY/AGRP/GABA neuron (LEPR)*; α/β -*MSH*; *AGRP (antagonist)*; *MC4R neuron in Paraventricular nucleus*; *BDNF (ventromedial nucleus)*; *SIM1*; arrows to “↓ Food intake, ↑ Energy expenditure.” Show leptin stimulating POMC and inhibiting NPY/AGRP.
- ▶ **Diagram 2 — Energy-balance / peripheral signals scheme.** Central box “Hypothalamus” with Brainstem relay; arrows in from Adipose (leptin), Pancreas (insulin, amylin), Stomach (ghrelin — orexigenic), Small intestine (GLP-1, GIP, CCK), Large intestine (PYY, oxyntomodulin), and vagus nerve. Adjacent pie chart of TEE: REE 70% / Physical activity 20% / TEF 10%.

Clinical / Diagnostic significance

- ▶ **Monogenic obesity (treatable forms):** *Congenital leptin deficiency* → severe early-onset obesity + hyperphagia, hypogonadotrophic hypogonadism — **treatable with recombinant leptin**; *leptin-receptor deficiency* is leptin-unresponsive. **MC4R mutations** are the **commonest monogenic obesity** (5–6% of severe early-onset obesity; ~1 in 300 of the population). **POMC deficiency** →

obesity + ACTH deficiency (adrenal crisis, cholestatic jaundice) + **red hair/pale skin**. PCSK1 deficiency → obesity + neonatal enteropathy + post-prandial hypoglycaemia.

- ▶ **Pharmacological exploitation of the pathway:** **setmelanotide** (MC4R agonist) is licensed for **leptin-receptor, POMC and PCSK1 deficiency** and trialled in hypothalamic (e.g. craniopharyngioma) obesity. The modern incretin-based anti-obesity drugs (GLP-1 RA e.g. **semaglutide**; dual GIP/GLP-1 e.g. **tirzepatide**; amylin analogues) act on these same satiety pathways; bariatric surgery works largely by **altering the gut-hormone milieu**, not merely by restriction/malabsorption.
- ▶ **Secondary causes to screen:** **hypothyroidism** (check TSH ± free T4 — ↓ REE), **Cushing's syndrome** (centripetal fat, striae, myopathy), **insulinoma**, and **hypothalamic damage** (craniopharyngioma, head injury) causing acquired hyperphagic obesity.
- ▶ **Bedside assessment:** BMI (WHO: overweight 25–29.9, obese ≥30 kg/m²; lower Asian cut-offs), **waist-to-hip ratio** (>0.9 women, >1.0 men) and waist circumference as surrogates of visceral fat and metabolic risk.

High-yield exam pointers

- ▶ TEE = REE (70%) + **physical activity/NEAT** (20%) + **thermic effect of food** (10%); REE is governed mainly by **thyroid hormone**.
- ▶ EER = REE × PAL; REE = 900 + 10m (M) / 700 + 7m (F); PAL 1.4 → 2.05. Macronutrient kcal/g: CHO 4, protein 4, fat 9, alcohol 7.
- ▶ **Arcuate nucleus** = first-order integrator: **POMC/CART** (anorexigenic) vs **NPY/AGRP/GABA** (orexigenic); leptin stimulates POMC, inhibits NPY/AGRP.
- ▶ The effector arm is the **leptin → POMC → α-MSH → MC4R (PVN)** axis; AGRP antagonises MC4R; BDNF/TrkB and SIM1 act downstream.
- ▶ **Ghrelin** = the only orexigenic gut hormone (rises pre-meal); **GLP-1, PYY, CCK, GIP, oxyntomodulin, amylin** = satiety/incretin signals.
- ▶ **Leptin** is a “fat-store” (adiposity) signal that defends *against starvation* more than against obesity → **leptin resistance** explains why high leptin fails to curb obesity.
- ▶ **Adaptive thermogenesis:** dieting lowers energy expenditure (~15–20%), driving weight regain — the metabolic basis of the **set-point**.
- ▶ A sustained surplus of just ~7 **kcal/day** can cause obesity over years; predisposition is mediated chiefly through **appetite (food intake)**, not low metabolic rate.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Pathobiology of Obesity” (physiologic regulation of energy balance; leptin–melanocortin/hypothalamic circuitry; adiposity and gut signals; leptin resistance; monogenic syndromes; setmelanotide) and “Nutrient

Requirements and Dietary Assessment” (EER, REE formulae, PAL, TEE components, macronutrient fuel values).

- ▶ **Williams Textbook of Endocrinology, 15e** — “Obesity and Neuroendocrine Control of Energy Stores” (energy homeostasis; homeostatic vs hedonic intake; arcuate POMC/NPY-AGRP and MC4R; MCH/orexin/endocannabinoid systems; gut peptides incl. GDF15/GFRAL and amylin; **energy expenditure components 70/20/10**; set-point and adaptive thermogenesis; NEAT).
- ▶ *Coverage note:* The corpus covers this topic richly. CMDT was not required (spec cmdt=false). Standard physiological attributions (CCK from duodenal I cells; ghrelin from gastric X/A-like cells) are stated per universally-accepted textbook physiology where Harrison’s prose is loosely phrased (“CCK from the stomach”).



Role of Glucagon Like Peptide 1 (GLP 1) in the pathogenesis and management of Type II diabetes mellitus

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — *Glucagon-like peptide 1 (GLP-1)* is an **incretin hormone**: an intestinally derived peptide that, together with *glucose-dependent insulintropic peptide (GIP)*, binds specific beta-cell receptors to **amplify glucose-stimulated insulin secretion and suppress inappropriate glucagon secretion**. Its action is *glucose-dependent* (operative only when blood glucose is above the fasting level), so it does not, by itself, cause hypoglycaemia. A relative deficiency of incretin action contributes to the impaired insulin secretion of type 2 DM, and harnessing the GLP-1 pathway — with **GLP-1 receptor agonists (GLP-1RAs)**, the dual GIP/GLP-1 agonist **tirzepatide**, and **DPP-4 inhibitors** — is now central to its management, with proven cardiorenal benefit.

Physiology of GLP-1 and the incretin axis

- ▶ **Source:** GLP-1 is classically released from **neuroendocrine L-cells of the gastrointestinal tract** after food ingestion; GIP is released from intestinal K-cells. Recent preclinical data suggest **intra-islet production of GLP-1 from pancreatic alpha cells** may also regulate insulin secretion.
- ▶ **Beta-cell action:** GLP-1 and GIP bind specific receptors on the beta cell and stimulate insulin secretion **through cyclic AMP production** — but *only when blood glucose is above the fasting level* (glucose-dependent insulintropic effect).
- ▶ **Alpha-cell action:** incretin hormones also **suppress glucagon production and secretion**.
- ▶ **Incretin effect:** this enteroinsular amplification (the augmented insulin response to enterally absorbed glucose) accounts for a large share of meal-stimulated insulin output. “Incretins”

thereby *amplify glucose-stimulated insulin secretion and suppress inappropriate glucagon secretion*.

- ▶ **Inactivation:** native GLP-1 and GIP are rapidly degraded by the enzyme **dipeptidyl peptidase IV (DPP-4)**, which is widely expressed on the surface of endothelial cells and some lymphocytes and degrades a wide range of peptides (i.e., it is *not incretin-specific*). This short half-life is the rationale for both DPP-4-resistant analogues and DPP-4 inhibitors.
- ▶ **Extrapankreatic actions:** the **GLP-1 receptor is expressed in several tissues, including the brain**; pharmacologically GLP-1RAs **slow gastric emptying** and promote **satiety and weight loss**.

Role of GLP-1 / incretins in the pathogenesis of type 2 DM

- ▶ Type 2 DM arises from the interaction of **insulin resistance, impaired (and progressively failing) insulin secretion, and increased hepatic glucose production**. Incretin biology intersects each of these.
- ▶ **Beta-cell secretory defect:** in early type 2 DM the secretory defect selectively involves **glucose-stimulated insulin secretion, with a greatly reduced first secretory phase**; overall beta-cell function is reduced by *as much as 50%* at onset and the defect is **progressive**. Because GLP-1/GIP normally augment glucose-stimulated insulin release, blunting of the **incretin axis** removes an important amplifier of meal-time insulin secretion.
- ▶ **Glucagon dysregulation:** a *decline in insulin secretion and/or increased glucagon secretion* drives hyperglycaemia. Loss of the incretin-mediated **suppression of glucagon** contributes to inappropriate post-prandial and fasting glucagon excess.
- ▶ **Hepatic glucose overproduction:** failure of hyperinsulinaemia to suppress gluconeogenesis produces fasting hyperglycaemia; glucagon excess aggravates this — both are partly counter-regulated by intact incretin signalling.
- ▶ **Islet milieu:** chronic hyperglycaemia (“glucose toxicity”), free-fatty-acid “lipotoxicity”, islet inflammation and **islet amyloid (amylin) deposition** further impair beta-cell function, compounding the deficient incretin response.
- ▶ *Coverage note:* Harrison establishes that incretins amplify glucose-stimulated insulin secretion and suppress glucagon, and that type 2 DM has a progressive secretory defect; that the **incretin effect is quantitatively diminished in established type 2 DM** is universally accepted physiology but is not separately quantified in these chapters (see Source).

GLP-1-based therapeutic agents (classification & key data)

GLP-1RAs are modified to **resist enzymatic inactivation by DPP-4**, giving sustained receptor activation. They are approved for type 2 DM **and obesity**; *higher doses of liraglutide and semaglutide than those used for glucose lowering are effective for weight loss in obesity*.

Class	Examples (per Harrison)	HbA1c reduction	Salient features
GLP-1 receptor agonists	Dulaglutide, exenatide (sustained-release), liraglutide, lixisenatide, semaglutide (oral formulation available)	0.5–1.0%	↑ glucose-stimulated insulin, ↓ glucagon, slow gastric emptying, satiety; weight loss; ↓ CV events, modest renoprotection; <i>no hypoglycaemia unless combined with a secretagogue/insulin</i>
Dual GIP + GLP-1 receptor agonist	Tirzepatide	1.8–2.4%	Once-weekly SC; dual agonism at GIPR and GLP-1R; <i>greater weight loss than a GLP-1RA alone</i>
DPP-4 inhibitors (enhance endogenous incretins)	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	0.5–0.8%	Inhibit degradation of native GLP-1/GIP → enhance the incretin effect ; oral; <i>no hypoglycaemia or weight gain</i> ; preferential post-prandial effect; reduce dose in renal impairment

- ▶ **Long-acting GLP-1RAs** (per Harrison: sustained-release exenatide, dulaglutide, lixisenatide, semaglutide) are **administered weekly** and are the most commonly used; **daily oral semaglutide** uses a formulation enabling gastric absorption that avoids proteolytic degradation in the small intestine.
- ▶ **GLP-1 action achieved is greater with GLP-1RAs than with DPP-4 inhibitors** — explaining the superior glucose lowering, weight loss and cardiovascular outcomes of the injectable/oral agonists.
- ▶ It is **not known** whether GLP-1RAs enhance beta-cell survival or proliferation, and it is unclear whether they alter the natural history of type 2 DM.

Place in management of type 2 DM

- ▶ **Glucose-dependent, low-hypoglycaemia control:** GLP-1RAs lower fasting and post-prandial glucose without intrinsic hypoglycaemia risk, an advantage over sulfonylureas/insulin.
- ▶ **Cardiorenal indication:** because GLP-1RAs (and SGLT-2 inhibitors) **reduce cardiovascular events and slow progression of renal disease**, a GLP-1RA or an SGLT-2 inhibitor should be **used in most individuals with type 2 DM**, with choice dictated by whether ASCVD, heart failure or CKD is present or whether **weight loss is a major goal**. Liraglutide, semaglutide and

dulaglutide each reduced CVD events in trials; dulaglutide also reduced composite microvascular (retinopathy/nephropathy) outcomes; semaglutide was associated with an *increased rate of retinopathy-related complications*.

- ▶ **Combination therapy:** useful regimens include **metformin + GLP-1RA** and **long-acting insulin + GLP-1RA**; fixed-dose long-acting-insulin/GLP-1RA combinations (**degludec + liraglutide**, **glargine + lixisenatide**) are effective and cause *less weight gain*. Adding a GLP-1RA to insulin **limits weight gain and reduces the insulin dose needed**. (The NIH-funded GRADE comparative-effectiveness study evaluated add-on agents to metformin, including **liraglutide** and basal insulin.)
- ▶ **Obesity / prediabetes:** GLP-1RAs and tirzepatide are weight-lowering and, given their greater weight loss, are transforming pharmacologic prevention of type 2 DM in prediabetes; intensive lifestyle measures remain foundational.
- ▶ **Practical use:** start at a **low dose and up-titrate** to minimise initial side effects (nausea being limiting); GLP-1RAs may **alter absorption of other oral drugs** because they slow gastric emptying.

Adverse effects, cautions and contraindications

- ▶ **Common:** nausea, vomiting and GI intolerance (dose-limiting; mitigated by slow titration).
- ▶ **Pancreatitis:** evidence of a **possibly increased risk of acute pancreatitis** with GLP-1RAs (less so DPP-4 inhibitors); avoid in pancreatic disease or risk factors — **heavy alcohol use, severely elevated triglycerides, hypercalcaemia**.
- ▶ **Thyroid:** FDA **black-box warning** for increased **thyroid C-cell tumours in rodents**; *contraindicated in medullary carcinoma of the thyroid or multiple endocrine neoplasia (MEN)*.
- ▶ **Other cautions:** renal disease; co-administration with agents that also slow GI motility; previous ileus; possible worsening of retinopathy. DPP-4 inhibitors: allergy/rash, hypersensitivity (anaphylaxis, angioedema, **Stevens-Johnson syndrome**), severe joint pain — reduce dose in renal insufficiency.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — The incretin axis and drug targets (flow diagram).** Labels: *Ingested nutrients* → *Intestinal L-cell* → *GLP-1* and *K-cell* → *GIP* → arrow to **Pancreatic beta cell** (↑ glucose-dependent insulin, via cAMP); arrow to **Pancreatic alpha cell** (↓ glucagon); arrow to **Stomach** (delayed gastric emptying); arrow to **Brain/hypothalamus** (↑ satiety, ↓ appetite) → net ↓ post-prandial glucose + weight loss. Mark DPP-4 (rapid inactivation of GLP-1/GIP), and the two drug actions: GLP-1RA (DPP-4-resistant agonist) and DPP-4 inhibitor (blocks inactivation).

- ▶ **Diagram 2 — Pathogenic triad of type 2 DM.** Central box *Hyperglycaemia* fed by three labelled arrows: (1) **Insulin resistance** (muscle, liver, adipose), (2) **Progressive beta-cell secretory defect — loss of first-phase insulin**, (3) **Increased hepatic glucose production / glucagon excess**, with a fourth contributing arrow **Reduced incretin (GLP-1/GIP) action**.

Clinical / Diagnostic significance

- ▶ **Outcome-driven prescribing:** GLP-1RAs are a preferred add-on (or partner to SGLT-2 inhibitors) when established ASCVD, high CV risk, CKD, or obesity coexist with type 2 DM.
- ▶ **Weight and metabolic dysfunction:** in type 2 DM with metabolic-dysfunction-associated steatotic liver disease/steatohepatitis, a GLP-1RA or GIP/GLP-1 RA ($\pm$ pioglitazone) should be considered.
- ▶ **Safety screening:** take a personal/family history of medullary thyroid carcinoma/MEN and pancreatitis risk before initiation; counsel on GI side effects and slow titration; review timing of orally absorbed drugs given delayed gastric emptying.
- ▶ **Hypoglycaemia logic:** glucose-dependence means hypoglycaemia occurs essentially only when combined with a sulfonylurea or insulin — pre-emptively reduce those agents.

High-yield exam pointers

- ▶ GLP-1 = incretin from intestinal L-cells; acts via cAMP, is glucose-dependent, and suppresses glucagon — hence low intrinsic hypoglycaemia risk.
- ▶ DPP-4 rapidly inactivates GLP-1/GIP $\rightarrow$ GLP-1RAs are engineered to resist DPP-4; DPP-4 inhibitors block this degradation.
- ▶ Four cardinal GLP-1RA actions: $\uparrow$ insulin, $\downarrow$ glucagon, $\downarrow$ gastric emptying, $\uparrow$ satiety/weight loss.
- ▶ HbA1c lowering: GLP-1RA 0.5–1.0%, DPP-4i 0.5–0.8%, tirzepatide 1.8–2.4%.
- ▶ Tirzepatide = once-weekly dual GIP/GLP-1 agonist $\rightarrow$ greater weight loss than a GLP-1RA alone.
- ▶ Weekly long-acting GLP-1RAs + oral semaglutide; GLP-1 action is greater with GLP-1RAs than DPP-4 inhibitors.
- ▶ Cardiorenal benefit (liraglutide, semaglutide, dulaglutide) $\rightarrow$ a GLP-1RA or SGLT-2 inhibitor in most type 2 DM.
- ▶ Key safety flags: acute pancreatitis caution, medullary thyroid carcinoma/MEN contraindication (rodent C-cell tumours, black-box), nausea/vomiting, semaglutide–retinopathy signal.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 416 “Diabetes Mellitus: Management and Therapies” (GLP-1RAs, tirzepatide, DPP-4 inhibitors, Table 416-6, combination/cardiorenal strategy) and Ch 415 “Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology” (incretin physiology — GLP-1/GIP, cAMP, glucose-dependence, glucagon suppression, L-cell/alpha-cell source; type 2 DM secretory defect). *Coverage note:* the chapters describe incretin amplification of insulin secretion and the progressive beta-cell defect of type 2 DM but do not separately quantify the magnitude of the *incretin effect* or explicitly state that it is *reduced* in type 2 DM — that statement and the broad “ominous octet” framing are standard textbook physiology included here for completeness, not verbatim from these two chapters.



Sick Euthyroid Syndrome (Nonthyroidal Illness Syndrome)

Asked in: Paper IV Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Sick euthyroid syndrome (SES)*, also termed *nonthyroidal illness syndrome (NTIS)* or *euthyroid sick syndrome*, refers to the constellation of abnormal circulating thyroid-function tests that arise in acutely or severely ill patients **in the absence of intrinsic hypothalamic–pituitary–thyroid (HPT) axis disease**. The hallmark is a fall in serum triiodothyronine (T3) with a reciprocal rise in reverse T3 (rT3), and in the most severely ill, a fall in thyroxine (T4) and thyrotropin (TSH). It is largely an **adaptive** response to systemic illness, fasting and inflammation rather than a true thyroid disorder, and it normalises with recovery. Its great clinical importance lies in the diagnostic confusion it creates and in the temptation to inappropriately treat it.

Pathophysiology

- ▶ **Triggers:** any acute, severe systemic illness — sepsis, trauma, burns, myocardial infarction, surgery, starvation/caloric deprivation, bone-marrow transplantation, critical illness in the ICU. The principal mediators are **pro-inflammatory cytokines, especially interleukin-6 (IL-6)** (also IL-12 and IL-18, implicated in the TSH changes).
- ▶ **Altered peripheral deiodination (the central mechanism):**
 - **Type 1 deiodinase (D1)** activity is *reduced* → impaired outer-ring (5') deiodination of T4 to active T3.
 - **Type 3 deiodinase (D3)** activity is *increased* (activated in muscle and liver, especially with hypoperfusion) → increased inner-ring (5) conversion of T4 to the inactive **reverse T3 (rT3)**; D3 is the most important source of rT3 in SES.
 - **Net effect: low T3, raised rT3, and a fall in the T3:rT3 ratio.**

- ▶ **Reverse-T3 kinetics:** rT3 is normally cleared by D1 (5'-deiodination). Because D1 is impaired, *decreased clearance* of rT3 — rather than increased production — is the major basis for the elevated rT3. T4 is also alternately metabolised to the inactive **T3 sulfate**.
- ▶ **Adaptive teleology:** the same low-T3 pattern can be induced in normal individuals by **fasting**; the fall in T3 is thought to limit catabolism and conserve energy/protein in the starved or ill patient.
- ▶ **Central (hypothalamic–pituitary) suppression — prolonged illness:** with sustained critical illness, **hypothalamic TRH gene expression falls**, pulsatile TSH secretion is lost, and TSH and T4 decline. Endogenous dopamine and hypercortisolaemia contribute; an altered feedback set-point via local type 2 deiodinase may also be involved.
- ▶ **Iatrogenic contributors** that further suppress the axis: dopamine, high-dose glucocorticoids, somatostatin, amiodarone, and iodine-containing contrast/wound dressings.

Biphasic model (acute vs prolonged critical illness)

Feature	Acute phase (hours–days)	Prolonged phase (weeks)
Dominant mechanism	Altered peripheral metabolism (↓D1, ↑D3)	Added central suppression (↓TRH, ↓pulsatile TSH)
T3	↓	↓↓ (further fall)
rT3	↑	Normalising / high-normal
T4	Brief rise → normal	↓
TSH	Brief rise → normal	Low / inappropriately normal
Interpretation	Adaptive (energy conservation)	Possibly maladaptive in part

Spectrum of biochemical patterns

- ▶ **Low T3 syndrome (most common):** ↓ total and unbound T3, with **normal T4 and TSH**; rT3 increased. Reflects impaired peripheral T4→T3 conversion.
- ▶ **Low T4 syndrome (very sick patients):** dramatic fall in both **total T4 and T3** — carries a **poor prognosis** (mortality rises as T4 falls). Driven by accelerated metabolism (muscle/liver D3 with hypoperfusion) and reduced TBG binding. Note: routine **free-T4 immunoassays are subject to artefact** when binding proteins are low and tend to *underestimate* the true free T4.
- ▶ **TSH fluctuations:** subnormal TSH (0.01–0.1 mIU/L) is seen in ~10% (especially with dopamine or glucocorticoids); raised TSH (>20 mIU/L) is seen in ~5%, characteristically during the **recovery phase**. A truly *undetectable* TSH (<0.01 mIU/L) makes **intrinsic thyroid disease (thyrotoxicosis)** more likely and warrants endocrine evaluation.
- ▶ **Recovery phase:** a rise in TSH (sometimes transiently >20 mIU/L) **precedes** normalisation of T3 and can mimic primary hypothyroidism if tested in isolation.

Disease-specific patterns (distinctive variants)

- ▶ **Acute liver disease:** initial rise in *total* (not unbound) T3 and T4 from TBG release; levels become subnormal as liver failure progresses.
- ▶ **Acute psychiatric illness:** transient rise in total and unbound T4 (usually with normal T3) in 5–30%; TSH may be low, normal or high.
- ▶ **HIV/AIDS:** T3 and T4 *rise* in early HIV (even with weight loss); T3 falls with progression to AIDS, but TSH usually stays normal.
- ▶ **Renal disease:** low T3 but with **normal rather than increased rT3** (an unusual feature) due to increased hepatic uptake of rT3.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — HPT axis in SES (acute vs prolonged):** Draw a vertical axis. Boxes top-to-bottom: *Hypothalamus (TRH) → Anterior pituitary (TSH) → Thyroid (mainly T4) → Peripheral tissues*. In peripheral tissues show two arrows from T4: one via **D1/D2 (5'-deiodination) → T3 (active)** and one via **D3 (5-deiodination) → rT3 (inactive)**. Label: *Acute phase — D1↓, D3↑, T3↓, rT3↑, T3:rT3↓, TSH and T4 normal/brief rise. Prolonged phase — TRH↓ → TSH↓ → T4↓, T3↓↓. Mark trigger arrow: Cytokines (IL-6), fasting, hypoperfusion.*
- ▶ **Diagram 2 — Deiodinase pathway:** Central T4 molecule; arrow labelled **D1/D2 (outer-ring 5')** to T3; arrow labelled **D3 (inner-ring 5)** to rT3; both T3 and rT3 converging by further deiodination to **T2 (diiodothyronine)**. Annotate D1↓ and D3↑ in SES.

Clinical / Diagnostic significance

- ▶ **Avoid routine thyroid testing in acutely ill patients** unless a thyroid disorder is strongly suspected — abnormal values are common, transient and misleading.
- ▶ **Distinguishing SES from true central hypothyroidism** is the key diagnostic challenge (both show low T4/T3 with non-elevated TSH):
 - **rT3 is high (or normal) in SES but low in true hypothyroidism** — the most useful discriminator.
 - Supportive: absence of thyroid history/antibodies, the clinical context and time-course of the acute illness, and review of drugs (dopamine, glucocorticoids, amiodarone, phenytoin) affecting hormone levels or binding.
 - A low/normal TSH does **not** exclude pre-existing primary hypothyroidism in the critically ill; conversely, an **elevated T3 is highly unusual** in critical illness and should raise suspicion of thyrotoxicosis/thyroid storm.
- ▶ **Confirmation is often presumptive** — only resolution of the abnormal tests with clinical recovery clearly establishes the diagnosis; **repeat thyroid function after recovery**.

- ▶ **Management** — treat the underlying illness, not the labs:
 - **Thyroid hormone replacement (T4 and/or T3) is generally NOT recommended.** Interventional trials of hormone supplementation in the acute phase have shown **no outcome benefit**; experimentally, lowering T4 appears deleterious while a low T3:rT3 ratio seems beneficial/adaptive. CMDT explicitly states levothyroxine is **not indicated** for euthyroid sick syndrome.
 - Monitor thyroid function through recovery; give thyroid hormone only where there is genuine historic/clinical evidence of hypothyroidism.
 - In patients with **pre-existing hypothyroidism**, continue usual levothyroxine; if switching to IV, reduce the dose by ~25% (oral bioavailability ~75%).
- ▶ **Prognostic marker:** the magnitude of T3/T4 fall (the **low T4 syndrome**) correlates with illness severity and mortality; a persistently low T3:rT3 ratio after recovery has been linked to poorer functional recovery (weaker handgrip, shorter 6-minute walk).

High-yield exam pointers

- ▶ Most common pattern = **low T3 syndrome** (↓T3, normal T4/TSH, ↑rT3).
- ▶ Mechanism = ↓ **type 1 deiodinase** + ↑ **type 3 deiodinase**, driven by IL-6; rT3 rises mainly from **reduced clearance**, not overproduction.
- ▶ **rT3 = high in SES, low in true hypothyroidism** — the single best differentiator.
- ▶ **Low T4 syndrome = poor prognosis** (marker of severity / mortality).
- ▶ **TSH >20 mIU/L during recovery** can mimic primary hypothyroidism; **TSH <0.01 mIU/L** suggests true thyrotoxicosis.
- ▶ The low-T3 state is **adaptive** — also reproduced by **fasting**.
- ▶ **Do NOT give thyroid hormone**; treat the underlying illness and recheck TFTs after recovery (no proven benefit of replacement; CMDT — levothyroxine not indicated).
- ▶ Aggravating drugs: **dopamine, glucocorticoids, somatostatin, amiodarone, iodinated contrast**.
- ▶ Renal failure variant = low T3 with **normal rT3**; acute liver disease = early rise then fall in total T3/T4.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Hyperthyroidism and Other Causes of Thyrotoxicosis” (Sick Euthyroid Syndrome / Nonthyroidal Illness section) and “Thyroid Gland Physiology and Testing” (deiodinases, rT3, laboratory interpretation).
- ▶ **Williams Textbook of Endocrinology, 15e** — “Endocrine Disorders of Critical Illness” (acute vs prolonged thyroid-axis alterations, TRH suppression, treatment evidence and recovery).

- **CMDT 2026** — “Disorders of the Pituitary, Thyroid, & Adrenal Glands” (euthyroid sick syndrome — diagnosis and that levothyroxine is not indicated).



Thyroid Functions Tests

Asked in: Paper II Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Thyroid function tests (TFTs) are the biochemical, immunological and radioisotopic investigations used to assess the **hypothalamic–pituitary–thyroid (HPT) axis**, to confirm and grade thyroid dysfunction, and to establish its aetiology. Because thyroid hormone secretion is governed by a classic **negative-feedback loop**, serum **TSH** is the single most useful physiologic marker of thyroid hormone action and the first-line screening test; it is interpreted alongside free hormone levels, autoantibodies, thyroglobulin and radioiodine studies. Rational testing follows a “**TSH-first**” strategy, since with rare exceptions a normal TSH excludes a primary thyroid abnormality.

Physiologic basis & the testing strategy

- The thyroid secretes **T4** and **T3**; T4 is secreted in ~**15-fold excess** over T3 and acts as a prohormone, being converted peripherally to the more potent T3 by **deiodinases** (Type I — liver/kidney/thyroid; Type II — pituitary/brain/brown fat; Type III — inactivates T4/T3 and is the chief source of **reverse T3**).
- **TRH** from the hypothalamus stimulates pituitary **TSH**; T4/T3 feed back (mainly via **TRβ2**) to suppress TRH and TSH. Reduced hormone raises TSH; high hormone rapidly suppresses TSH.
- TSH has a long plasma **half-life** (~**50 min**) and only modest pulsatility/diurnal variation (peak at night), so a **single random measurement** is adequate.
- Because TSH changes dynamically and *logarithmically* in response to small T4/T3 shifts, the logical approach is to **first determine whether TSH is suppressed, normal or elevated**, then confirm with circulating (preferably free) hormone levels.

Serum TSH — the primary screening test

- Measured by highly sensitive, specific **immunometric (immunoradiometric)** assays that easily separate normal from suppressed values. Modern “third-generation” assays detect TSH down to **≤0.004 mIU/L**; assays sensitive to **≤0.01 mIU/L** suffice for practice.
- **Low TSH** → primary hyperthyroidism/thyrotoxicosis; **High TSH** → primary hypothyroidism. A suppressed TSH **<0.01 mIU/L** usually indicates thyrotoxicosis.
- The sensitive TSH assay has rendered the **TRH stimulation test obsolete** — failure of TSH to rise after an IV bolus of **200–400 µg TRH** carries the same meaning as a suppressed basal TSH.

- **Caveat — central (secondary) disease:** in hypothalamic–pituitary disease, TSH is *inappropriately* low-to-high-normal for a low T4; TSH must therefore **not** be used as an isolated test when pituitary/hypothalamic disease is suspected. Rare causes of an *inappropriately normal/high* TSH *with high hormones* are TSH-secreting pituitary adenoma, resistance to thyroid hormone (RTH) and assay artefact.

Pattern	TSH	Free T4	Free T3	Interpretation
Primary hyperthyroidism	Low (<0.01)	High	High/normal	Graves', toxic nodule/MNG
T3 toxicosis	Low	Normal	High	2–5% of thyrotoxicosis
Subclinical hyperthyroidism	Low	Normal	Normal	Risk of AF, bone loss
Primary hypothyroidism	High	Low	Low/normal	Hashimoto's, post-ablation
Subclinical hypothyroidism	High	Normal	Normal	Antibody-positive at risk
Central hypothyroidism	Low/normal (inappropriate)	Low	Low	Pituitary/hypothalamic
Inappropriate TSH secretion	Normal/High	High	High	TSH-oma or RTH

Measurement of thyroid hormones — total vs free

- Automated immunoassays measure serum **total T4 and total T3**, but ~99.98% of T4 and 99.7% of T3 are **protein-bound**, so total levels track binding-protein changes. The biologically active fraction is the **free (unbound) hormone**, which is preferred.
- **Direct free-hormone methods:** (1) competition of unbound hormone with radiolabelled T4/analogue for a solid-phase antibody, and (2) physical separation by **equilibrium dialysis** or **ultracentrifugation** (reference standard, but technically demanding/expensive).
- **Indirect method (now less used):** the **Free T4/T3 index** = total hormone × **thyroid hormone binding ratio (THBR)**, where THBR is derived from the **T3-resin uptake** test (resin uptake rises when binding sites are reduced, e.g. TBG deficiency, and falls in the opposite situation). The index “corrects” anomalous total values caused by binding variation.
- **Free T4** usually suffices to confirm thyrotoxicosis, but because 2–5% **have isolated T3 toxicosis**, measure **free T3** when TSH is suppressed but free T4 is normal.

Binding proteins, drugs & analytic interferences

- Carrier proteins: TBG (low concentration 1–2 mg/dL but high affinity, carries ~80% of bound hormone), **albumin** (~3.5 g/dL, binds up to 10% of T4, 30% of T3) and **transthyretin/TTR** (formerly TBPA, ~10% of T4).

- ▶ These confound *total* (not free) hormone, so free-hormone assays are preferable when binding is altered.

Factor	Effect on binding	Total T4/T3	Free T4/T3	Thyroid status
Estrogen (pregnancy, OCP, HRT, tamoxifen/SERM), inflammatory liver disease	↑ TBG	↑	Normal	Euthyroid
Androgens, nephrotic syndrome	↓ TBG	↓	Normal	Euthyroid
X-linked TBG deficiency	↓↓ TBG	Very low	Normal	Euthyroid (do not treat)
FDH (albumin R218H), familial TTR excess	↑ affinity	↑	Normal	Euthyroid (normal TSH)

- ▶ **Drugs** displacing hormone or perturbing binding/conversion: salicylates, salsalate, NSAIDs, phenytoin, carbamazepine; **propranolol**, **amiodarone**, **ipodate**, **glucocorticoids**, **PTU** also impair T4→T3 conversion.
- ▶ **Biotin interference (high-yield)**: biotin supplements/multivitamins containing $\geq 1000 \mu\text{g}$ taken < 18 h before sampling interfere with biotinylated antibodies and streptavidin capture, giving **falsely low TSH and falsely high T4/T3** (mimicking Graves'). Advise stopping biotin ≥ 2 days before testing.

Tests to determine the aetiology — antibodies & thyroglobulin

- ▶ **Anti-TPO antibodies** are the key marker of autoimmune thyroid disease: present in *almost all* autoimmune (Hashimoto's) hypothyroidism and up to **80% of Graves' disease**, usually at high titre. Since anti-Tg antibodies alone are less common, measuring **TPO antibodies alone is reasonable**. About **5–15% of euthyroid women and up to 2% of euthyroid men** are antibody-positive and are at increased risk of future dysfunction.
- ▶ **TSH-receptor antibodies (TRAb / TSI)**: stimulating antibodies of **Graves' disease**, usually measured by tracer-displacement **TRAb** assays. Uses: confirm Graves' aetiology, predict **remission** after antithyroid-drug withdrawal (higher if TRAb disappears), and predict **fetal/neonatal thyrotoxicosis** when maternal TRAb/TSI is $> 3 \times$ the **upper limit of normal** in the last trimester.
- ▶ **Serum thyroglobulin (Tg)**: raised in all thyrotoxicoses *except thyrotoxicosis factitia* (helps distinguish factitious from endogenous disease) and markedly raised in **thyroiditis**. Its principal

role is **follow-up of differentiated thyroid cancer** — after total thyroidectomy + radioablation, Tg should be **<0.2 ng/mL** (in absence of anti-Tg antibodies); measurable Tg signals residual/recurrent disease. Always interpret with **anti-Tg antibodies**, which interfere with the assay.

Radioiodine uptake & thyroid scintigraphy

- ▶ The gland selectively traps/organifies iodine isotopes (^{123}I , ^{125}I , ^{131}I) and traps $^{99\text{m}}\text{Tc}$ -pertechnetate (imaged but not organified; fractional **uptake quantitation only for iodine isotopes**).
- ▶ 24-h RAIU is 10–25% in iodine-replete normals, rising to 70–90% in Graves'.

Disorder	RAIU	Scan appearance
Graves' disease	High (70–90%)	Diffuse, homogeneous ↑ uptake, enlarged
Toxic adenoma	Focal high	“Hot” nodule; rest of gland suppressed
Toxic multinodular goiter	Patchy	Multiple hot + suppressed/cold areas
Subacute/viral/postpartum thyroiditis	Very low	Patchy/absent (follicular damage)
Thyrotoxicosis factitia	Very low	Exogenous hormone suppresses TSH
Iodine contamination (contrast)	Reduced	Low uptake despite ↑ hormone

- ▶ Scintigraphy is **not routine** for thyroid nodules but is indicated when TSH is **subnormal** to identify autonomously functioning (“hot”) nodules — these are almost never malignant, so FNA is **not required**.

Thyroid testing in special situations

- ▶ **Pregnancy:** use **trimester-specific reference ranges**. hCG weakly stimulates the TSH-R → first-trimester TSH falls; estrogen raises TBG so **total T4/T3 are ~1.5× higher** throughout pregnancy, while free T4 falls toward/below the non-pregnant range by the third trimester.
- ▶ **Non-thyroidal illness (sick-euthyroid syndrome):** any severe illness can derange TSH and lower T3 (↑Type III deiodinase, ↑reverse T3); avoid testing in acute illness unless thyroid disease is strongly suspected.
- ▶ **End-organ tests** (basal metabolic rate, ankle-reflex relaxation time, serum cholesterol) are insensitive and not used clinically.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **HPT feedback axis:** boxes for *Hypothalamus (TRH) → Anterior pituitary (TSH) → Thyroid (T4, T3) → Peripheral tissues*; draw **negative-feedback arrows** from T4/T3 back to pituitary and hypothalamus. Label *TSH-R, negative feedback*, and the deiodinase step *T4 → T3*.
- ▶ **TSH-first testing algorithm:** top box *Measure serum TSH* branching to **Low TSH → free T4 (±free T3) → thyrotoxicosis / T3 toxicosis**, **Normal TSH → euthyroid**, **High TSH → free T4 → primary hypothyroidism**; side-branch *discordant pattern → suspect central disease / RTH / assay (biotin) artefact*. Label *anti-TPO, TRAb, RAIU/scan*.

Clinical / Diagnostic significance

- ▶ TSH is the screening and monitoring test for primary thyroid disease and for titrating levothyroxine and antithyroid therapy.
- ▶ **Free T4 + TSH** together classify overt vs **subclinical** dysfunction and identify central disease (discordant TSH–T4).
- ▶ **Anti-TPO** confirms autoimmune aetiology and stratifies risk of progression; **TRAb** confirms Graves', predicts relapse and neonatal thyrotoxicosis.
- ▶ **RAIU/scan** differentiates high-uptake thyrotoxicosis (Graves', toxic nodule/MNG) from low-uptake states (thyroiditis, factitia, iodine load) — directing therapy.
- ▶ **Thyroglobulin** is the tumour marker for differentiated thyroid cancer surveillance.
- ▶ Recognising **binding-protein and biotin artefacts** prevents misdiagnosis and inappropriate treatment.

High-yield exam pointers

- ▶ **Test TSH first** — a normal TSH (with rare exceptions) excludes primary thyroid disease.
- ▶ Sensitive TSH assay detects ≤ 0.004 mIU/L; it made the **TRH stimulation test obsolete**.
- ▶ Always measure **free** hormones; total T4/T3 are misleading because **~99.98% T4 / 99.7% T3 are protein-bound** (TBG carries ~80%).
- ▶ **T3 toxicosis (2–5%)** — measure **free T3** when TSH is low but free T4 normal.
- ▶ **Biotin ≥ 1000 μg → falsely low TSH, high T4/T3; stop biotin 2 days before testing.**
- ▶ **Anti-TPO** in ~all autoimmune hypothyroidism and up to **80% of Graves'**; **TRAb = Graves' marker** and predicts **neonatal thyrotoxicosis ($>3\times$ ULN)**.
- ▶ Post-thyroidectomy/ablation **Tg <0.2 ng/mL**; rising Tg = recurrence (interpret with anti-Tg antibodies).
- ▶ **24-h RAIU:** normal 10–25%, Graves' 70–90%; **low uptake = thyroiditis / factitia / iodine load**.
- ▶ Central hypothyroidism = **low free T4 with inappropriately non-elevated TSH** — never rely on TSH alone in pituitary disease.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 394 “Thyroid Gland Physiology and Testing” (Jameson, Weetman, Mandel), with cross-references to Ch 395 (hypothyroidism), Ch 396 (thyrotoxicosis) and Ch 397 (nodules) as cited in the chapter. Coverage note: the TSH/free-T4/free-T3 interpretation grid and the deiodinase/sick-euthyroid summary are standard textbook syntheses consistent with the chapter; quantitative limits (RAIU 10–25%/70–90%, Tg <0.2 ng/mL, biotin ≥1000 µg, TRAb >3× ULN, TRH 200–400 µg) are verbatim from Ch 394.



Thyroid Hormones: Physiology

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — The thyroid gland produces two related iodothyronine hormones, **thyroxine (T4)** and **triiodothyronine (T3)**, derived by iodination and coupling of tyrosyl residues on the precursor protein **thyroglobulin (Tg)**. Acting via nuclear **thyroid hormone receptors (TR) α and β**, they are critical for cell differentiation and organogenesis during development and for maintaining **thermogenic and metabolic homeostasis** in the adult. T4 is essentially a *prohormone* that is converted in peripheral tissues to the more potent T3, the principal active hormone. Output is governed by a classic negative-feedback endocrine loop — the **hypothalamic–pituitary–thyroid (HPT) axis**.

Functional anatomy and the synthetic unit

- ▶ The gland (*Greek thyreos*, shield + *eidos*, form) has two lobes joined by an isthmus, lies anterior to the trachea between the cricoid cartilage and suprasternal notch, weighs **12–20 g**, and is highly vascular.
- ▶ It develops from the floor of the primitive pharynx in the **3rd week of gestation** and descends along the **thyroglossal duct** — explaining ectopic *lingual thyroid* and thyroglossal duct cysts. Hormone synthesis begins at **~11 weeks**.
- ▶ Development is orchestrated by transcription factors **TTF1, TTF2, NKX2-1, FOXE1 and PAX8**, which induce thyroid-specific proteins: **Tg, thyroid peroxidase (TPO), the sodium–iodide symporter (NIS) and the TSH receptor (TSH-R)**.
- ▶ The functional unit is the **follicle** — follicular cells surrounding colloid (rich in Tg). Cells are *polarized*: the **basolateral** membrane faces blood (bears NIS, TSH-R), the **apical** membrane faces the lumen (bears TPO, pendrin).
- ▶ Neural-crest–derived **parafollicular C cells** (from the ultimobranial body) secrete **calcitonin** (minimal role in human calcium homeostasis) and are the origin of medullary thyroid cancer.

Hypothalamic–Pituitary–Thyroid (HPT) axis and its regulation

- ▶ Hypothalamic TRH is the major positive regulator of TSH synthesis/secretion by anterior-pituitary thyrotropes; TSH then stimulates all steps of thyroid hormone production. Peak TSH occurs ~15 min after TRH.
- ▶ TSH is a 31-kDa glycoprotein with α and β subunits; the α subunit is shared with LH, FSH and hCG, whereas the β subunit is unique to TSH and confers specificity.
- ▶ T4 and T3 exert **negative feedback** predominantly through the TR β 2 isoform in the hypothalamus and pituitary, inhibiting both TRH and TSH. High hormone levels rapidly suppress TSH gene expression; low levels increase basal TSH and enhance TRH responsiveness — establishing the axis “set point.”
- ▶ Dopamine, glucocorticoids and somatostatin suppress TSH (significant only at pharmacologic doses).
- ▶ TSH is secreted in a **pulsatile** fashion with a **diurnal rhythm** (highest at night) but has a long plasma half-life (~50 min), so a *single TSH measurement* reliably reflects circulating levels.
- ▶ TSH acts via the TSH-R, a seven-transmembrane G-protein-coupled receptor linked to G α → adenylyl cyclase → cyclic AMP; it also activates phospholipase C (phosphatidylinositol turnover).

Biosynthesis of thyroid hormones (sequential steps)

- ▶ **Iodide trapping** — NIS on the basolateral membrane actively concentrates iodide; in the iodine-replete state the gland takes up 10–25% of a tracer dose over 24 h, rising to 70–90% in Graves’ disease. NIS is up-regulated by low iodine/TSH and suppressed by high iodine. (Pendrin on the apical membrane effluxes iodide into the lumen; its mutation causes Pendred syndrome — defective organification, goiter, sensorineural deafness.)
- ▶ **Organification** — at the apical surface, TPO with H₂O₂ (generated by DUOX/DUOXA) oxidises iodide and adds it to tyrosyl residues of Tg, forming **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT)**.
- ▶ **Coupling** — TPO catalyses ether-linkage coupling of iodotyrosines: DIT + DIT → T₄; MIT + DIT → T₃, stored within Tg in colloid.
- ▶ **Storage and release** — TSH triggers reuptake (endocytosis) of Tg into the follicular cell, lysosomal proteolysis, and secretion of T₄ and T₃. Uncoupled MIT/DIT are deiodinated by **iodotyrosine deiodinase**, recycling iodide.
- ▶ **Autoregulation** — excess iodide transiently inhibits its own organification, the **Wolff–Chaikoff effect**; a normal gland “escapes” this within days.
- ▶ **Iodine requirement**: RDA 220 μ g/day (pregnancy) and 290 μ g/day (lactation); the ATA advises prenatal supplements containing 150 μ g/day; urinary iodine >100 μ g/L indicates sufficiency.

Transport, binding proteins and peripheral metabolism

- T4 is secreted in ~15-fold excess over T3. Both circulate almost entirely **protein-bound** — ~99.98% of T4 and ~99.7% of T3 — to **thyroxine-binding globulin (TBG)**, **transthyretin (TTR)** / **thyroxine-binding prealbumin**) and **albumin**. Only the small **unbound (free)** fraction is biologically active; homeostasis defends free-hormone levels.

Binding protein	Plasma level / affinity	Share of bound hormone
TBG	Low conc. (1–2 mg/dL), high affinity (T4 > T3)	carries ~80%
Albumin	High conc. (~3.5 g/dL), low affinity	binds up to 10% T4, 30% T3
Transthyretin (TTR)	Intermediate	~10% of T4, little T3
Property (Table 394-1)	T4	T3
Total serum concentration	8 µg/dL	0.14 µg/dL
Fraction unbound (free)	0.02%	0.3%
Production rate (incl. peripheral conversion)	90 µg/d	32 µg/d
Fraction arising directly from thyroid	100%	~20% (rest = peripheral conversion)
Serum half-life	~7 days	~1 day
Relative metabolic potency	0.3	1

- **Deiodinases** convert/inactivate hormone in the periphery and determine local T3 availability:

Enzyme	Reaction / site	Physiologic role
Type I (D1)	5'-deiodination; thyroid, liver, kidney; low T4 affinity	major source of circulating T3
Type II (D2)	5'-deiodination; pituitary, brain, brown fat, thyroid; high T4 affinity	local intracellular T3; induced in hypothyroidism; important during levothyroxine (T4) replacement
Type III (D3)	5-(inner-ring) deiodination; placenta, muscle/liver in illness	inactivates T4 & T3; chief source of reverse T3 (rT3); up in sick-euthyroid syndrome; large hemangiomas → consumptive hypothyroidism

- **Drugs/states impairing T4 → T3 conversion** (raising rT3): **propylthiouracil, propranolol, amiodarone, glucocorticoids**, iodinated contrast (ipodate, iopanoic acid), fasting, acute illness/trauma — the basis of the **sick-euthyroid (low-T3) syndrome**.

Mechanism of action

- ▶ Thyroid hormones enter cells by passive diffusion and via specific transporters — **MCT8, MCT10 and OATP1C1**; *MCT8* mutations cause X-linked psychomotor retardation (low T₄, high T₃, high TSH).
- ▶ They act mainly through **nuclear receptors TR α and TR β** (tissue distribution: **TR α** — brain, kidney, gonads, **muscle, heart**; **TR β** — pituitary, liver; **TR β 2** — hypothalamus/pituitary feedback).
- ▶ **T₃ binds TR with 10–15× greater affinity than T₄**, explaining its greater potency; receptors are occupied mainly by T₃.
- ▶ TR forms heterodimers with the **retinoid X receptor (RXR)** and binds **thyroid response elements (TREs)** in target-gene promoters. *Without hormone*, TR binds **co-repressors** that silence transcription; *T₃ binding* dissociates co-repressors and recruits **co-activators**, altering transcription (stimulating e.g. myosin heavy chain α , or repressing e.g. TSH β -subunit).
- ▶ **Non-genomic actions** also occur via mitochondrial enzymes and **integrin receptors** on blood vessels and heart.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **HPT axis feedback loop:** Hypothalamus → **TRH (+)** → Anterior pituitary → **TSH (+)** → Thyroid → **T₄ / T₃** → negative feedback (–) arrows back to pituitary (via **TR β 2**) and hypothalamus. Label modulators: dopamine/glucocorticoids/somatostatin (–), peripheral **deiodinase (T₄→T₃)**.
- ▶ **Follicular cell synthesis schematic:** Label **bloodstream**, **basolateral membrane (NIS, TSH-R)**, **apical membrane (TPO, pendrin)**, **colloid/lumen with Tg**, steps — **iodide trapping (NIS) → organification (TPO + H₂O₂) → MIT/DIT → coupling → T₄/T₃**; cAMP second messenger from TSH-R.

Clinical / Diagnostic significance

- ▶ **TSH is the single best first-line test** of thyroid status: high in primary hypothyroidism, low in thyrotoxicosis; modern assays detect ≤ 0.01 mIU/L. An abnormal TSH is confirmed with **free T₄ ($\pm$ free T₃)**.
- ▶ **TSH is unreliable** in central (secondary) hypothyroidism, recent treatment of thyrotoxicosis, severe non-thyroidal illness and TSH-secreting adenoma — here measure **free T₄** directly.
- ▶ Altered binding proteins (estrogen/pregnancy raise **TBG**; androgens/nephrotic syndrome lower it; **FDH, RTH**) change **total** but not **free** hormone — measure free fractions to avoid misdiagnosis.

- ▶ **Pregnancy physiology:** hCG weakly stimulates TSH-R (first-trimester TSH dip $\pm$ gestational thyrotoxicosis/hyperemesis); estrogen raises TBG (total T4/T3 $\sim 1.5\times$); placental D3 increases hormone turnover; levothyroxine needs rise by up to 45%.
- ▶ Etiologic tests: **anti-TPO/anti-Tg antibodies** (autoimmune disease), **TRAb/TSI** (Graves'), serum **Tg** (thyroid-cancer follow-up), and **radioiodine uptake/scan** (high homogeneous in Graves', focal "hot" toxic adenoma, low in thyroiditis/factitia).

High-yield exam pointers

- ▶ DIT + DIT $\rightarrow$ T4; MIT + DIT $\rightarrow$ T3; coupling and organification are both TPO-catalysed.
- ▶ NIS = basolateral (iodide in); pendrin = apical (iodide to lumen) — Pendred syndrome = goiter + deafness.
- ▶ T4 half-life ~ 7 days, T3 ~ 1 day; T4:T3 secretion $\sim 15:1$; $>99\%$ protein-bound; only free hormone is active.
- ▶ D1 (liver/kidney) $\rightarrow$ circulating T3; D2 (pituitary/brain/brown fat) $\rightarrow$ local T3; D3 $\rightarrow$ inactivation + rT3.
- ▶ TR β 2 mediates pituitary feedback; RTH is usually a dominant-negative TR β mutation (high T4/T3 with non-suppressed TSH).
- ▶ Wolff–Chaikoff effect = iodide excess transiently blocks organification; TSH-R = Gsa/cAMP GPCR.
- ▶ Drugs blocking T4 $\rightarrow$ T3: PTU, propranolol, amiodarone, glucocorticoids, iodinated contrast — recall in sick-euthyroid syndrome.
- ▶ TSH α -subunit is shared (LH/FSH/hCG); β -subunit is hormone-specific.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 394 "Thyroid Gland Physiology and Testing" (Jameson, Weetman, Mandel). Fully covers the ask. *Coverage note:* T3 serum half-life is stated here as the standard textbook value (~ 1 day) as the source Table 394-1 OCR value is ambiguous; MCT8-mutation eponym (Allan–Herndon–Dudley syndrome) is standard medicine and not named verbatim in the provided text.



Vitamin D in Health and Disease

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Vitamin D is a fat-soluble *secosteroid* that functions as a **hormone precursor** rather than a true vitamin, since in the proper biologic setting it can be synthesised endogenously in skin. Its active metabolite, **1,25-dihydroxyvitamin D** [1,25(OH) $_2$ D, **calcitriol**], is the

major steroid hormone regulating mineral-ion homeostasis, acting through the nuclear **vitamin D receptor (VDR)** to maintain serum calcium and phosphate and to mineralise the skeleton. Deficiency produces **rickets** in children and **osteomalacia** in adults, while the wide tissue distribution of the VDR underlies proposed (largely unproven) non-skeletal roles.

SOURCE & COVERAGE

- ▶ **Two forms, equal activity:** Vitamin D₂ (**ergocalciferol**) from plant sources; vitamin D₃ (**cholecalciferol**) from animal sources and cutaneous synthesis. Both are activated equally by human vitamin D hydroxylases.
- ▶ **Cutaneous synthesis (major source):** UV-B radiation (290–320 nm) cleaves 7-dehydrocholesterol in skin to vitamin D₃. Reduced by **melanin, high-SPF sunblock, ageing, and limited sun exposure**, increasing reliance on diet (fortified cereals/dairy, fish oils, egg yolks).
- ▶ **Transport:** Vitamin D circulates bound to **vitamin D-binding protein (DBP)**, an α -globulin made in the liver.
- ▶ **First hydroxylation (liver):** A hepatic cytochrome P450 oxidase performs 25-hydroxylation $\rightarrow$ **25-hydroxyvitamin D [25(OH)D]**, the major circulating and storage form. This step is *not tightly regulated*. Half-life $\sim$ 2–3 weeks; $\sim$ 88% bound to DBP, $\sim$ 0.03% free.
- ▶ **Second hydroxylation (kidney) — the rate-limiting, regulated step:** The 25(OH)D-1 α -hydroxylase (CYP27B1) in proximal convoluted tubule cells produces active 1,25(OH)₂D.
 - *Inducers:* PTH and hypophosphatemia. *Repressors:* calcium, FGF23, and 1,25(OH)₂D itself.
- ▶ **Extra-renal 1 α -hydroxylase:** Present in keratinocytes, placental trophoblast, and macrophages of granulomas and lymphomas — induced by IFN- γ and TNF- α , unregulated by calcium $\rightarrow$ cause of **PTH-independent hypercalcemia** (e.g., sarcoidosis).
- ▶ **Inactivation:** 24-hydroxylase (CYP24A1) adds a hydroxyl group; induced by 1,25(OH)₂D (negative feedback) and FGF23. *CYP24A1 loss-of-function* causes infantile hypercalcemia, hypercalciuria, nephrocalcinosis and nephrolithiasis.

Mechanism of Action and Physiological Roles

- ▶ **VDR:** Member of the nuclear-receptor superfamily; binds DNA as a **heterodimer with the retinoid X receptor (RXR)** at vitamin D response elements, recruiting coactivators to regulate transcription. Affinity for 1,25(OH)₂D is **$\sim$ 1000-fold** higher than for other metabolites.
- ▶ **Intestine (the dominant action):** Induces **calbindin-9K** and the calcium channels **TRPV5 and TRPV6**, increasing the efficiency of **active calcium absorption**. (Phosphate is absorbed efficiently even without vitamin D.)

- ▶ **Bone:** In osteoblasts upregulates **osteocalcin** and **osteopontin** and represses type I collagen; with PTH induces **RANK ligand**, driving osteoclast differentiation and **bone resorption**; induces FGF23 in osteocytes (phosphate regulation).
- ▶ **Parathyroid:** Antiproliferative on parathyroid cells and **suppresses transcription of the PTH gene** — the rationale for vitamin D analogue therapy in renal hyperparathyroidism.
- ▶ **Non-classical:** Antiproliferative effects on keratinocytes, breast and prostate cancer cells; roles proposed in muscle, immune function and inflammation. Alopecia of VDR mutation is *ligand-independent*.

Vitamin D Deficiency: Causes and Pathophysiology

Mechanistically, deficiency arises from defective production, intake, loss, activation, or resistance (Table 421-6):

Mechanism	Representative causes
Impaired cutaneous production	Ageing, dark skin, sunblock, northern latitude, institutionalisation
Dietary absence / malabsorption	Poor intake; short-gut syndrome, gastric bypass , fat malabsorption
Accelerated loss / inactivation	Barbiturates, phenytoin, rifampin (P450 induction); impaired enterohepatic circulation (terminal ileal disease); nephrotic syndrome (urinary DBP loss); CYP3A4 gain-of-function
Impaired 25-hydroxylation	Severe liver disease, isoniazid , 25-hydroxylase mutation
Impaired 1 α -hydroxylation	Hypoparathyroidism , ketoconazole, CYP27B1 mutation, FGF23 excess / oncogenic osteomalacia , X-linked hypophosphatemia, chronic kidney disease
Target-organ resistance	VDR mutation , phenytoin
Other	Obesity

- ▶ **Pathophysiologic cascade:** ↓ intestinal calcium absorption → ↓ serum (ionised) calcium → **secondary hyperparathyroidism** → ↑ bone turnover (raised **alkaline phosphatase**), ↓ urinary calcium and **phosphaturia** → **hypophosphatemia**, which worsens the mineralisation defect.
- ▶ **Rickets (children, before epiphyseal fusion):** Growth retardation with **expansion of the hypertrophic chondrocyte zone** of the growth plate (impaired apoptosis of late hypertrophic chondrocytes); clinically rachitic rosary, bowed legs, frontal bossing.
- ▶ **Osteomalacia (adults):** Defective mineralisation of bone matrix → biomechanically inferior bone, **bowing of weight-bearing limbs and fractures**.

- ▶ **Proximal myopathy:** Striking feature in severe deficiency; resolves rapidly with treatment.
- ▶ Severe acute hypocalcemia is uncommon unless precipitated by concurrent **hypomagnesemia** or potent bisphosphonates.

Inherited Rickets — VDDR Type I vs Type II

Feature	Pseudovitamin D–deficiency rickets (VDDR I)	Hereditary vitamin D–resistant rickets (VDDR II)
Defect	Mutation in renal 1 α -hydroxylase (CYP27B1)	VDR mutation (hormone resistance)
Inheritance	Autosomal recessive	Autosomal recessive
Serum 1,25(OH) ₂ D	Low (despite normal 25(OH)D)	Markedly elevated
PTH	Elevated	Elevated
Alopecia	Absent	Often present (ligand-independent VDR role in hair follicle)
Treatment	Calcitriol / 1,25(OH) ₂ D (bypasses block)	High-dose calcium $\pm$ phosphate, often IV infusions

Assessment, Treatment, Prevention and Toxicity

- ▶ **Best test:** Serum 25(OH)D (reflects stores). Levels <37 nmol/L (<15 ng/mL) associate with rising PTH and lower bone density.
- ▶ **Sufficiency (National Academy of Medicine):** >50 nmol/L (>20 ng/mL); some experts advocate >30 ng/mL for non-skeletal endpoints (to convert ng/mL $\rightarrow$ nmol/L, $\times 2.496$).
- ▶ **RDA:** 600 IU/d (15 μ g/d) for most adults; 800 IU/d (20 μ g/d) for those >70 years.
- ▶ **Treatment of deficiency:** 50,000 IU vitamin D weekly for 6–8 weeks, then maintenance 800 IU/d (20 μ g/d) from food and supplements once levels normalise. D₂ and D₃ have similar long-term effect.
- ▶ **Glucocorticoid-induced osteoporosis prevention:** Calcium 1000–1200 mg/d + vitamin D 600–800 IU/d with weight-bearing exercise.
- ▶ **Toxicity:** Tolerable **upper limit** 4000 IU/d; true intoxication is rare and usually from excessive supplements or faulty fortification $\rightarrow$ **hypercalcemia** (high 1,25(OH)₂D and very high 25(OH)D displacing 1,25(OH)₂D from DBP). Manage by stopping vitamin D/calcium and treating hypercalcemia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Vitamin D activation cascade (Fig 421-4/421-5):** Boxes/arrows — *Skin:* 7-dehydrocholesterol $\rightarrow$ (UV-B) $\rightarrow$ Vitamin D₃; *Diet:* D₂/D₃; $\rightarrow$ *Liver:* 25-hydroxylase $\rightarrow$

25(OH)D (major circulating form); → Kidney: 1 α -hydroxylase (CYP27B1) → 1,25(OH)₂D.
Label regulators on the renal step — + PTH, + low PO₄ / – Ca²⁺, – FGF23, – 1,25(OH)₂D
— and the 24-hydroxylase (CYP24A1) → inactivation branch. Show targets: Intestine
(↑Ca absorption), Bone, Parathyroid (– PTH).

- ▶ **Deficiency feedback loop:** ↓Vitamin D → ↓intestinal Ca → ↓serum Ca → ↑PTH (secondary hyperPTH) → ↑bone resorption + phosphaturia → ↓PO₄ → impaired mineralisation (rickets/osteomalacia).

Clinical / Diagnostic significance

- ▶ **Diagnostic panel of deficiency:** ↓ or low-normal calcium, low phosphate, high alkaline phosphatase, high PTH, low 25(OH)D; radiographs show osteopenia/Looser zones/rachitic changes.
- ▶ **Vitamin D analogues** suppress PTH gene transcription — used in **secondary hyperparathyroidism** of CKD.
- ▶ **Granulomatous/lymphoma hypercalcemia** (extra-renal 1 α -hydroxylase) responds to glucocorticoids, ketoconazole or chloroquine.
- ▶ Calcium + vitamin D supplementation reduces **hip fractures** in deficient elderly/nursing-home residents; deficiency is associated with increased overall and cardiovascular mortality.
- ▶ **Evidence caveat (high-yield):** Recent placebo-controlled trials show **no therapeutic benefit** of vitamin D for prevention of cancer, cardiovascular disease, type 2 diabetes, depression, tuberculosis or respiratory infection — supplementation is justified mainly for **bone health/correction of deficiency**, not as a population-wide disease-prevention strategy.

High-yield exam pointers

- ▶ Active hormone = 1,25(OH)₂D (calcitriol); storage/best-test form = 25(OH)D.
- ▶ Rate-limiting, regulated step = renal 1 α -hydroxylase (CYP27B1): ↑ by PTH/low phosphate, ↓ by Ca/FGF23/1,25(OH)₂D.
- ▶ VDR acts as **VDR–RXR heterodimer**; chief action is **intestinal calcium absorption** (calbindin, TRPV5/6).
- ▶ **Deficiency biochemistry:** ↓Ca, ↓PO₄, ↑ALP, ↑PTH, ↓25(OH)D.
- ▶ **Rickets** = growth-plate (hypertrophic-zone) expansion; **osteomalacia** = defective matrix mineralisation; **proximal myopathy** reversible.
- ▶ **VDDR I** = enzyme defect → low 1,25(OH)₂D, give calcitriol; **VDDR II** = receptor defect → high 1,25(OH)₂D + **alopecia**, resistant.
- ▶ Sufficiency >20 ng/mL; RDA 600 IU/d (800 if >70 y); treat with 50,000 IU/week ×6–8 wk; upper limit 4000 IU/d.

- **Sarcoidosis/lymphoma** → $1,25(\text{OH})_2\text{D}$ -mediated hypercalcemia, steroid-responsive.

SOURCE & COVERAGE

Harrison 22e — Ch 421 “Bone and Mineral Metabolism in Health and Disease” (vitamin D synthesis, metabolism, VDR action, deficiency, rickets/osteomalacia, VDDR I/II, diagnosis) + Ch 344 “Vitamin and Trace Mineral Deficiency and Excess” (dietary sources, reference ranges, RDA/treatment dosing, toxicity, non-skeletal-disease evidence). *Coverage note:* All classifications, doses, enzyme/gene names and cut-offs above are drawn from these two chapters; standard deficiency-panel correlations (Looser zones, frontal bossing) are universally accepted textbook medicine added for completeness.



Vitamin D physiology

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — *Vitamin D* is best regarded as a **prohormone**, not a true vitamin: in the proper biologic setting it can be synthesised endogenously in skin, and its active metabolite **1,25-dihydroxyvitamin D** [$1,25(\text{OH})_2\text{D}$, **calcitriol**] is the major **steroid hormone** regulating mineral-ion (calcium and phosphate) homeostasis. The native vitamin is biologically inert and must undergo **two sequential hydroxylations** — 25-hydroxylation in the liver and tightly regulated 1α -hydroxylation in the kidney — to become active. It acts through a nuclear **vitamin D receptor (VDR)** to optimise intestinal calcium and phosphate absorption, support skeletal mineralisation, and complete the parathyroid–calcium feedback loop.

SOURCE & COVERAGE

- **Cutaneous synthesis (major source):** ultraviolet (UV-B) radiation of skin causes photochemical cleavage of **7-dehydrocholesterol** → **vitamin D₃**. This is the dominant physiological source.
- Cutaneous production is **reduced** by melanin (dark skin), high-SPF sunblocks (which block UV-B skin penetration), reduced solar exposure, and ageing — driving increased reliance on dietary vitamin D.
- **Dietary sources:** fortified cereals and dairy products, fish oils, egg yolks.
 - **Vitamin D₂ (ergocalciferol)** — from plant sources.
 - **Vitamin D₃ (cholecalciferol)** — from animal sources.
 - Both forms have **equivalent biologic activity** and are activated equally well by human vitamin D hydroxylases.

Synthesis and two-step metabolic activation

Whether absorbed from the gut or synthesised in skin, vitamin D enters the circulation bound to **vitamin D-binding protein (DBP)**, an α -globulin made in the liver, then undergoes ordered activation:

Step	Site / enzyme	Product	Regulation
25-hydroxylation	Liver — cytochrome P450 oxidase (mitochondria + microsomes)	25-hydroxyvitamin D [25(OH)D]	Not tightly regulated; reflects substrate supply
1 α -hydroxylation	Kidney — CYP27B1 (25-OH-D-1 α -hydroxylase) in proximal convoluted tubule	1,25(OH) ₂ D (calcitriol) — the active hormone	Tightly regulated
24-hydroxylation (inactivation)	Most tissues — CYP24A1 (24-hydroxylase)	24,25(OH) ₂ D / 1,24,25(OH) ₃ D (inactive)	Induced by 1,25(OH) ₂ D and FGF23

- ▶ 25(OH)D is the **major circulating and storage form**: ~88% bound to DBP, ~0.03% free, the remainder bound to albumin; half-life ~2–3 weeks. Hence it is the **best index of vitamin D status**.
- ▶ DBP affinity is lower for the D₂ metabolites, so 25(OH)D₂ has a shorter half-life than 25(OH)D₃; half-life also shortens when DBP is lost (e.g., **nephrotic syndrome**).

Regulation of the active hormone (hormonal control loop)

- ▶ CYP27B1 (1 α -hydroxylase) is the key control point:
 - Induced ($\uparrow$ 1,25(OH)₂D) by: PTH and hypophosphatemia.
 - Repressed ($\downarrow$ 1,25(OH)₂D) by: calcium, FGF23, and the product 1,25(OH)₂D itself (negative feedback).
- ▶ **Integrated calcium loop**: a fall in serum calcium below ~2.2 mmol/L (8.8 mg/dL) stimulates PTH secretion $\rightarrow$ mobilises bone calcium and stimulates renal 1,25(OH)₂D synthesis $\rightarrow$ 1,25(OH)₂D enhances **intestinal calcium absorption** and, with PTH, restores serum calcium; 1,25(OH)₂D in turn **suppresses PTH gene transcription** (closing the loop).
- ▶ **Auto-limitation**: 1,25(OH)₂D is the major inducer of its own catabolising enzyme CYP24A1, promoting its own inactivation and limiting biologic effect.
- ▶ **Extrarenal 1 α -hydroxylase** is expressed in keratinocytes, the placental trophoblast, and **macrophages of granulomas and lymphomas**, where it is induced by IFN- γ and TNF- α and is NOT regulated by calcium or 1,25(OH)₂D — explaining the **hypercalcemia of sarcoidosis/granulomatous disease and lymphoma** (responsive to glucocorticoids, ketoconazole, chloroquine in sarcoid).

Mechanism of action — VDR and target-organ effects

1,25(OH)₂D binds the **vitamin D receptor (VDR)**, a member of the nuclear-receptor superfamily (related to thyroid hormone, retinoid, and PPAR receptors). The VDR heterodimerises with the **retinoid X receptor (RXR)**, binds vitamin D response elements, and recruits coactivators to modulate target-gene transcription. The VDR's affinity for 1,25(OH)₂D is **~1000-fold (three orders of magnitude)** higher than for other metabolites.

Target tissue	Action of 1,25(OH) ₂ D
Intestine	Induces calbindin-9K and calcium channels TRPV6 (gut) / TRPV5 (renal); increases efficiency of active calcium absorption and stimulates phosphate absorption (Na ⁺ /PO ₄ cotransporters, e.g., Npt2b)
Bone (osteoblast)	Upregulates osteocalcin , osteopontin ; represses type I collagen ; with PTH induces RANK ligand → osteoclast differentiation and bone resorption
Osteocyte	Induces FGF23 → regulates phosphate homeostasis
Parathyroid	Antiproliferative ; suppresses PTH gene transcription
Skin / other	Antiproliferative on keratinocytes, breast and prostate cancer cells; VDR mutation → alopecia (a ligand-independent effect, not seen in simple deficiency); regulates the bone–tendon attachment (enthesis)

- ▶ Active (transcellular, 1,25(OH)₂D-dependent) calcium transport occurs mainly in **duodenum/proximal jejunum** and normally accounts for **20–70%** of dietary calcium absorption; passive paracellular absorption (~5%) is vitamin D-independent.

Vitamin D deficiency — causes and consequences

Biochemical cascade: deficiency → impaired intestinal calcium absorption → **hypocalcemia** → **secondary hyperparathyroidism** → increased bone turnover (↑**alkaline phosphatase**), **phosphaturia** → **hypophosphatemia** → impaired skeletal **mineralisation**.

- ▶ **Children (before epiphyseal fusion): rickets** — expansion of the growth-plate **hypertrophic chondrocyte zone** (of the reserve, proliferating, hypertrophic zones).
- ▶ **Adults: osteomalacia** — defective mineralisation of bone matrix; plus **proximal myopathy**, osteopenia/low BMD; associated with **increased overall (incl. cardiovascular) mortality**.

Mechanism	Examples (Table 421-6)
Vitamin D deficiency	Impaired cutaneous production; dietary absence; malabsorption (short-gut, gastric bypass)
Accelerated loss / catabolism	Hepatic P450 inducers — barbiturates , phenytoin , rifampin ; impaired enterohepatic circulation

Mechanism	Examples (Table 421-6)
	(terminal ileal disease); nephrotic syndrome; CYP3A4 mutation
Impaired 25-hydroxylation	Liver disease, isoniazid; 25-hydroxylase mutation
Impaired 1 α -hydroxylation	Hypoparathyroidism; ketoconazole; CYP27B1 (1 α -hydroxylase) mutation; FGF23 excess; oncogenic osteomalacia; chronic kidney disease
Target-organ resistance	VDR mutation; obesity

- ▶ **Pseudovitamin D–deficiency rickets (vitamin D–dependent rickets type I):** autosomal-recessive 1 α -hydroxylase (CYP27B1) mutation — low 1,25(OH) $_2$ D, normal/high 25(OH)D, high PTH; responds to calcitriol.
- ▶ **Hereditary vitamin D–resistant rickets (type II):** VDR mutation with end-organ resistance — markedly elevated 1,25(OH) $_2$ D, often alopecia; needs calcium $\pm$ phosphate infusions to bypass the defect.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Vitamin D synthesis and activation cascade (vertical flow):** Skin: 7-dehydrocholesterol $\rightarrow$ (UV-B) $\rightarrow$ Vitamin D $_3$ and Diet: D $_2$ /D $_3$ $\rightarrow$ DBP-bound transport $\rightarrow$ Liver: 25-hydroxylase $\rightarrow$ 25(OH)D $\rightarrow$ Kidney (PCT): 1 α -hydroxylase/CYP27B1 $\rightarrow$ 1,25(OH) $_2$ D $\rightarrow$ target organs. Side label: 24-hydroxylase/CYP24A1 $\rightarrow$ inactive 24,25(OH) $_2$ D.
- ▶ **Hormonal control loop (Harrison Fig. 421-5):** central box Blood calcium; arrows to Parathyroid glands (PTH), Kidney (1,25(OH) $_2$ D), Bone, Intestine. Labels: $\downarrow$ Ca $^{2+}$ $\rightarrow$ $\uparrow$ PTH; PTH + $\downarrow$ PO $_4$ $\rightarrow$ $\uparrow$ 1 α -hydroxylase; 1,25(OH) $_2$ D $\rightarrow$ $\uparrow$ gut Ca $^{2+}$ /PO $_4$ absorption; Ca $^{2+}$, FGF23, 1,25(OH) $_2$ D $\rightarrow$ $\downarrow$ 1 α -hydroxylase; 1,25(OH) $_2$ D $\rightarrow$ $\downarrow$ PTH gene (negative feedback).

Clinical / Diagnostic significance

- ▶ **Best screening test:** serum 25(OH)D (reflects stores). <37 nmol/L (<15 ng/mL) associates with rising PTH and lower bone density; National Academy of Medicine defines sufficiency as >50 nmol/L (>20 ng/mL) (higher may be needed in the elderly/obese).
- ▶ Do **not** use serum 1,25(OH) $_2$ D to assess deficiency — it may be normal or high (driven by secondary hyperparathyroidism) despite depleted stores.
- ▶ **Deficiency biochemistry:** $\downarrow$ Ca, $\downarrow$ PO $_4$, $\uparrow$ PTH, $\uparrow$ alkaline phosphatase, low 25(OH)D.
- ▶ **At-risk groups:** elderly/nursing-home residents (skin synthesis and gut absorption both decline with age), malabsorption/short-gut/bariatric surgery, terminal ileal disease, nephrotic syndrome, chronic liver/kidney disease, obesity, enzyme-inducing drugs.
- ▶ **Management principles (from chapter):** calcium + vitamin D supplementation reduces hip-fracture incidence in deficient elderly; in CKD/hypoparathyroidism use calcitriol/active

analogues to bypass the 1α -hydroxylation block; type II resistant rickets needs calcium/phosphate infusions.

- ▶ **Hypercalcemia of granulomatous disease/lymphoma** is driven by unregulated extrarenal 1α -hydroxylase — treat with glucocorticoids ($\pm$ ketoconazole/chloroquine).
- ▶ **CYP24A1 loss-of-function** mutation $\rightarrow$ impaired inactivation $\rightarrow$ **infantile hypercalcemia**, later hypercalciuria, nephrocalcinosis, nephrolithiasis.

High-yield exam pointers

- ▶ Vitamin D is a **prohormone**; $1,25(\text{OH})_2\text{D}$ (**calcitriol**) is the active steroid hormone.
- ▶ Activation = liver 25-hydroxylase (**not regulated**) then renal CYP27B1/ 1α -hydroxylase (**tightly regulated**).
- ▶ **1α -hydroxylase**: $\uparrow$ by PTH + hypophosphatemia; $\downarrow$ by calcium, FGF23, $1,25(\text{OH})_2\text{D}$.
- ▶ $25(\text{OH})\text{D}$ = best status marker (half-life 2–3 weeks, $\sim 88\%$ DBP-bound); sufficiency >20 ng/mL.
- ▶ Action via **VDR–RXR heterodimer**; affinity for $1,25(\text{OH})_2\text{D}$ **1000 $\times$ higher** than other metabolites.
- ▶ Gut: induces **calbindin-9K** + TRPV6 $\rightarrow$ calcium absorption (duodenum/jejunum, 20–70%).
- ▶ Deficiency $\rightarrow$ $\downarrow$ Ca, **secondary hyperPTH**, $\downarrow\text{PO}_4$, $\uparrow$ ALP $\rightarrow$ **rickets (children)/osteomalacia (adults)** + proximal myopathy.
- ▶ **CYP24A1 (24-hydroxylase)** inactivates vitamin D; mutation $\rightarrow$ infantile hypercalcemia.
- ▶ **Type I rickets** = CYP27B1 mutation (treat calcitriol); **Type II** = VDR mutation + alopecia (very high $1,25(\text{OH})_2\text{D}$).

SOURCE & COVERAGE

Harrison 22e — Ch 421 “Bone and Mineral Metabolism in Health and Disease” (Vitamin D: synthesis/metabolism, actions, deficiency; Figs 421-4 and 421-5; Tables 421-6). **Coverage note:** the chapter names the dietary forms as “vitamin D_2/D_3 ” but does not use the terms *ergocalciferol/cholecalciferol*; these (and *calcitriol* for $1,25(\text{OH})_2\text{D}$) are added as universally accepted standard nomenclature. Harrison Ch 421 does not specify numeric vitamin D RDA/IU or repletion **dosing regimens**, so quantitative treatment doses are deliberately omitted; only the chapter’s qualitative management points are stated.

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Environment & poisonings

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Carbon Monoxide Poisoning

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Carbon monoxide (CO) is a colourless, odourless, non-irritant gas produced by incomplete combustion of carbon-containing fuels. It is a prototype “**asphyxiant**” (systemic chemical hypoxia) poison that binds haemoglobin with ~200–250 times the affinity of oxygen, forming **carboxyhaemoglobin (COHb)**, thereby reducing oxygen-carrying capacity, impairing oxygen delivery and disrupting cellular oxidative metabolism. It is one of the leading causes of poisoning death worldwide — in the United States alone it accounts for >50,000 emergency-department visits and ~2000 deaths per year — and is frequently lethal before the patient reaches hospital.

SOURCE & COVERAGE

- ▶ **Common sources:** automobile exhaust, smoke inhalation in house/structural fires, improperly vented or defective domestic gas heaters/geysers, generators and industrial appliances, and degradation of some anaesthetic gases by CO₂ adsorbents.
- ▶ **Intent:** about half of non-lethal exposures are deliberate (self-harm); the **motor vehicle is the commonest source of intentional poisoning**. Accidental poisoning clusters in **cold weather** when faulty heating systems are used in poorly ventilated rooms.
- ▶ It is the **third leading cause of death from poisoning** overall, but is under-represented in hospital statistics because victims are often found dead and referred directly to medical examiners.
- ▶ The **fetus and newborn are especially susceptible** because fetal haemoglobin has a high affinity for CO.

Pathophysiology — mechanisms of toxicity

CO produces injury by several overlapping mechanisms, not by hypoxaemia alone:

Mechanism	Consequence
Binds Hb → carboxyhaemoglobin (affinity ~200–250× O ₂)	Reduced oxygen-carrying capacity → anaemic-type (histotoxic) hypoxia
COHb shifts the oxy-Hb dissociation curve to the LEFT	O ₂ unloaded only at very low tissue tensions → worsened tissue hypoxia
Binds myoglobin	Impaired O ₂ storage/use in cardiac and skeletal muscle
Binds cytochrome a/a3 (cytochrome c oxidase)	Blockade of mitochondrial electron transport / oxidative metabolism → lactic acidosis
Lipid peroxidation in brain, leukocyte adherence to endothelium, oxidative stress	Delayed neuronal injury and neuropsychiatric sequelae

- ▶ The **brain and heart** are the most sensitive target organs (high blood flow, high O₂ demand, poor tolerance of hypoxia).

- ▶ CO is also a low-affinity **anaesthetic agent** and an endogenous gaseous neurotransmitter linked to nitric oxide metabolism.

Clinical features (correlate with COHb saturation)

COHb saturation	Typical clinical features
10–20%	Headache, dizziness, nausea, abdominal pain, lethargy, poor concentration
20–40% (higher)	Confusion, impaired short-term memory, dyspnoea on exertion, syncope, visual disturbance, irritability
>50–60%	Hypotension, seizures, coma , cardiac ischaemia/arrhythmia, sudden collapse, death

- ▶ Symptoms are **non-specific and “flu-like”**, so the diagnosis is easily missed; suspect CO in any patient with severe headache or acutely altered mental status, **especially during cold weather** or when multiple household members are simultaneously ill.
- ▶ *Classic “cherry-red” skin* is the traditionally described sign but is **unreliable and usually a late/post-mortem finding**; importantly, CO does NOT produce true cyanosis — carboxyhaemoglobinaemia is listed as a cause of skin discolouration that is *not true cyanosis*.
- ▶ Other features: myocardial ischaemia (even in young patients), rhabdomyolysis, non-cardiogenic pulmonary oedema, and (with concurrent fire exposure) **co-existent cyanide poisoning and thermal airway injury**.

Diagnosis and investigations

- ▶ **Diagnosis rests on direct measurement of arterial or venous COHb saturation by CO-oximetry.** A normal smoker may have 5–10%; non-smokers <2–3%.
- ▶ **Pitfalls:** routine **pulse oximetry (SpO₂) is falsely normal/elevated** — it cannot distinguish COHb from oxyhaemoglobin; **arterial blood gas PaO₂ is also falsely normal** because dissolved O₂ is unaffected. Calculated O₂ saturation is normal but measured (co-oximetry) saturation is low — a *discordant* picture characteristic of asphyxiants. Specialised pulse CO-oximeters can estimate COHb with variable accuracy.
- ▶ **Admission COHb level confirms exposure but does NOT reliably reflect severity or prognosis,** and falls rapidly once high-flow oxygen is started.
- ▶ Supporting tests: ABG showing **elevated anion-gap (lactic) metabolic acidosis**; ECG and troponin for myocardial ischaemia; serum lactate; CK for rhabdomyolysis; and in selected cases neuroimaging (CT/MRI may show **basal ganglia / globus pallidus changes** — a standard radiological association).

Management

A. Emergency and supportive measures

- ▶ Remove the patient from the source of exposure immediately.
- ▶ Secure airway, assist ventilation; treat coma, seizures and hypotension along standard poisoning lines.
- ▶ If smoke inhalation/fire is involved, anticipate and treat **concurrent cyanide poisoning** (IV hydroxocobalamin ± sodium nitrite/sodium thiosulfate) and thermal airway injury.

B. Specific treatment — OXYGEN is the antidote

- ▶ The elimination half-life of COHb is ~4–5 h (~5.5 h) **breathing room air**, falling to ~60–90 min (~71 min) on 100% oxygen at 1 ATA, and to ~20 min (~21 min) on oxygen at 2.0 ATA.
- ▶ Give 100% oxygen by tight-fitting high-flow non-rebreather reservoir mask or via endotracheal tube; continue until the patient is asymptomatic and COHb is near-normal.

C. Hyperbaric oxygen (HBO) therapy

- ▶ HBO delivers 100% O₂ at supra-atmospheric pressure, dramatically shortening COHb half-life and (more importantly) is thought to reduce **delayed neuropsychiatric sequelae** via mechanisms beyond reversal of hypoxia — displacing CO from cytochromes, upregulating antioxidant defences, reducing leukocyte adherence and lipid peroxidation.
- ▶ CO poisoning is a **recognised primary indication** for HBO (Undersea & Hyperbaric Medical Society list), including poisoning **complicated by cyanide**.
- ▶ **Commonly recommended indications for HBO** (criteria differ between sources — RCTs disagree on benefit):

Source	Indications / risk markers for HBO referral
CMDT 2026	History of loss of consciousness; COHb >25%; metabolic acidosis; age >50 years; cerebellar findings on examination
Harrison (Hyperbaric & Diving Medicine)	Moderate–severe poisoning; age >35 years; metabolic acidosis on ABG; lengthy exposure (>24 h); history of unconsciousness; pregnancy is also a widely accepted indication

- ▶ **Evidence:** the most rigorous RCT (Weaver et al.) showed cognitive sequelae at 6 weeks in 25% with HBO vs 46% with normobaric oxygen ($p = .007$, NNT = 5) and a persisting benefit at 12 months (18% vs 32%, NNT = 7). A Cochrane review found insufficient pooled evidence, so HBO use remains individualised and time-sensitive (ideally first sessions within 24 h).

Delayed neuropsychiatric syndrome and prognosis

- ▶ Survivors of severe poisoning may develop **persistent or delayed neuropsychiatric deficits** — characteristically after an interval of *days to weeks* of apparent recovery.

- ▶ Reported features: cognitive impairment/dementia, short-term memory loss, **parkinsonism and other movement disorders**, peripheral neuropathy, hearing loss, vestibular dysfunction, personality change and psychosis.
- ▶ **Risk factors for poor outcome:** age >35 years, exposure >24 h, metabolic acidosis, and loss of consciousness.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Oxygen–haemoglobin dissociation curve:** plot S_{aO_2} (y-axis) vs P_{o_2} (x-axis); show the normal sigmoid curve and a left-shifted curve in CO poisoning. Label: *normal curve, left shift due to COHb, P_{50} reduced, O₂ unloaded only at low tissue P_{o_2} → tissue hypoxia.*
- ▶ **Pathophysiology flow diagram:** *Inhaled CO → binds Hb (200–250× O₂ affinity) → ↓ O₂-carrying capacity + LEFT shift of ODC; binds myoglobin; inhibits cytochrome c oxidase → impaired oxidative phosphorylation → lactic acidosis + brain/heart hypoxia → coma, seizures, delayed neuropsychiatric sequelae.*

Clinical / Diagnostic significance

- ▶ Never rely on SpO_2 or PaO_2 to exclude CO poisoning — both are falsely reassuring; demand a CO-oximetry COHb level.
- ▶ Consider CO in clusters of simultaneously ill household members, in winter, and in all fire/smoke-inhalation victims (screen for cyanide too).
- ▶ An unexplained **high-anion-gap lactic acidosis** with normal PaO_2 should trigger consideration of asphyxiant poisoning (CO, cyanide, H₂S).
- ▶ Pregnant patients warrant lower thresholds for 100% O₂ and HBO because of fetal vulnerability.
- ▶ Counsel survivors and arrange neuropsychological follow-up given the risk of the delayed syndrome.

High-yield exam pointers

- ▶ CO affinity for Hb = ~200–250× that of O₂; forms **carboxyhaemoglobin** and shifts the oxy-Hb curve to the LEFT.
- ▶ Diagnosis = **CO-oximetry**; **pulse oximetry & PaO_2 are falsely normal**; admission COHb does not predict severity/prognosis.
- ▶ COHb half-life: ~5 h (air) → ~71 min (100% O₂, 1 ATA) → ~21 min (O₂ at 2 ATA).
- ▶ **Antidote = oxygen**; 100% O₂ by non-rebreather is first-line; HBO for severe/high-risk cases.
- ▶ HBO indications (CMDT): LOC, **COHb >25%**, metabolic acidosis, **age >50**, cerebellar signs; (Harrison risk markers): age >35, acidosis, prolonged exposure, LOC, pregnancy.
- ▶ Toxicity is multi-mechanistic: Hb + **myoglobin** + **cytochrome c oxidase** binding → lactic acidosis; brain and heart are most vulnerable.

- ▶ CO does not cause true cyanosis; “cherry-red” skin is classic but unreliable/late.
- ▶ Beware concurrent cyanide toxicity and airway burns in fire victims.
- ▶ Delayed neuropsychiatric syndrome (parkinsonism, cognitive/memory deficits) can appear days–weeks after recovery; basal ganglia (globus pallidus) lesions on imaging.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Poisoning and Drug Overdose” (asphyxiant toxic syndromes, oxygen/antidotal therapy); “Hyperbaric and Diving Medicine” (dedicated Carbon Monoxide Poisoning section — epidemiology, mechanisms, COHb half-lives, HBO indications and Weaver RCT data); “Hypoxia and Cyanosis” (CO intoxication, left-shift of dissociation curve, carboxyhaemoglobinaemia is not true cyanosis).
- ▶ **CMDT 2026** — “Poisoning” (Carbon Monoxide: clinical findings by COHb level, diagnosis by CO-oximetry, HBO indication criteria) and “Pulmonary Disorders — Smoke Inhalation” (combined CO/cyanide injury).
- ▶ *Coverage note:* The corpus does not present a formal staging or a discrete table of cherry-red-skin/retinal signs for CO; the “cherry-red skin” and basal-ganglia/parkinsonism associations included are universally accepted standard internal medicine and are stated with appropriate caveats. HBO benefit is genuinely debated across the cited sources, reflected faithfully above.



Clinical features and management of organophosphorus poisoning

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — Organophosphorus (OP) compounds are anticholinesterase insecticides (e.g. diazinon, malathion, parathion, chlorpyrifos, acephate) and chemical-warfare nerve agents (tabun, sarin, soman, VX) that **irreversibly inhibit acetylcholinesterase**, causing accumulation of acetylcholine at muscarinic, nicotinic and central synapses — a *cholinergic crisis*. OP poisoning, usually deliberate self-poisoning, is a leading cause of pesticide death in the developing world; **>150,000 pesticide poisoning deaths occur worldwide each year**, with insecticides accounting for the majority. Death is from bronchorrhoea, respiratory-muscle paralysis and CNS depression; management hinges on aggressive resuscitation, atropine and an oxime.

Toxicokinetics & Mechanism (Pathophysiology)

- ▶ **Absorption** is by all routes — inhalational (fastest onset), transdermal, transconjunctival, mucous-membrane and gastrointestinal; most OPs are lipophilic and formulated in aromatic-hydrocarbon solvents (e.g. xylene), aiding skin penetration.
- ▶ **Two cholinesterases are inhibited:** *true (RBC) acetylcholinesterase* — found in erythrocyte membranes, nervous tissue and skeletal muscle; and *plasma cholinesterase (pseudocholinesterase / butyrylcholinesterase)* — found in serum, liver, pancreas, heart and brain.
- ▶ OP **phosphorylates** the enzyme's active site, blocking acetylcholine hydrolysis → ACh accumulates at: CNS synapses, autonomic ganglia, post-ganglionic *muscarinic* parasympathetic and sympathetic (sweat-gland) endings, and *nicotinic* neuromuscular junctions.
- ▶ ***Aging** = *permanent, irreversible covalent binding of the OP to cholinesterase after loss of an alkyl group; once aged, the enzyme is destroyed and recovery requires resynthesis over weeks. Time-to-aging is highly agent-dependent (minutes for soman to >24 h). Oximes work only before aging** — hence the urgency.

Clinical Features — the four syndromes

Most patients are symptomatic within **8 hours** and nearly all within **24 hours**. The hallmark acute toxidrome combines muscarinic, nicotinic and CNS effects:

Receptor / system	Manifestations	Mnemonic
Muscarinic	Salivation, Lacrimation, Urination, Defaecation, GI cramps, Emesis; Miosis; Bradycardia, Bronchorrhoea, Bronchospasm (“Killer Bs”)	SLUDGE / DUMBELS
Nicotinic	Muscle fasciculations, cramps, weakness (incl. diaphragm) → paralysis; mydriasis, pallor, tachycardia, hypertension (sympathetic ganglia/adrenal)	“days of the week” – MTWtHF
CNS	Anxiety, restlessness, emotional lability, tremor, headache, dizziness, confusion, delirium, hallucinations, seizures, coma	—

- ▶ **Mixed autonomic picture:** parasympathetic effects usually predominate, but nicotinic stimulation of sympathetic ganglia/adrenal medulla can produce *early* tachycardia, hypertension, pallor and mydriasis — so a normal/raised pulse does **not** exclude OP poisoning.
- ▶ **Severe poisoning** classically presents with **altered mental status, pinpoint pupils, profuse sweating and difficulty breathing**; a *garlic-like / hydrocarbon odour* on breath or clothing is a useful clue.

- ▶ *Other features*: abdominal pain (rarely pancreatitis), aspiration/lipoid pneumonia from hydrocarbon solvent, pulmonary oedema, early myocardial ischaemia; ECG may show QT prolongation, ST/T changes, AV block, torsades, VT/VF.

The four recognised clinical syndromes

- ▶ **Acute cholinergic crisis** — the muscarinic/nicotinic/CNS toxidrome above; onset minutes (inhalation/large ingestion) to hours.
- ▶ **Intermediate syndrome** — 1–5 days after exposure (up to ~40% of ingestions); weakness of **neck flexors, cranial-nerve-innervated muscles, proximal limbs and respiratory muscles** (may need ventilation). *Cholinergic features are absent*; EMG aids diagnosis; usually resolves within 7 days. **Not** caused by nerve agents.
- ▶ **Organophosphate-induced delayed neuropathy (OPIDN)** — cognitive dysfunction, impaired memory, mood change, autonomic dysfunction, distal **peripheral neuropathy** and extrapyramidal signs (related to neuropathy-target-esterase inhibition).
- ▶ **Chronic toxicity** — in chronically exposed agricultural workers; a symmetrical **sensorimotor axonopathy** beginning as leg cramps progressing to weakness/paralysis, *mimicking Guillain-Barré syndrome*.

Diagnosis / Investigations

- ▶ **Clinical** — diagnosis rests on the history and a suggestive cholinergic toxidrome; **never delay antidote** awaiting laboratory confirmation.
- ▶ **Cholinesterase assays** (confirmatory markers):
 - *Plasma butyrylcholinesterase* — easier, more available, falls first; may drop ~50% in asymptomatic exposure; normalises in **28–42 days** (if no oxime given).
 - *RBC acetylcholinesterase* — better reflects synaptic inhibition; falls to **10–20% of normal in moderate** and **<10% in severe** poisoning; full recovery may take up to **120 days** (needs RBC turnover).
 - As a rule, plasma + RBC cholinesterase activity is **<50% of normal** in significant intoxication.
 - *Caveats*: BuChE is low in genetic variants, liver disease, malnutrition, pregnancy; standardisation between labs is poor.
- ▶ **Ancillary** — pancreatic enzymes, glucose (hypo/hyper), leucocytosis, deranged LFTs; CXR (pulmonary oedema/aspiration); ECG; EMG quantifies NMJ block (intermediate syndrome).

Management

Principles — *protect rescuers, decontaminate, resuscitate (ABC), give atropine + oxime, support ventilation*. Manage in an ICU for significant poisoning.

- ▶ **Staff & decontamination**: wear **nitrile/neoprene** gloves, gown, mask/face-shield (latex is inadequate); remove and bag all clothing as hazardous waste; wash

skin/hair/nails/conjunctivae/skin-folds with copious **soap (mild detergent) and water**; contain runoff. *Dilute hypochlorite (household bleach 1:10)* breaks down OP/nerve agent on equipment. Avoid skin abrasion.

- **Airway & breathing:** 100% O₂ via non-rebreather; gentle suction of secretions; **endotracheal intubation and ventilation** for coma, seizures, respiratory failure, severe bronchospasm/bronchorrhoea. **Avoid succinylcholine** (metabolised by plasma BuChE → prolonged paralysis) — use a *non-depolarising* blocker; avoid ester anaesthetics and β -blockers.
- **GI decontamination:** gastric lavage has **no proven benefit** (may consider within 1 h of a large ingestion *after* the airway is secured, never delaying antidote); single/multiple-dose activated charcoal is of unproven benefit; haemodialysis/haemoperfusion are of no proven value.

Specific antidotes

Antidote	Action	Regimen (adult)
Atropine	Competitive antagonist at muscarinic receptors — reverses bronchorrhoea, bronchospasm, secretions, bradycardia, cramps; does <i>not</i> affect nicotinic weakness	Bolus 1.2–3.0 mg IV (child 0.05 mg/kg); double the dose every 5 min until <i>atropinised</i> : clear chest, HR >80/min, SBP >80 mmHg. Then infusion at 10–20%/h of the total atropinising dose (~0.4–4 mg/h). Massive ingestions may need hundreds of mg.
Pralidoxime (2-PAM)	Oxime — reactivates cholinesterase by displacing OP from the active site; reverses nicotinic weakness/paralysis <i>if given before aging</i>	30 mg/kg IV over 5–10 min loading (WHO), then infusion 8 mg/kg/h for 24–48 h . (<i>CMDT alternative: 1–2 g IV load, then 200–500 mg/h.</i>) Continue while signs of ACh excess persist.
Benzodiazepines	Control seizures / agitation	IV diazepam/lorazepam; atropine may abort early cholinergic seizures.

- **Atropine end-points:** titrate to *adequate atropinisation* (above); **pupillary dilatation and tachycardia are NOT end-points** and tachycardia is *not* a contraindication (it may be hypoxia/bronchospasm-driven, reversible by atropine). Watch for atropine toxicity: absent bowel sounds, hyperthermia, delirium, urinary retention. **Glycopyrrolate** (no CNS penetration) is an alternative for peripheral muscarinic control.
- **Pralidoxime caveats:** give as **early as possible** (before aging); still worth giving even **24–48 h** after exposure; **not** for asymptomatic patients or single-agent **carbamate** poisoning (carbamylated enzyme reactivates spontaneously and 2-PAM may worsen carbaryl toxicity). Use it if the agent is unknown or a mixed OP–carbamate exposure.

- ▶ **Adjuncts of uncertain benefit (not routine):** magnesium sulphate, calcium-channel blockers, clonidine, sodium bicarbonate.
- ▶ **Disposition:** minor exposure → decontaminate + observe 6–8 h. Significant poisoning → ICU; most respond to oxime with rising cholinesterase within 48 h; with early treatment and no hypoxic brain injury, symptomatic recovery by ~10 days. Lipid-soluble agents (fenthion, dimethoate) cause prolonged/recurrent toxicity needing continued atropine/oxime over weeks. End-point of oxime therapy = no recurrence of signs on withholding it.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Cholinergic synapse / mechanism schematic:** pre-synaptic neuron releasing acetylcholine into the synaptic cleft → post-synaptic **muscarinic** and **nicotinic receptors**; **acetylcholinesterase** in the cleft with a red “X” showing **OP-induced inhibition** (phosphorylation → aging); arrow to **ACh accumulation**. Side boxes: *Muscarinic effects* (SLUDGE / DUMBELS, Killer Bs), *Nicotinic effects* (fasciculations, weakness, tachycardia, HTN), *CNS effects* (seizures, coma). Label antidote actions: **Atropine** → **blocks muscarinic receptor**; **Pralidoxime** → **reactivates acetylcholinesterase**.
- ▶ **Time-course bar:** *Acute crisis* (0–24 h) → *Intermediate syndrome* (1–5 days) → *OPIDN* (delayed, weeks).

Clinical / Diagnostic significance

- ▶ The triad **miosis + sweating/secretions + diarrhoea (with a garlic odour)** in a collapsed patient should prompt empirical atropine even before assay results.
- ▶ **Inadequate atropinisation** (persistent bronchorrhoea/hypoxia) is a common, fatal pitfall — titrate hard against chest auscultation, not pupils.
- ▶ Recognising the **intermediate syndrome** prevents fatal *unmonitored* respiratory failure 1–5 days after apparent recovery — keep monitoring even after the cholinergic crisis settles.
- ▶ **Carbamates** (reversible, do not age) need atropine but generally not pralidoxime, and recover within ~24 h — distinguishing them changes management.
- ▶ Serial RBC AChE/plasma BuChE help confirm diagnosis and gauge recovery, but treatment must never wait for them.

High-yield exam pointers

- ▶ OP **irreversibly** inhibits acetylcholinesterase; carbamates do so **reversibly** (no aging) → carbamate course is shorter and milder.
- ▶ ***Aging** = *irreversible OP–enzyme binding* → *oxime ineffective*; *soman ages in minutes**, leaving almost no oxime window.
- ▶ **SLUDGE/DUMBELS** = muscarinic; **fasciculations + weakness + tachycardia/HTN** = nicotinic; **seizures/coma** = CNS.

- ▶ **Atropinisation end-points:** clear chest, HR >80, SBP >80 — *not* pupils; tachycardia is **not** a contraindication to atropine.
- ▶ **Pralidoxime** reverses *nicotinic* weakness and must be given **early, before aging**; atropine does *not* reverse muscle weakness.
- ▶ **Avoid succinylcholine** (prolonged paralysis via BuChE inhibition); use non-depolarising relaxants.
- ▶ **Four syndromes:** acute crisis → **intermediate syndrome** (1–5 d, proximal/respiratory/neck-flexor weakness, **no cholinergic signs**) → OPIDN (delayed neuropathy) → chronic sensorimotor axonopathy (GBS-like).
- ▶ **Death is from respiratory failure** (bronchorrhoea + respiratory-muscle paralysis + CNS depression).
- ▶ Cholinesterase activity <50% of **normal** supports significant poisoning; plasma BuChE falls first, RBC AChE reflects synaptic inhibition.

SOURCE & COVERAGE

- ▶ Tintinalli's Emergency Medicine — “Pesticides” (Organophosphates: pathophysiology, four syndromes, cholinesterase assays, atropine/pralidoxime regimens, carbamate contrast) — primary depth source.
- ▶ Harrison's Principles of Internal Medicine, 22e — “Poisoning and Drug Overdose” (cholinergic toxidrome; acetylcholinesterase-inhibitor mechanism; atropine + 2-PAM principles).
- ▶ CMDT 2026 — “Poisoning: Pesticides — Cholinesterase Inhibitors” (current atropine 2 mg escalating-dose and pralidoxime 1–2 g load/200–500 mg/h regimens; decontamination; pralidoxime + atropine for OP-induced seizures).



Clinical features, management and complications of scorpion envenomation

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — Scorpion envenomation (scorpionism) is systemic poisoning following the sting of an arachnid of the order Scorpiones, which injects peptide-rich venom from the **aculeus** (**stinger**) at the tip of the tail (telson). Of ~1000–1500 known species, only about 30 (almost all of the family *Buthidae*) are dangerous to humans, together causing several thousand deaths annually. The clinical hallmark is an “**autonomic storm**” — a massive, biphasic outpouring of acetylcholine and catecholamines — so that systemic and especially **cardiorespiratory** features are grossly out of proportion to the trivial local sting. In India the lethal species is the *Indian red scorpion* (*Mesobuthus* /

Hottentotta tamulus), against which the α 1-blocker **prazosin** is the pharmacological cornerstone of treatment.

Epidemiology & medically important species

- ▶ Worldwide an estimated >1.2 million serious stings and ~3250 deaths per year; children and the elderly suffer the most severe envenomation and highest mortality.
- ▶ Scorpions are nocturnal, hiding by day under rocks, bark, woodpiles or inside shoes, clothing and bedding; they sting only when threatened.
- ▶ The dangerous species belong almost exclusively to the family **Buthidae**.

Region	Important species	Distinguishing toxicity
India / South Asia	<i>Mesobuthus (Hottentotta) tamulus</i> — Indian red scorpion	Catecholamine storm, myocarditis, pulmonary oedema
Middle East / N. Africa	<i>Leiurus quinquestriatus</i> , <i>Androctonus</i> spp.	Catecholamine excess, hypertensive crisis, arrhythmias
Brazil	<i>Tityus serrulatus</i> (<i>tityustoxin</i>)	Childhood deaths; <i>T. trinitatis</i> (Trinidad) → pancreatitis
Iran / Iraq	<i>Hemiscorpius lepturus</i>	Cytotoxic — haemolysis, haemoglobinuria, AKI, skin necrosis
South Africa	<i>Parabuthus</i> , <i>Buthotus</i> spp.	CNS toxicity
SW USA (Arizona)	<i>Centruroides sculpturatus / exilicauda</i> — bark scorpion	Neuromuscular & cranial-nerve dysfunction

Venom & pathophysiology — the “autonomic storm”

- ▶ Venom contains low-molecular-weight **peptide neurotoxins** plus 5-hydroxytryptamine, histamine and kinins.
- ▶ Neurotoxins act on **voltage-gated sodium channels**, holding them **open** (prolonged depolarisation), and **block potassium channels** → repetitive, uncontrolled firing of autonomic and somatic nerves.
- ▶ This drives **massive release of acetylcholine and endogenous catecholamines** at autonomic ganglia, adrenal medulla and neuromuscular junctions, producing the characteristic **biphasic response**:
 - *Early transient parasympathetic (cholinergic) phase* — vomiting, profuse salivation, lacrimation, sweating, bronchorrhoea, bradycardia, hypotension, priapism.
 - *Sustained sympathetic (adrenergic) phase* — hypertension, tachycardia, cool clammy peripheries, mydriasis, myocardial injury and pulmonary oedema.

- ▶ *Tityustoxin* binds Na^+/K^+ channels causing sialorrhoea, lacrimation and rhinorrhoea; *Hemiscorpius* venom (**hemicalcin**) acts on ryanodine-sensitive calcium channels and is cytotoxic/haemolytic.

Clinical features

- ▶ **Local** — immediate, severe **burning pain** and **hyperaesthesia**; swelling, erythema and ecchymosis are usually minimal and *out of proportion* to symptoms. Pain is accentuated by gently tapping the site (positive “**tap test**”). Pain may persist for days to weeks.
- ▶ **Autonomic** — restlessness, profuse sweating, hypersalivation, lacrimation, rhinorrhoea, nausea/vomiting; cool extremities, alternating hypotension/hypertension, brady- then tachy-arrhythmia, priapism.
- ▶ **Neuromuscular / cranial nerve** — muscle twitching, jerking and fasciculation (may be **mistaken for seizures**), blurred vision, roving/abnormal eye movements, slurred speech and difficulty handling secretions.
- ▶ **Course** — systemic features progress to maximal severity by ~5 h and usually subside within 1–2 days, though pain and paraesthesia may last weeks. **Appearance of gastrointestinal/autonomic features within the first few hours signals progression to severe envenomation.**
- ▶ Children and the elderly deteriorate fastest; **fatal respiratory arrest** is the dominant mode of death in these groups.

Complications

- ▶ **Cardiovascular** — *scorpion-sting myocarditis* / catecholamine (stress) cardiomyopathy, tachy- and brady-arrhythmias, hypertensive crisis, and **cardiogenic shock**.
- ▶ **Respiratory** — acute **pulmonary oedema** (both cardiogenic from LV dysfunction and capillary-leak/non-cardiogenic) and **respiratory failure/arrest** — the leading cause of death.
- ▶ **Acute pancreatitis** — notably with *Tityus* stings.
- ▶ **Renal / haematological** — **rhabdomyolysis**, intravascular **haemolysis**, haemoglobinuria and **acute kidney injury** (especially *Hemiscorpius lepturus*).
- ▶ **Metabolic** — hyperthermia, lactic acidosis.
- ▶ **Local** (cytotoxic species) — purpura, bullae, tissue necrosis and ulceration.
- ▶ Allergic reactions to venom (rarely anaphylaxis); secondary bacterial infection.

Management

- ▶ **First aid** — reassure and **keep the patient calm and immobile**; apply a **cold pack / pressure dressing** to the site to slow venom absorption; **infiltrate local anaesthetic without a vasoconstrictor** for pain; clean the wound and give **tetanus prophylaxis**. Avoid incision and tourniquets.

- **Triage** — most stings (non-lethal species) need only ice packs, analgesics or antihistamines and can be observed at home, returning if cranial-nerve or neuromuscular signs appear.

Problem	Drug / intervention
Agitation, involuntary movements	Continuous IV midazolam infusion (monitor for respiratory depression)
Hypertension & pulmonary oedema	Prazosin (drug of choice), nifedipine, hydralazine, sodium nitroprusside
Bradycardia	IV atropine
Severe / systemic envenomation	Species-specific antivenom (e.g. FDA-approved equine <i>Centruroides</i> IgG F(ab') ₂)
Cardiogenic pulmonary oedema / shock	Oxygen, vasodilators/afterload reduction, inotropes, ventilatory support, ICU care

- **Prazosin** — the pharmacological antidote of choice for the **Indian red scorpion autonomic storm**: this α_1 -adrenergic blocker abolishes catecholamine-driven vasoconstriction, reduces preload and afterload, and **reverses/prevents pulmonary oedema**, giving accelerated recovery with preserved myocardial function. (Conventional Indian teaching: oral ~30 $\mu\text{g/kg}$, repeated ~3-hourly until peripheries are warm, dry and the patient stabilises — see Coverage note.)
- **Antivenom** — available in endemic regions and, with supportive care, reduces morbidity and mortality from severe envenomation; IV administration rapidly reverses cranial-nerve and neuromuscular dysfunction. (Its role relative to prazosin in *M. tamulus* envenomation is debated; prazosin remains the Indian mainstay.)
- **Supportive/ICU** — close cardiorespiratory monitoring, oxygen and mechanical ventilation for pulmonary oedema/respiratory failure, fluid and electrolyte correction, and treatment of rhabdomyolysis/AKI and pancreatitis as they arise.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Scorpion external morphology (labelled)**: pedipalps/pincers (chela), cephalothorax (prosoma), four pairs of legs, mesosoma (abdomen), metasoma (segmented “tail”), and **telson bearing the aculeus (stinger)** with venom gland.
- **“Autonomic storm” flow diagram**: *Venom neurotoxin* $\rightarrow$ *Na⁺ channel held open + K⁺ channel block* $\rightarrow$ *repetitive nerve firing* $\rightarrow$ *massive ACh + catecholamine release* $\rightarrow$ *biphasic response* — label the **parasympathetic/cholinergic (early)** limb (vomiting, salivation, lacrimation, sweating, bradycardia) and the **sympathetic/adrenergic (late)** limb (hypertension, tachycardia, myocarditis, pulmonary oedema); show **prazosin blocking the α_1 receptor**.

Clinical / Diagnostic significance

- ▶ Diagnosis is **clinical** (history of sting + autonomic storm); **identifying the species** guides prognosis and the need for antivenom.
- ▶ Suspect **myocarditis/cardiomyopathy** in any stung child with tachypnoea, gallop or pulmonary oedema — obtain ECG (ST–T changes, arrhythmia), **echocardiography** (global LV hypokinesia), and cardiac biomarkers.
- ▶ Monitor for **rhabdomyolysis and AKI** (CK, urine myoglobin, creatinine), and consider **serum amylase/lipase** where *Tityus*-type pancreatitis is plausible.
- ▶ The combination of **minimal local signs with florid systemic/cranial-nerve toxicity** is the key clue distinguishing dangerous scorpionism from a trivial sting.

High-yield exam pointers

- ▶ Lethal species belong to family **Buthidae**; India = ***Mesobuthus (Hottentotta) tamulus*** (Indian red scorpion).
- ▶ Mechanism = neurotoxin keeps **Na⁺ channels open** + blocks **K⁺ channels** → **autonomic storm** (cholinergic then adrenergic).
- ▶ Local signs are **out of proportion** to severe pain; **positive tap test**.
- ▶ **Pulmonary oedema, myocarditis and respiratory arrest** are the chief killers; children/elderly worst affected.
- ▶ **Prazosin** is the drug of choice for the Indian red scorpion (reverses autonomic storm, preserves myocardium).
- ▶ **IV midazolam** for agitation/involuntary movements; **atropine** for bradydysrhythmia; **nifedipine/nitroprusside/hydralazine** for hypertensive pulmonary oedema.
- ▶ Species-specific **antivenom** (equine *Centruroides* F(ab')₂ is FDA-approved) reverses cranial-nerve/neuromuscular signs.
- ▶ Remember **pancreatitis** (*Tityus*) and **haemolysis + AKI + skin necrosis** (*Hemiscorpius lepturus*).
- ▶ First aid = reassurance, immobilisation, cold pack/pressure dressing, local anaesthetic **without vasoconstrictor**, tetanus prophylaxis; **avoid incision/tourniquet**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Ectoparasite Infestations and Arthropod Injuries” (Scorpion Stings section: species, sodium-channel mechanism, catecholamine release, complications, and treatment including midazolam, prazosin, nifedipine, nitroprusside, atropine and antivenom).
- ▶ ***Bologna, Dermatology, 5e** — “Bites and Stings” (*clinically important scorpion species table; symptoms out of proportion to cutaneous signs; cardiorespiratory deaths in children <10 y; pancreatitis; prazosin reverses the autonomic storm of Hottentotta tamulus****).

- ▶ **Rook's Textbook of Dermatology, 10e** — “Arthropods” (Buthidae, venom components, epidemiology ~1.2 million serious stings/~3250 deaths, tityustoxin and hemicalcin mechanisms, biphasic clinical features, antivenom/supportive management).
- ▶ **CMDT 2026** — “Poisoning: Spider Bites & Scorpion Stings” (*Centruroides* features; FDA-approved species-specific antivenom; analgesia).

Coverage note: The corpus covers scorpion envenomation only moderately and from a largely non-Indian standpoint. It confirms *Mesobuthus tamulus* as the Indian species and **prazosin** as the antidote for its autonomic storm, but does **not** state the prazosin dose or any formal severity grading; the dose given (~30 µg/kg orally, ~3-hourly) and the biphasic cholinergic→adrenergic framing reflect standard, widely accepted Indian internal-medicine teaching (Bawaskar protocol) and should be applied per local guidelines rather than as verbatim corpus content.



Discuss clinical features and management of Organophosphorus poisoning

Asked in: Paper IV 17 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Organophosphorus (OP) compounds are **cholinesterase inhibitors** (“anticholinesterases”) widely used as agricultural and household insecticides (parathion, malathion, diazinon, chlorpyrifos) and weaponised as chemical-warfare **nerve agents** (GA *tabun*, GB *sarin*, GD *soman*, VX). They irreversibly inhibit acetylcholinesterase, producing accumulation of acetylcholine at **muscarinic, nicotinic and central** cholinergic synapses — a life-threatening cholinergic toxidrome. OP self-poisoning is one of the commonest causes of fatal poisoning in South Asia, killing chiefly through respiratory failure; management rests on aggressive resuscitation, **atropine** and the oxime **pralidoxime** (2-PAM).

Toxicology and mechanism

- ▶ **Agents** — OP insecticides (diazinon, chlorpyrifos-ethyl, malathion, parathion); related **carbamate** insecticides (aldicarb, carbaryl, propoxur) and medicinals (neostigmine, physostigmine); nerve gases (sarin, soman, tabun, VX).
- ▶ **Mechanism** — Inhibition of **acetylcholinesterase** leads to increased synaptic acetylcholine at muscarinic and nicotinic cholinergic receptor sites, causing stimulation of CNS, postganglionic parasympathetic (muscarinic) receptors, autonomic ganglia and the neuromuscular junction (nicotinic) receptors.
- ▶ **Pharmacokinetics** — Most OPs are **poorly water-soluble**, commonly formulated with an **aromatic hydrocarbon solvent** (e.g. **xylene**), and are **well absorbed through intact skin**, as well as by ingestion and inhalation — hence decontamination and staff protection are essential.

- **Persistence / “aging”** — Highly lipid-soluble agents (e.g. **fenthion, dimethoate**) cause prolonged or recurrent toxicity over days. Over time the OP–enzyme bond becomes covalent and irreversible (“aging”), after which oxime reactivation fails — the rationale for giving pralidoxime early. Carbamates inhibit cholinesterase only **transiently** and do not age, so are generally self-limiting.

Clinical features

The toxidrome reflects acetylcholine excess at three receptor populations.

Receptor / site	Clinical features
Muscarinic (postganglionic parasympathetic)	Miosis; excessive secretions — lacrimation, salivation, bronchorrhoea, wheezing/bronchospasm, diaphoresis ; nausea, vomiting, diarrhoea, abdominal cramps, faecal and urinary incontinence; bradycardia
Nicotinic (ganglia + neuromuscular junction)	Initial hypertension and tachycardia ; muscle cramps, fasciculations, weakness and paralysis
CNS	Anxiety, agitation, confusion, seizures , respiratory-centre depression, coma

- **Diagnostic clues** — The triad of **miosis, sweating and diarrhoea** should raise immediate suspicion; the patient may smell of solvent/garlic.
- **Cardiovascular sequence** — **Initial tachycardia is usually followed by bradycardia.**
- **Cause of death** — Usually **respiratory failure** from the combination of bronchorrhoea, bronchospasm, central apnoea and skeletal-muscle (including diaphragmatic) weakness.
- **Course** — Signs may **persist or recur over several days**, especially with lipophilic agents (fenthion, dimethoate).
- **Recognised later neuromuscular syndromes** (see Coverage note):
 - **Intermediate syndrome** — 24–96 h after the cholinergic phase: proximal limb, neck-flexor, cranial-nerve and **respiratory muscle weakness**, requiring ventilatory support.
 - **OP-induced delayed polyneuropathy (OPIDP/OPIDN)** — 1–3 weeks later: distal sensorimotor neuropathy from inhibition of *neuropathy target esterase*.

Investigations

- **Cholinesterase assay** — **Serum (plasma/butryl) and RBC (true) cholinesterase activity is depressed $\geq 50\%$ below baseline** in severe intoxication; RBC cholinesterase correlates better with synaptic enzyme and with severity, plasma cholinesterase recovers faster. Confirms diagnosis and guides recovery.
- **Supportive labs** — Electrolytes, glucose, ABG (hypoxia, acidosis), renal function, creatine kinase, and ECG (sinus bradycardia, prolonged QT, AV block, ventricular dysrhythmias).

- Diagnosis is fundamentally **clinical** — therapeutic atropine must never be delayed pending laboratory confirmation.

Management

Management follows the universal poisoning framework — **support of vital signs, decontamination, specific antidotes, and prevention of re-exposure** — with two specific antidotes (atropine + pralidoxime).

A. Resuscitation and supportive care (first priority)

- **Airway protection, high-flow oxygen and ventilation** — suction copious secretions; intubate and ventilate early for respiratory failure (avoid **suxamethonium**, which is metabolised by the inhibited cholinesterase and causes prolonged paralysis — standard caveat).
- Treat **seizures** with benzodiazepines/barbiturates; correct hypoxia and metabolic derangements; haemodynamic support.

B. Decontamination and staff protection

- **Skin/hair** — remove contaminated clothing and **wash repeatedly with soap/shampoo and water**; staff must wear **gloves and waterproof aprons** to avoid secondary exposure. **Dilute hypochlorite (household bleach 1:10)** helps break down OP/nerve agents on equipment.
- **GI** — if recently ingested, consider **nasogastric aspiration** of the liquid followed by **activated charcoal**.

C. Specific antidote 1 — Atropine (physiological antidote)

- **Reverses excessive muscarinic stimulation** — dries bronchial secretions, relieves bronchospasm/wheeze, abdominal cramps and sweating. It **does not act at nicotinic (ganglionic/neuromuscular) receptors and has no direct effect on muscle weakness**.
- **Dose**: give **2 mg IV**; if no response after 5 minutes, repeat in **rapidly escalating (doubling) boluses** until secretions dry and wheeze clears. Severe poisoning may require **several hundred milligrams**; an infusion is used once atropinised.
- **End-point of atropinisation**: clear chest on auscultation/drying of secretions, with heart rate and blood pressure maintained (avoid over-atropinisation — delirium, hyperthermia, ileus, urinary retention).

D. Specific antidote 2 — Pralidoxime (2-PAM, Protopam — cholinesterase reactivator)

- **Reactivates acetylcholinesterase** by reversing OP binding to the enzyme; being an oxime it works at the **neuromuscular junction (nicotinic)** as well as muscarinic/nicotinic sites, thereby treating **muscle weakness/fasciculations** that atropine cannot.
- Most effective if **started very soon after exposure**, before irreversible “aging” permanently binds the OP to cholinesterase.

- ▶ **Dose:** 1–2 g IV loading, then continuous infusion 200–500 mg/hour titrated to clinical response; continue as long as there is evidence of acetylcholine excess. (The WHO-recommended regimen of a 30 mg/kg bolus followed by ≥ 8 mg/kg/h infusion is also widely used — standard, see Coverage note.)
- ▶ **Carbamate poisoning:** pralidoxime is of **questionable benefit** because carbamates inhibit cholinesterase only transiently; atropine alone usually suffices.
- ▶ **Evidence:** randomised trials have given **conflicting results** on whether pralidoxime reduces mortality, but it remains standard alongside atropine.

E. Adjunctive / unproven therapies

- ▶ **Magnesium sulphate, sodium bicarbonate, clonidine and extracorporeal removal** have been tried but remain unproven.
- ▶ Observe for **delayed deterioration** (intermediate syndrome) and provide prolonged ventilatory support as needed.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Cholinergic synapse schematic** — label: *presynaptic terminal, acetylcholine (ACh) vesicles, synaptic cleft with accumulated ACh, acetylcholinesterase (inhibited by OP), muscarinic receptor (postganglionic parasympathetic), nicotinic receptor (ganglion + neuromuscular junction), pralidoxime reactivating the enzyme, atropine blocking the muscarinic receptor.*
- ▶ **Toxidrome “stick-man”** — label muscarinic effects (*miosis, lacrimation, salivation, bronchorrhoea, bradycardia, vomiting/diarrhoea, incontinence, sweating*) on one side and nicotinic effects (*fasciculations, weakness, paralysis, tachycardia, hypertension*) on the other, with central effects (*seizures, coma, respiratory depression*) at the head.

Clinical / Diagnostic significance

- ▶ The combination **miosis + sweating + diarrhoea + bronchorrhoea** is a near-pathognomonic bedside toxidrome — treat empirically with atropine.
- ▶ **Respiratory failure** (bronchorrhoea + bronchospasm + neuromuscular weakness) is the principal killer — early airway control saves lives.
- ▶ **RBC and plasma cholinesterase** confirm diagnosis and severity and track recovery; do not await them to start atropine.
- ▶ Distinguish OP (irreversible, may “age”, oxime indicated) from **carbamate poisoning** (reversible, self-limiting, oxime of questionable value).
- ▶ Anticipate **biphasic/recurrent toxicity** with lipophilic agents and the **intermediate syndrome** — keep the patient monitored and ready for re-ventilation.

High-yield exam pointers

- ▶ OP = **acetylcholinesterase inhibitor** → ACh excess at **muscarinic + nicotinic + CNS** receptors.
- ▶ Muscarinic toxidrome mnemonics: **DUMBELS** (Defecation, Urination, Miosis, Bradycardia/Bronchorrhoea, Emesis, Lacrimation, Salivation) / **SLUDGE**; the lethal “**killer Bs**” = bronchorrhoea, bronchospasm, bradycardia.
- ▶ Nicotinic features: **fasciculations, weakness, paralysis, tachycardia, hypertension** — atropine does NOT correct these; **pralidoxime** does.
- ▶ **Atropine** 2 mg IV, **double-dose escalation** to dry secretions; end-point = clear chest.
- ▶ **Pralidoxime (2-PAM)** reactivates the enzyme — give **early, before “aging”**; 1–2 g IV load then 200–500 mg/h infusion.
- ▶ Serum/RBC cholinesterase **<50% of normal** in severe poisoning.
- ▶ **Avoid suxamethonium**; death is from **respiratory failure**.
- ▶ Carbamates: transient inhibition → atropine yes, **oxime usually unnecessary**.
- ▶ Decontaminate skin/clothing; protect staff (gloves/aprons, dilute bleach on equipment).

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Poisoning and Drug Overdose” (cholinergic / acetylcholinesterase-inhibitor toxidrome — muscarinic vs nicotinic features, atropine and 2-PAM, cholinesterase <50%; general fundamentals of poisoning management).
- ▶ **CMDT 2026** — “Poisoning” — *Pesticides: Cholinesterase Inhibitors* (agents, pharmacokinetics, clinical findings, atropine and pralidoxime dosing, carbamate caveat) and the *Cholinergic Syndrome* toxidrome.

Coverage note: The Harrison corpus covers the OP/anticholinesterase toxidrome largely in tabular form, and neither Harrison nor CMDT in this corpus explicitly details the **intermediate syndrome**, **OP-induced delayed polyneuropathy (OPIDP)**, the **suxamethonium caveat**, or the **WHO pralidoxime regimen / atropinisation end-points**. These are included as universally accepted standard internal-medicine teaching and are flagged here; all drug names, doses (atropine 2 mg with double-dose escalation; pralidoxime 1–2 g load + 200–500 mg/h), the $\geq 50\%$ cholinesterase fall, and the muscarinic/nicotinic feature lists are verbatim-grounded in CMDT 2026 and Harrison 22e.



Management of Paracetamol (Acetaminophen) Overdose

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — Paracetamol (acetaminophen) is the analgesic-antipyretic most frequently implicated in self-poisoning and is the single commonest cause of drug-induced **acute liver failure**

(ALF) in the Western world, accounting for at least 45% of ALF cases. Toxicity is **dose-related and predictable**: it follows a single acute ingestion of >150–200 mg/kg ($\approx$ 8–10 g in an average adult) or repeated supratherapeutic dosing. Hepatic necrosis is caused by the reactive metabolite **NAPQI** once hepatic glutathione is depleted. Because a proven, safe antidote (**N-acetylcysteine, NAC**) exists and is highly effective when given early, management hinges on rapid risk-stratification using the serum level and timely antidote administration.

Toxicokinetics and mechanism (basis of treatment)

- ▶ Paracetamol is normally metabolised by **phase II conjugation** — glucuronidation and sulfation — to innocuous, water-soluble metabolites excreted in urine.
- ▶ A small fraction undergoes **phase I oxidation** by cytochrome P450 CYP2E1 to the highly reactive electrophile **N-acetyl-p-benzoquinone-imine (NAPQI)**.
- ▶ NAPQI is normally detoxified by conjugation with **hepatic glutathione** to harmless **mercapturic acid** (renally excreted).
- ▶ In overdose the conjugation pathways saturate, glutathione is **depleted and overwhelmed**, and NAPQI binds covalently to nucleophilic hepatocyte macromolecules (forming **acetaminophen-protein adducts**), producing **dose-related centrilobular (zone 3) hepatic necrosis**.
- ▶ **NAC works by repleting/substituting glutathione** (provides sulfhydryl groups), detoxifying NAPQI; it also has antioxidant and microcirculatory benefits in established failure — the rationale for its use even late.
- ▶ **Potentiating factors** (lower the toxic threshold): chronic alcohol use and isoniazid (**induce CYP2E1**), phenobarbital, and **glutathione-depleting states** — starvation, fasting during febrile illness, malnutrition. In chronic alcoholics the toxic dose may be as low as ~2 g; the FDA has lowered the maximum daily dose recommendation from 4 g to 3 g and capped the paracetamol component of opioid-combination tablets at **325 mg**.

Clinical course — the four phases

Phase	Time after ingestion	Features
I (pre-injury)	0.5–24 h (often 4–12 h)	Nausea, vomiting, anorexia, diaphoresis, malaise; <i>often asymptomatic</i> — normal LFTs
II (latent / early hepatic)	24–48 h	Initial symptoms abate; right-upper-quadrant pain; aminotransferases begin to rise, INR rising
III (hepatic)	72–96 h (3–5 days)	Peak injury: AST/ALT often >10,000 IU/L (towering), jaundice, coagulopathy,

Phase	Time after ingestion	Features
		encephalopathy, AKI, lactic acidosis; $\pm$ myocardial injury
IV (recovery / outcome)	4 days–2 weeks	Resolution in survivors (rarely any sequela) or progressive ALF and death

- ▶ **Biochemical signature:** very high aminotransferases with *disproportionately low bilirubin* early — characteristic of this hyperacute injury.
- ▶ **AKI** complicates ~75% of severe cases and is virtually always self-limited.
- ▶ **Massive ingestion** (serum levels ~500–1000 mg/L) can rarely cause early-onset coma, seizures, hypotension and **anion-gap metabolic acidosis** *unrelated* to hepatic injury.

Risk assessment and investigations

- ▶ **Serum paracetamol level:** the key investigation — draw ≥ 4 h after a single acute ingestion and plot on the **Rumack-Matthew (acetaminophen) nomogram** against time.
 - Treat if the level lies **above the nomogram treatment line**; Harrison cites levels >200 $\mu\text{g/mL}$ at 4 h or >100 $\mu\text{g/mL}$ at 8 h as indications. Levels >300 $\mu\text{g/mL}$ at 4 h predict severe damage; <150 $\mu\text{g/mL}$ suggest injury is highly unlikely.
 - **Nomogram limitations:** valid only for a *single acute ingestion within a known 24-h window*. It **cannot be used** for staggered/chronic overdose, unknown time of ingestion, or sustained-release/anticholinergic co-ingestion (delayed peaks). In such cases treat empirically based on dose history and LFTs.
- ▶ **Baseline and serial labs:** LFTs (AST/ALT, bilirubin, ALP), INR/PT, serum creatinine and urea, blood glucose (hypoglycaemia), arterial blood gas/pH and lactate, phosphate, ammonia, and a pregnancy test. Importantly, **paracetamol is undetectable in plasma in ~50%** of patients who already present in liver failure.

Management — stepwise

1. Resuscitation and supportive care (priority).

- ▶ Secure airway, breathing, circulation; intubate for grade 3–4 encephalopathy.
- ▶ IV fluids to maintain intravascular volume; **correct hypoglycaemia**, acidosis and electrolyte disturbance; **norepinephrine** is the preferred vasopressor in ALF.

2. Gastrointestinal decontamination.

- ▶ **Activated charcoal** if the patient presents within 1–2 h of ingestion (especially large/co-ingestions). Charcoal's interference with oral NAC absorption is *not clinically significant*.
- ▶ **Gastric lavage** is rarely used today; if performed it should precede oral agents.

3. Specific antidote — N-acetylcysteine (NAC). *The cornerstone of treatment.*

- ▶ **Start within 8–10 h** for maximal effect; routine use has substantially reduced fatal hepatotoxicity. NAC is still at least **partially effective up to 24–36 h**, and benefits even *established* ALF — when in doubt, give it.
- ▶ **Indications:** level above the nomogram line; or presentation >8 h with a history of significant ingestion (start NAC, then check level); or staggered/late presentation with abnormal LFTs; or any established hepatotoxicity.

Route	Regimen
IV (FDA-approved 21-h, “three-bag” Acetadote)	150 mg/kg over 60 min → 50 mg/kg over 4 h → 100 mg/kg over 16 h (total ~300 mg/kg/21 h)
Oral (traditional 72-h protocol)	Loading 140 mg/kg, then 70 mg/kg every 4 h × 17 doses; dilute to ~5%

- ▶ IV is generally preferred (vomiting often limits oral NAC); give IV if oral is not tolerated.
- ▶ **High-risk ingestions** (reported >30 g, or measured level >twice the nomogram line): higher/extended NAC dosing — **contact a poison-control centre / medical toxicologist.**
- ▶ **Endpoint of therapy:** continue (and extend, for massive overdose) until **serum paracetamol is undetectable, aminotransferases are normal or clearly falling, and INR is improving** with a clinically well patient.
- ▶ **Adverse effect:** IV NAC can cause rate-related **anaphylactoid (histaminoid) reactions** — flushing, urticaria, bronchospasm; managed by pausing the infusion and antihistamine, then resuming slower.
- ▶ **Fomepizole** (a CYP2E1 inhibitor) has been proposed as an adjunct in massive overdose but is **not routinely used**; haemodialysis is rarely needed except in massive ingestion with very high levels/coma.

4. Management of established acute liver failure.

- ▶ **Early transfer to a liver-transplant centre** is essential; continue NAC.
- ▶ **Cerebral oedema / intracranial hypertension** (leading cause of death): head-of-bed elevation to 30°, intubate stage 3–4 encephalopathy, **mannitol 0.5 g/kg** or hypertonic saline (target Na⁺ 145–155 mmol/L) for raised ICP. **Lactulose/rifaximin are of uncertain value.**
- ▶ **Coagulopathy** should generally **not** be routinely corrected (it guides prognosis); treat clinically significant bleeding only.
- ▶ **AKI:** use **continuous renal replacement therapy** if needed — *avoid intermittent haemodialysis*, which raises ICP.
- ▶ Stress-ulcer prophylaxis (PPI/H₂ blocker); sepsis surveillance cultures with broad-spectrum cover for suspected infection (prophylactic antibiotics do not improve survival); maintain glucose; enteral protein 1–1.5 g/kg/day.

5. Liver transplantation — prognostication.

- ▶ Refer for emergency transplantation using the **King's College Hospital** criteria for paracetamol-induced ALF:
 - **Arterial pH <7.3** (after adequate fluid resuscitation), **OR**
 - **All three of: INR >6.5, serum creatinine >3.4 mg/dL (>300 µmol/L), and grade III–IV encephalopathy.**
- ▶ **Early arterial lactate >3.5 mmol/L** also identifies patients likely to need transplantation. A *rising* α-fetoprotein predicts a favourable (regenerating) outcome. With modern care, transplant-free survival in paracetamol ALF is ~75%.

6. **Psychosocial care.** After intentional overdose, arrange **psychiatric assessment** and risk-of-suicide evaluation before discharge; counsel and warn about combination products to prevent re-exposure.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Metabolic pathway of paracetamol.** Boxes/arrows: *Paracetamol* → (major, ~90%) **Glucuronidation + Sulfation** → non-toxic conjugates → renal excretion; and → (minor, **CYP2E1**) → **NAPQI (toxic)**. From NAPQI: + **Glutathione** → **Mercapturic acid** (non-toxic, urine). Label: “*Glutathione depleted* → *NAPQI binds hepatocyte macromolecules* → *centrilobular necrosis*.” Show **NAC** arrow replenishing glutathione. Label inducers: *alcohol, isoniazid, starvation*.
- ▶ **Rumack-Matthew nomogram.** Axes: x = *time since ingestion (4–24 h)*; y = *serum paracetamol (µg/mL, log scale)*. Draw the descending “**treatment line**” (≈150 µg/mL at 4 h falling to ≈4.7 at 24 h); shade the region **above the line** = “**Treat with NAC.**” Mark the **4-h sampling point**.

Clinical / Diagnostic significance

- ▶ The **single 4-h (or later) level on the nomogram** is the decisive triage tool — it converts an asymptomatic patient into a defined risk category and dictates antidote need.
- ▶ **Time-to-NAC is the strongest modifiable determinant of outcome** — never delay NAC awaiting a level if presentation is late or ingestion is large.
- ▶ The **AST/ALT >10,000 IU/L with low bilirubin** pattern should prompt suspicion of paracetamol toxicity even when the history is denied or obscure.
- ▶ NAC also has evidence of benefit in **non-paracetamol ALF** with early-stage encephalopathy (off-label).
- ▶ Persistent acidosis, rising INR/creatinine and encephalopathy mandate **transplant-centre referral** by King's College criteria.

High-yield exam pointers

- ▶ Toxic threshold: >150–200 mg/kg or ~8–10 g acute; fatal fulminant disease usually ≥ 25 g; maximum therapeutic dose 4 g/day (FDA-advised 3 g; ~2 g toxic in alcoholics).
- ▶ Toxic metabolite = NAPQI, generated via CYP2E1, detoxified by **glutathione**; necrosis is **centrilobular** (zone 3).
- ▶ Antidote = N-acetylcysteine; most effective <8 h, useful up to 24–36 h and in established failure.
- ▶ IV three-bag NAC: 150 mg/kg/1 h $\rightarrow$ 50 mg/kg/4 h $\rightarrow$ 100 mg/kg/16 h. Oral: 140 mg/kg then 70 mg/kg q4h $\times$ 17 doses.
- ▶ Rumack-Matthew nomogram guides treatment; **invalid** for staggered/chronic/unknown-time ingestions.
- ▶ Activated charcoal useful within 1–2 h; does not meaningfully impair NAC.
- ▶ King's College criteria (paracetamol ALF): pH <7.3, or the triad INR >6.5 + creatinine >3.4 mg/dL + grade III–IV encephalopathy; lactate >3.5 mmol/L predicts need for transplant.
- ▶ IV NAC can cause **anaphylactoid reactions**; paracetamol is **undetectable** in ~50% of patients already in liver failure.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Toxic and Drug-Induced Hepatitis” (acetaminophen hepatotoxicity: NAPQI/CYP2E1 mechanism, dose thresholds, NAC regimen, nomogram thresholds) and “Poisoning and Drug Overdose” (general approach: supportive care, decontamination, antidotes).
- ▶ **CMDT 2026** — “Poisoning: Acetaminophen” (risk stratification, nomogram, activated charcoal, IV/oral NAC regimens, fomepizole) and “Acute Liver Failure” (ALF management, prognostic indices/poor-outcome thresholds, transplantation).
- ▶ *Coverage note:* The corpus supplies all clinical components but does not use the exact labels “Rumack-Matthew nomogram,” the named “four phases,” or “King's College criteria” verbatim — these are universally accepted standard internal-medicine eponyms used here for organisation; their underlying values (pH <7.3, INR >6.5, creatinine >3.4 mg/dL, grade III–IV encephalopathy; nomogram cut-offs; phase timings) are all grounded in the cited chapters.



Ethylene glycol poisoning

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Ethylene glycol (EG) is a colourless, sweet-tasting toxic alcohol used in antifreeze, brake fluid and windshield washer/de-icer fluids; poisoning follows accidental, suicidal or substitute-alcohol ingestion. EG itself is relatively non-toxic and produces only an ethanol-like

inebriation, but its sequential oxidation by **alcohol dehydrogenase (ADH)** generates organic-acid metabolites (glycolate, oxalate) that cause a life-threatening **high-anion-gap metabolic acidosis (AGMA)** with damage to the CNS, heart, lungs and kidneys. The combination of a **high anion gap plus a high osmolar gap** is the diagnostic signature, and rational therapy (fomepizole, hemodialysis, cofactors) is built around blocking and removing the toxic metabolites.

SOURCE & COVERAGE

- ▶ **Sources:** antifreeze, brake fluid, windshield washer/de-icer fluids. EG is a low-molecular-weight solute, so it raises serum osmolality and the **osmolal gap** while the parent compound predominates.
- ▶ **Parent vs metabolite toxicity:** EG is one of the agents whose *metabolites are more toxic than the parent compound* (alongside acetaminophen and methanol) — hence early high blood levels mandate antidote/dialysis even before symptoms peak.
- ▶ **Metabolic cascade (rate-limiting step = ADH):** EG → (ADH) → glycoaldehyde → (aldehyde dehydrogenase) → **glycolic acid (glycolate)** → glyoxylic acid → **oxalic acid (oxalate)**.
- ▶ **Mechanisms of injury (Harrison Ch 470):**
 - EG causes **CNS depression** and **increased serum osmolality**.
 - Metabolites — *primarily glycolic acid* — cause the **AGMA, CNS depression and renal failure**.
 - Lactic acid (l-lactate) production rises because metabolites inhibit the **tricarboxylic acid cycle** and alter the intracellular redox state, adding to the anion gap.
 - **Oxalic acid** precipitates as **calcium oxalate** in tissues and urine → **hypocalcaemia**, tissue oedema and **crystalluria**; acute tubular injury is caused *initially by glycolate* and *later amplified by tubular obstruction from oxalate crystals*.

Clinical features — the evolving stages

EG poisoning classically evolves through overlapping phases; the parent alcohol intoxicates early, while delayed metabolite toxicity drives the acidosis, cardiopulmonary collapse and renal failure.

Phase	Dominant mediator	Clinical features
Neurological (early)	Parent EG	“Ethanol-like” intoxication <i>without the smell of alcohol</i> , nausea, vomiting, increased osmolar gap , early calcium-oxalate crystalluria; severe cases → coma, seizures
Cardiopulmonary	Glycolate / organic acids	Tachypnoea (Kussmaul breathing), hypotension , cardiac

Phase	Dominant mediator	Clinical features
		dysfunction, ARDS in severe cases
Renal (delayed)	Oxalate / glycolate	Delayed AGMA, flank/back pain, oliguria and acute renal failure (ATN), hypocalcaemia ($\pm$ tetany)

Biochemical hallmarks — the dual “gap”

- ▶ **High anion-gap metabolic acidosis:** EG is a leading toxic cause of severe AGMA (with methanol and salicylates). The unmeasured anions are **glycolate and oxalate**, so the measured **anion gap exceeds the lactate level** (a clue that the acidosis is *not* primarily lactic).
- ▶ **Osmolal gap:** difference of >10 mmol/L between **measured osmolality** (by freezing-point depression) and **calculated osmolality** = $2[\text{Na}^+] + [\text{glucose}]/18 + [\text{BUN}]/2.8$. EG (a low-MW glycol) widens this gap.
- ▶ **Temporal dissociation of the two gaps:** the **osmolar gap rises early** (parent EG present) and **falls as it is metabolised**, while the **anion gap rises later** as glycolate/oxalate accumulate — so a *normal osmolar gap does not exclude EG late after ingestion*, and a high AG may appear once the osmolar gap has fallen.
- ▶ The combination of **high AG + high osmolar gap** is *highly suspicious for EG or methanol* and should be taken as **evidence of EG toxicity before confirmatory EG levels return** — **do not delay treatment** awaiting the level.

Diagnosis and investigations

- ▶ **History** of antifreeze/solvent ingestion or unexplained inebriation with severe acidosis.
- ▶ **ABG + electrolytes:** severe metabolic acidosis with a **high anion gap**; calculate the AG.
- ▶ **Serum osmolality** (measured, freezing-point depression) vs calculated $\rightarrow$ **osmolal gap**.
- ▶ **Quantitative EG level** — useful but treatment is not deferred for it; levels guide antidote/dialysis thresholds.
- ▶ **Serum calcium** — **hypocalcaemia** (also seen in fluoride and oxalate poisoning); check ECG for QT prolongation.
- ▶ **Renal function / urinalysis** — rising creatinine, ATN; **calcium-oxalate crystalluria** (envelope-shaped / needle crystals).
- ▶ **Lactate** — may be mildly elevated; the AG typically *exceeds* measured lactate.
- ▶ Some EG products fluoresce under **Wood’s lamp** (fluorescein additive) — supportive, *standard toxicology, not in the provided chapters*.

Management

Therapy targets three goals: **block ADH** (stop metabolite formation), **correct acidaemia** and **divert metabolism with cofactors**, and **remove EG/metabolites by dialysis**. (Harrison Ch 58 treatment box + Ch 470 table.)

Intervention	Detail / indication
Supportive	IV isotonic fluids; airway protection/ventilation for CNS depression, seizures; treat shock
Correct acidaemia	IV sodium bicarbonate for severe acidaemia
ADH blockade — antidote of choice	Fomepizole (4-methylpyrazole): 15 mg/kg IV over 30 min loading dose, then 10 mg/kg every 12 h for four doses. Predictable fall in EG level without the obtundation seen with ethanol. Continue until blood pH normal or osmolar gap <10 mOsm/kg H ₂ O
Ethanol (alternative)	Of historic interest; competes with EG for ADH; used only if fomepizole is unavailable
Antidote thresholds	Start ethanol/fomepizole for AGMA, crystalluria/renal dysfunction, EG level >3 mmol/L (20 mg/dL), or ethanol-like intoxication / raised osmolal gap when the level is not readily obtainable
Cofactors (divert metabolism)	Thiamine, high-dose pyridoxine, magnesium and folinic acid — push glyoxylate toward non-toxic glycine/α-hydroxy-β-ketoadipate rather than oxalate
Hemodialysis	Indicated when arterial pH <7.3, persistent high-AG acidosis, osmolar gap >20 mOsm/kg H ₂ O, or end-organ damage (CNS, renal failure); also enhances EG elimination and shortens treatment when EG level >8 mmol/L (50 mg/dL)

- ▶ Fomepizole and ethanol both act by **competing with EG for alcohol dehydrogenase**; fomepizole is preferred (no CNS depression, no level monitoring, predictable kinetics).
- ▶ Hemodialysis removes both the parent EG and the dialysable metabolites/anions and corrects the acidosis simultaneously.

Toxic alcohols compared

Feature	Ethylene glycol	Methanol	Isopropyl alcohol
Key enzyme	Alcohol dehydrogenase	Alcohol dehydrogenase	Alcohol dehydrogenase
Toxic metabolite	Glycolate, oxalate	Formic acid	Acetone (parent toxic)
Anion gap	High AGMA	High AGMA	No high AG (unless shock)

Feature	Ethylene glycol	Methanol	Isopropyl alcohol
Osmolar gap	Raised	Raised	Raised
Target organ	CNS, heart, lungs, kidney	Optic nerve / retina, CNS	CNS; haemorrhagic gastritis
Specific cofactor	Thiamine, pyridoxine, Mg, folinic acid	Folinic acid / folate	(none; supportive)
Antidote / dialysis	Fomepizole + HD	Fomepizole + HD	Supportive + HD if level >400 mg/dL

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Metabolic pathway with antidote block (label exactly):** *Ethylene glycol* → [Alcohol dehydrogenase (ADH)] → *Glycoaldehyde* → [Aldehyde dehydrogenase] → *Glycolic acid (glycolate)* → *Glyoxylic acid* → *Oxalic acid (oxalate)* → *Calcium oxalate crystals*. Mark *Fomepizole / Ethanol* = ADH inhibition (block) at the first step; show *Thiamine and Pyridoxine* diverting *Glyoxylate* to non-toxic α -hydroxy- β -keto adipate / *Glycine*. Annotate metabolite effects: AGMA, renal failure, hypocalcaemia.
- ▶ **Time-course graph of the two gaps:** x-axis = *time after ingestion (hours)*; two curves — *Osmolar gap* (peaks early, then declines) and *Anion gap* (rises later); shade overlap labelled *high osmolar gap + high anion gap = window of EG toxicity*.

Clinical / Diagnostic significance

- ▶ A patient with severe high-AG metabolic acidosis + high osmolar gap + calcium-oxalate crystalluria + hypocalcaemia is EG poisoning until proven otherwise.
- ▶ Empirical fomepizole + bicarbonate must not be delayed for confirmatory EG levels — early ADH blockade prevents metabolite-driven renal failure and death.
- ▶ The osmolar gap normalises before the anion gap, so timing of presentation changes which gap is abnormal; rely on the clinical picture, not a single gap.
- ▶ Hemodialysis is both detoxifying (removes EG + anions) and corrective (treats acidosis/renal failure) — a key therapeutic decision point.
- ▶ EG is a “toxic time-bomb”: an apparently well, inebriated patient can deteriorate hours later as metabolites accumulate — observe and re-check gaps.

High-yield exam pointers

- ▶ Source = antifreeze; ADH converts EG to glycolate (acidosis) and oxalate (renal failure + hypocalcaemia).
- ▶ Diagnostic dyad = high anion gap + high osmolar gap; calcium-oxalate crystalluria is the urinary clue.

- ▶ Calculated osmolality = $2\text{Na}^+ + \text{glucose}/18 + \text{BUN}/2.8$; osmolal gap $>10 \text{ mmol/L}$ is significant (measured by freezing-point depression).
- ▶ Fomepizole 15 mg/kg load, then 10 mg/kg q12h $\times 4$ doses — antidote of choice; continue until pH normal or osmolar gap <10 .
- ▶ Hemodialysis if pH <7.3 , osmolar gap >20 , end-organ damage, or EG level $>8 \text{ mmol/L}$ (50 mg/dL); antidote threshold EG $>3 \text{ mmol/L}$ (20 mg/dL).
- ▶ Cofactors: thiamine, pyridoxine, magnesium, folinic acid; alkali with NaHCO_3 .
- ▶ Ethanol is now second-line, used only when fomepizole is unavailable.
- ▶ Distinguish from methanol (formate $\rightarrow$ blindness, folinic acid) and isopropanol (acetone, *no* high AG).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 470 "Poisoning and Drug Overdose" (EG mechanism/clinical/treatment table, osmolal-gap and AGMA discussion) and Ch 58 "Acidosis and Alkalosis" (toxic-alcohol section, osmolar-gap calculation, fomepizole dosing and hemodialysis criteria). *Coverage note:* the precise phase **timing windows** (hours), Wood's-lamp fluorescence, urinary crystal morphology, and the named intermediates *glycoaldehyde/glyoxylic acid* are standard textbook toxicology not spelled out in the provided chapters (the chapters explicitly name ADH, glycolate, oxalate); they are accurate, universally accepted additions for completeness.



List the delayed effects of organophosphorus (OP) toxicity. Discuss the management options for OP poisoning

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — Organophosphorus (OP) compounds are anticholinesterase agents used chiefly as agricultural insecticides (parathion, malathion, chlorpyrifos, diazinon, fenthion, dimethoate) and as chemical-warfare "nerve agents" (tabun [GA], sarin [GB], soman [GD], VX). They are well absorbed through intact skin, by inhalation and by the gastrointestinal route, and **phosphorylate acetylcholinesterase (AChE)**, causing accumulation of acetylcholine at muscarinic, nicotinic and CNS synapses. The acute illness is a cholinergic crisis, but OP toxicity is biphasic/triphasic — a constellation of **delayed neurological syndromes** (intermediate syndrome, OP-induced delayed polyneuropathy, chronic neuro-behavioural sequelae) may emerge days to weeks after the acute episode, and lipophilic agents may produce a **relapsing** cholinergic phase. This makes OP poisoning a sustained ICU and rehabilitative challenge, not a single-event intoxication.

Acute cholinergic toxidrome (context for the delayed phase)

- ▶ **Muscarinic (DUMBBELS):** *Diarrhoea/Defaecation, Urination, Miosis, Bradycardia/Bronchorrhoea/Bronchospasm, Emesis, Lacrimation, Salivation/Sweating* — plus abdominal cramps and wheeze.
- ▶ **Nicotinic:** muscle fasciculations, weakness, paralysis, tachycardia, hypertension; initial tachycardia is usually followed by bradycardia.
- ▶ **CNS:** anxiety, headache, seizures, coma; **death is usually due to respiratory failure** (bronchorrhoea + bronchospasm + respiratory-muscle weakness).
- ▶ **Diagnosis** is clinical (miosis, sweating, diarrhoea) and confirmed by **plasma (pseudo-/butyryl-) and RBC (true) cholinesterase activity depressed $\geq 50\%$ below baseline** in significant intoxication.

Delayed effects of OP toxicity (the core list)

Delayed syndrome	Onset after exposure	Receptor / mechanism	Cardinal features
Intermediate syndrome (IMS)	Within ~24–96 h (≤ 4 days), after the cholinergic crisis resolves	Persistent nicotinic AChE inhibition at the neuromuscular junction	Proximal limb, neck-flexor, bulbar, cranial-nerve and respiratory-muscle weakness → respiratory failure; resolves in 2–3 weeks
OP-induced delayed polyneuropathy (OPIDN)	~2–3 weeks (even without preceding cholinergic toxicity)	Phosphorylation + inhibition and “ageing” of neuropathy target esterase (NTE)	Distal sensorimotor axonopathy: calf cramps, paraesthesiae, ascending distal→proximal weakness, areflexia; later upper-motor-neuron signs
Recurrent / prolonged cholinergic toxicity	Hours–days, fluctuating	Re-release of agent stored in fat	Recurrent muscarinic/nicotinic signs, esp. highly lipid-soluble agents (fenthion, dimethoate)
Chronic neuro-behavioural sequelae (COPIND)	Weeks–months	Uncertain; ?central axonal injury, hypoxic insult	Persisting cognitive/behavioural dysfunction; “dipper’s flu” after low-level exposure
Extrapyramidal / central effects	Days–weeks	Basal-ganglia/corticospinal involvement	Dystonia, parkinsonism; spasticity unmasked as the neuropathy recovers

Intermediate syndrome (IMS) — detail

- ▶ Occupies the **interval between the acute cholinergic crisis and the delayed neuropathy**, typically becoming manifest within ~4 days of exposure and resolving over 2–3 weeks (originally described by *Senanayake and Karalliedde*).
- ▶ Reflects **excessive cholinergic stimulation of nicotinic receptors** and **prolonged inhibition of AChE activity**; it correlates with severity of poisoning but **not** with the later development of OPIDN.
- ▶ Clinically: **respiratory and bulbar weakness with proximal limb weakness** (neck flexors, ocular and cranial muscles); the danger is unheralded **respiratory arrest**, so it is an indication for close respiratory monitoring/elective ventilation.

OP-induced delayed polyneuropathy (OPIDN) — detail

- ▶ A **delayed polyneuropathy** appearing ~2–3 weeks after acute exposure, even in the absence of **cholinergic toxicity**. The classic historical epidemic was contamination of illicit alcohol (“*Jake*”/Ginger-Jake leg) with **tri-ortho-cresyl phosphate (TOCP)**; other culprits include **leptophos, trichlorfon and mipafox**.
- ▶ **Clinical course**: paraesthesiae in the feet and **calf-muscle cramps**, followed by progressive weakness beginning **distally** and spreading proximally; maximal deficit within ~2 weeks; **quadriplegia in severe cases**. Sensory complaints are inconspicuous though deficits are found on examination. The **Achilles reflex is typically lost**; **cranial-nerve function is spared**. With time the peripheral neuropathy improves but **upper-motor-neuron involvement is then unmasked** and determines functional prognosis.
- ▶ **Mechanism**: phosphorylation and inhibition of **neuropathy target esterase (NTE)**, followed by “**ageing**” (loss of a side-group leaving a negatively charged phosphoryl-protein) — ageing of inhibited NTE is required for the neuropathy to develop. Pathologically there is a **central–peripheral distal axonopathy** with degeneration of the **gracile fasciculus and corticospinal tracts** in addition to peripheral nerve.
- ▶ **Electrodiagnosis**: an **axonopathy** — partial denervation, small/absent compound muscle action potentials, with **normal or only minimally reduced motor conduction velocity**.
- ▶ **There is no specific treatment** to arrest progression or hasten recovery; management is supportive and rehabilitative. Lymphocyte NTE has been used to monitor occupational exposure.

Other delayed / chronic effects

- ▶ **Relapsing cholinergic crisis**: with highly lipid-soluble OPs (fenthion, dimethoate), symptoms may **persist or recur over several days** as the agent is redistributed from fat — mandating prolonged atropine therapy and observation.
- ▶ **Chronic OP-induced neuropsychiatric disorder (COPIND)** and “**dipper’s flu**” (headache, rhinitis, pharyngitis, myalgia, flu-like symptoms in sheep-dippers): a meta-analysis has linked

low-level exposure to impaired neuro-behavioural function, although causation after a single acute exposure remains uncertain.

- ▶ **Susceptibility:** **paraoxonase (PON1)** status (a hepatic/serum enzyme that hydrolyses OPs) is a biomarker modulating individual vulnerability to acute toxicity.

Management of OP poisoning

Care proceeds along four axes — **resuscitation/decontamination, antidotes (atropine + an oxime), control of seizures, and monitoring for the delayed syndromes.**

1. Resuscitation & supportive care (priority)

- ▶ **Airway, oxygenation and ventilation first** — secure the airway, give high-flow O₂, suction copious secretions; intubate and mechanically ventilate for respiratory failure (bronchorrhoea, weakness, IMS). *Ensure adequate ventilatory support before giving atropine.*
- ▶ Treat seizures with **benzodiazepines** (diazepam/lorazepam); correct hypotension, arrhythmias and metabolic derangements.

2. Decontamination

- ▶ **Skin/hair:** remove contaminated clothing and **wash repeatedly with soap/shampoo and water**; staff must wear **gloves and waterproof aprons** to avoid secondary exposure (dilute hypochlorite ~1:10 helps degrade OP on equipment/clothing).
- ▶ **GI** (recent ingestion): consider **nasogastric aspiration of liquid followed by activated charcoal**; eye decontamination if ocular exposure.

3. Specific antidotes

Antidote	Action	Regimen (per CMDT)
Atropine	Competitively blocks muscarinic effects (dries secretions, relieves bronchospasm/bradycardia); no effect on nicotinic weakness	2 mg IV ; if no response in 5 min, repeat doubling boluses rapidly, titrated to drying of bronchial secretions and reduced wheeze — <i>several hundred mg</i> may be needed in severe cases
Pralidoxime (2-PAM)	Reactivates phosphorylated cholinesterase by removing the OP — acts at nicotinic and muscarinic sites	1–2 g IV loading dose , then continuous infusion 200–500 mg/h , titrated and continued as long as acetylcholine excess persists

- ▶ **Atropine** controls the muscarinic crisis but does not reverse muscle weakness; the **oxime** is the agent that can reverse the nicotinic component and so attenuate weakness/respiratory paralysis.
- ▶ **Timing is critical:** pralidoxime is most effective **given very early**, before “ageing” makes OP–enzyme binding permanent (irreversible); efficacy data in trials are conflicting on mortality, but it remains standard for OP and nerve-agent poisoning.

- ▶ Pralidoxime is of questionable benefit in carbamate poisoning — carbamates inhibit AChE only transiently (no ageing); carbamate toxicity is milder and atropine alone usually suffices.

4. Monitoring and delayed-phase care

- ▶ Prolonged ICU observation: watch for IMS (respiratory failure within 1–4 days) and recurrent cholinergic toxicity with lipophilic agents; serial cholinesterase levels guide recovery.
- ▶ OPIDN/IMS care is supportive — ventilatory support, physiotherapy and rehabilitation; there is no antidote for the established neuropathy.
- ▶ Unproven adjuncts mentioned in the literature include magnesium, sodium bicarbonate, clonidine and extracorporeal removal — not established therapy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ “Phases / timeline of OP toxicity” arrow diagram (a horizontal time axis from exposure): label Acute cholinergic crisis (minutes–hours: muscarinic + nicotinic + CNS) → Intermediate syndrome (24–96 h / ≤4 days: proximal, neck-flexor, bulbar & respiratory-muscle weakness) → OPIDN (2–3 weeks: distal sensorimotor axonopathy → later UMN signs) → Chronic neuro-behavioural sequelae (weeks–months).
- ▶ Synapse schematic of AChE inhibition: label presynaptic terminal, acetylcholine, synaptic cleft, acetylcholinesterase, OP phosphorylating AChE, “ageing” → irreversible enzyme, muscarinic receptor (→ atropine block), nicotinic receptor (→ pralidoxime reactivation).

Clinical / Diagnostic significance

- ▶ Diagnosis rests on the toxidrome (miosis, sweating, diarrhoea, bronchorrhoea, fasciculations) plus RBC and plasma cholinesterase depressed ≥50%; RBC (true) cholinesterase best reflects synaptic enzyme and recovery.
- ▶ Recognising the delayed phases changes disposition — an apparently recovering patient can develop IMS-related respiratory arrest, so early extubation and ward transfer are hazardous.
- ▶ OPIDN mimics Guillain–Barré/toxic neuropathy but is distal, motor-predominant, areflexic with cranial sparing and may later show spasticity (corticospinal degeneration) — an important neurology cross-over.
- ▶ Early, adequately titrated atropinisation + oxime + ventilation are the determinants of survival in the acute phase.

High-yield exam pointers

- ▶ Three classic delayed effects: Intermediate syndrome (1–4 days, nicotinic, respiratory/bulbar/proximal weakness), OPIDN (2–3 weeks, NTE inhibition + ageing, distal

axonopathy), chronic neuro-behavioural sequelae ($\pm$ relapsing cholinergic crisis with lipophilic agents).

- ▶ **OPIDN agents:** tri-ortho-cresyl phosphate (Ginger-Jake/"Jake"), leptophos, trichlorfon, mipafox; lesion = **central–peripheral distal axonopathy** (gracile fasciculus + corticospinal tracts).
- ▶ **Mechanism keyword for OPIDN:** inhibition + “ageing” of neuropathy target esterase (NTE) — *not* AChE.
- ▶ **Atropine** reverses muscarinic signs (endpoint = **dry chest/secretions**); **pralidoxime (2-PAM)** reverses the **nicotinic/weakness** component and must be given **early** (before ageing).
- ▶ **Atropine 2 mg IV, doubling boluses; pralidoxime 1–2 g IV load then 200–500 mg/h infusion.**
- ▶ **Carbamates:** shorter-acting, milder, atropine usually sufficient, oxime of questionable benefit (no ageing).
- ▶ **Death is usually from respiratory failure;** ventilate early. **PON1 (paraoxonase)** modulates susceptibility.
- ▶ **Decontamination:** remove clothes, soap-and-water skin wash, **protect staff (gloves/aprons)**; NG aspiration + activated charcoal for ingestion.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Poisoning and Drug Overdose” (anticholinesterase/cholinergic toxidrome, cholinesterase $\geq 50\%$ depression, fundamentals of poisoning management) and “Peripheral Neuropathy” (OP binding/inhibition of neuropathy target esterase; gracile-fasciculus + corticospinal axonal degeneration).
- ▶ **Bradley's Neurology in Clinical Practice, 8e** — “Effects of Toxins and Physical Agents on the Nervous System” (intermediate syndrome timing/features; OPIDN — TOCP/leptophos/trichlorfon/mipafox, NTE inhibition and ageing, clinical course, electrodiagnosis; dipper's flu; PON1) and “Disorders of Peripheral Nerves.”
- ▶ **CMDT 2026** — “Poisoning: Pesticides – Cholinesterase Inhibitors” (clinical findings, decontamination, atropine and pralidoxime regimens, recurrence with fenthion/dimethoate, carbamate caveat, unproven adjuncts).
- ▶ *Coverage note:* Harrison 22e covers OP only within the general poisoning chapter (toxidrome and antidote table); the deep delayed-effect detail (IMS, OPIDN mechanism, ageing) is drawn from Bradley's Neurology and the management regimens from CMDT 2026 — together these fully support the answer.



Management of Poisonous Snake Bite

Asked in: Paper IV May 2022 — RGUHS MD General Medicine

Definition / Introduction — Snake envenomation is the injection of venom — a complex mixture of enzymes, polypeptides, glycoproteins and other constituents — through hollow or grooved maxillary fangs, producing **local tissue necrosis, coagulopathy, organ dysfunction and/or neuromuscular-junction paralysis**. Globally there are an estimated 1.2–5.5 million snakebites/year with 421,000–1,200,000 envenomations, and the WHO aims to halve snakebite deaths by 2030. Notably, ~20–25% of pit-viper bites (and up to 75% of sea-snake bites) are “**dry**” bites with no venom delivered, so management is driven by *evidence of envenomation*, not the fact of the bite alone. The cornerstone of treatment is rapid transport to a facility with airway support and **species-appropriate antivenom**, which is the only specific antidote.

Venomous snakes & clinical syndromes (orientation)

- ▶ **Viperids** (pit vipers, Russell’s viper *Daboia russelii*, saw-scaled viper): triangular head, elliptical pupils, long mobile fangs, loreal heat-pits — predominantly **cytotoxic + haemotoxic** (local swelling/necrosis, coagulopathy, bleeding).
- ▶ **Elapids** (cobras *Naja*, kraits *Bungarus*, coral snakes *Micrurus*): fixed small erect fangs (fewer puncture marks), predominantly **neurotoxic** — descending paralysis.
- ▶ **Sea snakes**: predominantly **myotoxic** — myalgia, trismus, rhabdomyolysis, flaccid paralysis (often delayed hours).

Syndrome	Key features (source-grounded)
Local (cytotoxic)	Pain, soft-tissue swelling, ecchymosis, haemorrhagic/serum-filled vesicles & bullae, tissue loss/necrosis
Haemotoxic	Spontaneous bleeding, haemolysis, venom-induced consumptive coagulopathy, thrombocytopenia
Neurotoxic	Nausea/headache/paraesthesia → cranial-nerve signs (<i>ptosis</i> , dysphagia) → peripheral weakness → diaphragmatic paralysis & respiratory failure
Systemic	Fatigue, vomiting, taste change, mouth numbness, tachy-/bradycardia, hypotension, fasciculations, pulmonary oedema, renal dysfunction, rhabdomyolysis

First-aid / Field management (pre-hospital)

- ▶ **Rapid transport** to a medical facility equipped to provide airway/breathing/circulation support and antivenom is the single most important step; discourage delay with traditional healers.
- ▶ **Reassure and immobilise**: remove jewellery/tight clothing (anticipated swelling), clean wound with soap and running water, cover with a sterile dressing — but *wound care must not delay transport*.

- ▶ **Splint** the bitten extremity to limit movement; keep it in a neutral position of comfort at approximately heart level.
- ▶ Do **not** attempt to capture the snake — take digital photographs from a safe distance to aid identification.
- ▶ **Abandon harmful traditional measures**: do NOT incise or apply suction (worsens tissue damage, infection, ineffective); do NOT apply tourniquets or lympho-occlusive bandages (“venom sequestration devices”) — they intensify local necrosis and risk ischaemia/loss of function.
- ▶ **Pressure-immobilisation bandage**: reserved **ONLY** for bites by a *reliably identified, primarily neurotoxic elapid* with no local tissue effect — wrap the entire limb and immobilise to restrict lymphatic spread; **never for viperid bites**. Wrap pressure 40–70 mmHg (upper limb), 55–70 mmHg (lower limb) — snug but loose enough to slip a finger under; the victim must be *carried* (walking pumps venom systemically).

Hospital management — resuscitation, monitoring & investigations

- ▶ **ABC first**: bites to face/neck may need **early endotracheal intubation** before swelling occludes the airway. Monitor vitals, cardiac rhythm, SpO₂ and urine output.
- ▶ Establish **two large-bore IV lines in unaffected limbs**; because of coagulopathy, minimise venipunctures and avoid non-compressible sites (e.g. subclavian).
- ▶ **Hypotension**: early shock is due to bradykinin-potentiating factors (vasodilation, splanchnic/pulmonary pooling), systemic bleeding, haemolysis and third-spacing → give isotonic crystalloid (**normal saline or Ringer’s lactate 20–40 mL/kg IV**). Add a **vasopressor (noradrenaline/adrenaline)** only if shock persists after volume + antivenom (consider concurrent anaphylaxis).
- ▶ Remove any field bandages **cautiously** (sudden release of stagnant acidotic venom-laden blood can cause hypotension/dysrhythmia).
- ▶ **Mark and measure**: outline the leading edge of swelling/ecchymosis/tenderness and measure limb circumference at three points **every 15 min until stable**, then 1–2 hourly; keep the limb above heart level. Watch neurotoxic victims for *ptosis* heralding airway compromise.
- ▶ **Investigations**: CBC (haemorrhage/haemolysis/thrombocytopenia), blood group & cross-match, renal & hepatic panel, PT/INR, **fibrinogen**, **FDP/D-dimer**, CK (rhabdomyolysis), urine for blood/myoglobin; ECG and chest X-ray in severe cases. In resource-limited settings the **20-minute whole-blood clotting test (20WBCT)** detects coagulopathy: 1–2 mL venous blood in a clean dry glass tube left undisturbed 20 min — *failure to clot = coagulopathy*. Recheck labs every 6 h after antivenom.

Antivenom therapy (the mainstay)

- ▶ **Principle:** antivenoms are antibodies (or Fab/F(ab')₂ fragments) raised in horses or sheep that bind and neutralise *circulating, unbound* venom before it reaches target tissue. They may be **monospecific** or **polyspecific**; selection must match the offending species (no cross-protection unless venoms are homologous).
- ▶ **Key limitation:** antivenom reverses only *active* venom toxicity — it does **not** reverse established effects such as established paralysis or renal failure (these need time + supportive care).
- ▶ **Indications —**
 - *Viperid / cytotoxic bites:* progressive local findings (rapidly spreading swelling, swelling >½ the limb, extensive blistering/bruising, severe pain) **or** any systemic envenomation (systemic symptoms or laboratory abnormality).
 - *Neurotoxic elapid bites:* give at the **first sign of neurotoxicity** (cranial-nerve dysfunction, peripheral neuropathy).
 - Isolated mild pain/swelling after an unidentified bite may be from a harmless species — antivenom is then useless and potentially harmful.
- ▶ **Administration:** **IV only**, started *slowly* with the clinician at the bedside, then titrated up to deliver the full starting dose over ~1 h; redose if the patient worsens or venom effects recur. Antivenom should generally continue for viperid bites until definite improvement (reduced pain, stable vitals, restored coagulation).

Severity (US grading)	Findings	Antivenom approach
None	Fang marks only (“dry” bite)	None; observe
Mild	Local findings only, non-progressive	Usually none; observe
Moderate	Progressing swelling, systemic symptoms/signs, lab abnormality	Antivenom (e.g. CroFab 4–6 vials)
Severe	Neurologic dysfunction, respiratory distress, CV instability/shock	Antivenom (e.g. CroFab 6 vials); ICU

Antivenom reactions & their treatment

- ▶ **Early (anaphylactic / anaphylactoid):** tachycardia, rigors, vomiting, urticaria, dyspnoea, laryngeal oedema, bronchospasm, hypotension. **Skin testing is neither sensitive nor specific and is not recommended;** prophylactic antihistamines/glucocorticoids are *not* proven beneficial (limited Sri Lankan data support low-dose SC adrenaline pretreatment 0.25 mg of 1:1000). Adrenaline and airway equipment must always be ready.
- ▶ **Treatment of acute reaction:** STOP the infusion → **IM adrenaline 0.01 mg/kg (max 0.5 mg) + IV antihistamine (diphenhydramine 1 mg/kg, max 50 mg) + IV glucocorticoid (hydrocortisone 2 mg/kg, max 100 mg).** Once controlled, **restart antivenom at 5–10 mL/h** and titrate up; for

refractory hypotension run a concomitant IV adrenaline infusion in a monitored (ED/ICU) setting.

- ▶ **Late (serum sickness):** 1–2 weeks later — myalgia, arthralgia, fever, chills, urticaria, lymphadenopathy, renal/neurologic dysfunction. Treat with **oral prednisone 1–2 mg/kg/day** until resolution, then taper over 1–2 weeks, plus antihistamines/analgesics.

Management of complications & supportive care

- ▶ **Coagulopathy / bleeding:** blood products are *rarely* needed and factors rebound after adequate antivenom — give FFP/platelets **only after adequate antivenom** (otherwise they fuel ongoing consumption).
- ▶ **Neurotoxicity:** for **post-synaptic** neurotoxin bites (e.g. cobra) give a trial of an **acetylcholinesterase inhibitor** — pretreat with **atropine 0.6 mg IV**, then **edrophonium 10 mg IV** (or **neostigmine 0.02 mg/kg IV/IM**); if objective improvement at 30 min, continue **neostigmine 0.5 mg IV/IM/SC hourly**. These are *adjuncts*, not substitutes for intubation/antivenom; intubate and ventilate established paralysis (may need days–weeks).
- ▶ **Rhabdomyolysis / AKI:** IV fluids and urine-output monitoring; AKI (usually reversible acute tubular necrosis) may need **haemodialysis/peritoneal dialysis**; bilateral cortical necrosis carries a poorer renal prognosis.
- ▶ **Compartment syndrome** (deep IM venom; pain, weakness, altered sensation, cyanosis, apparent pulselessness): measure intracompartmental pressure — **>30–40 mmHg → give more antivenom and elevate the limb**. Fasciotomy is NOT recommended for North-American crotalids (no benefit, increased morbidity) and is a last resort even where Asian-species data allow it; true compartment syndrome requiring fasciotomy occurs in <1%.
- ▶ **Wound care & adjuncts:** clean with soap/water, sterile dressing, splint with padding between digits, elevate after antivenom started; **tetanus immunisation**; analgesia with **paracetamol or opioids** — **avoid salicylates/NSAIDs** (impair clotting). Prophylactic antibiotics are usually unnecessary after North-American bites but warranted where secondary infection is common or if first-aid included incision/suction. Debride frank necrosis only after coagulopathy reverses; leave intact blebs alone; start **physiotherapy** early.
- ▶ **Observation/disposition:** observe any envenomed patient ≥24 h; an apparently “dry” viperid bite ≥8–12 h (delayed toxicity); observe ≥24 h after coral-snake (*Micrurus*), hump-nosed pit viper (*Hypnale*) and sea-snake bites (delayed onset). ICU for progressive findings despite antivenom, head/neck bites or antivenom hypersensitivity. **At discharge** warn about wound infection, serum sickness, recurrent coagulopathy and long-term sequelae such as **pituitary insufficiency after Russell’s viper (Daboia russelii) envenomation**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Algorithm box (“Management of snakebite”)** with labelled arrows: *Bite* → *Reassure/immobilise/splint, remove constrictions* → *Transport (avoid incision/suction/tourniquet)* → *ABC + 2 IV lines + crystalloid* → *Assess envenomation (local progression / 20WBCT / labs)* → *Antivenom if local-progressive or systemic/neurotoxic* → *Treat reactions (adrenaline)* → *Manage complications (intubation, ACh-esterase inhibitor, dialysis, blood products)* → *Observe ≥24 h* → *Discharge advice*.
- ▶ **Labelled snake-head identification figure:** labels — *Viperid: triangular head, elliptical pupil, long mobile fang, loreal pit; Elapid: rounded head, round pupil, short fixed fang; mark fang/puncture marks and local swelling/ecchymosis at bite site.*

Clinical / Diagnostic significance

- ▶ The decision to give antivenom rests on **objective evidence of envenomation** (progressive local signs, systemic features, abnormal 20WBCT/coagulation, neurotoxic signs) — not on the bite alone, since dry bites are common.
- ▶ The **20WBCT** is a cheap, bedside, resource-independent test that confirms venom-induced consumptive coagulopathy and guides antivenom in district/rural settings.
- ▶ *Ptosis* and bulbar weakness are early warnings of impending respiratory failure — secure the airway **before** decompensation.
- ▶ Antivenom both treats and *causes* anaphylaxis; readiness with adrenaline at the bedside is mandatory before every infusion.

High-yield exam pointers

- ▶ **Antivenom is the only specific treatment** and acts only on circulating (unbound) venom — give early; useless for established paralysis/renal failure.
- ▶ **Never** incise, suck, or apply a tourniquet/tight bandage; pressure-immobilisation is only for *neurotoxic elapid* bites, never viperid.
- ▶ Crystalloid 20–40 mL/kg for hypotension; vasopressors only after volume + antivenom.
- ▶ Acute antivenom reaction → stop infusion, **IM adrenaline 0.01 mg/kg (max 0.5 mg)** + antihistamine + steroid, restart at 5–10 mL/h.
- ▶ **Serum sickness** at 1–2 weeks → oral prednisone 1–2 mg/kg/day with taper.
- ▶ Neostigmine (with atropine) helps **post-synaptic** neurotoxic (cobra-type) bites; not a substitute for ventilation/antivenom.
- ▶ Snakebite coagulopathy → give blood products **only after** adequate antivenom; avoid NSAIDs/aspirin.
- ▶ Fasciotomy is rarely needed (<1%); rising compartment pressure → **more antivenom**, not the knife.

- ▶ Observe ≥ 24 h (≥ 8 –12 h for “dry” viperid bites); beware delayed toxicity from kraits, coral snakes, hump-nosed viper and sea snakes; warn of late Russell’s-viper hypopituitarism.

SOURCE & COVERAGE

Harrison 22e — Ch 471 “Disorders Caused by Venomous Snakebites and Marine Animal Exposures” (incl. Tables 471-1 and 471-2). **Coverage note:** Harrison’s management protocol and named antivenoms (CroFab/Anavip, *Micrurus* antivenin) are US/Canada-specific and, as the text states, should not be transposed to other regions. India-specific standards relevant to RGUHS — the “**Big Four**” (Russell’s viper, common krait, Indian cobra, saw-scaled viper) and **Indian polyvalent anti-snake venom** dosing — are universally-accepted Indian internal medicine but are not detailed in this US-focused chapter; only *Daboia russelii*, kraits (*Bungarus*) and cobras (*Naja*) are explicitly named in the source. Indian polyvalent ASV vial regimens and WHO/national snakebite protocols fall outside the provided text and should be confirmed against a national guideline.



Organophosphorus (Organophosphate) Compound Poisoning

Asked in: Paper IV Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Organophosphorus (OP) compounds are organic esters of phosphoric/phosphorothioic acid used as insecticides (diazinon, malathion, parathion, chlorpyrifos, acephate) and as chemical-warfare nerve agents (tabun [GA], sarin [GB], soman [GD], VX). They produce poisoning by **irreversibly inhibiting acetylcholinesterase**, causing accumulation of acetylcholine and an overwhelming **cholinergic crisis** at muscarinic, nicotinic and CNS receptors. OP poisoning — most often **deliberate self-poisoning** in agrarian Asia — accounts for the bulk of the >150,000 pesticide-poisoning deaths each year worldwide and is a leading cause of acute-poisoning ICU admission in India.

Pathophysiology — cholinesterase inhibition and “aging”

- ▶ **Two cholinesterases are inhibited:**
 - *Acetylcholinesterase (AChE; “true” or RBC cholinesterase)* — in erythrocyte membranes, nervous tissue and skeletal muscle; the better index of synaptic enzyme inhibition.
 - *Plasma butyrylcholinesterase (BuChE; pseudocholinesterase)* — in serum, liver, pancreas, heart and brain; easier to assay, falls first, but is less specific.
- ▶ OP compounds **phosphorylate** the active (esteratic) site of AChE, inactivating it. Acetylcholine is therefore not hydrolysed and accumulates at synapses → initial **overstimulation** of cholinergic receptors, followed by **depolarising blockade/paralysis** of transmission in the CNS, autonomic

ganglia, parasympathetic and selected sympathetic (sweat-gland) endings, and at the neuromuscular junction.

- ▶ “**Aging**” = loss of an alkyl group from the phosphorylated enzyme, making the OP–enzyme bond *permanent and irreversible*. Time to aging is agent-specific (minutes for **soman**, up to >24–48 h for others). **Oximes can only reactivate the enzyme before aging occurs** — hence the urgency of antidote therapy. Once aged, recovery requires **resynthesis of new enzyme over weeks**.
- ▶ Many formulations contain an **aromatic hydrocarbon solvent (xylene)** and surfactants — these add aspiration (lipoid) pneumonitis and CNS depression, and OP is **well absorbed transdermally**, by inhalation, transconjunctivally and by ingestion.
- ▶ **Carbamates** (carbaryl, aldicarb, propoxur) inhibit the same enzyme but the carbamylated bond is **reversible and does not age**, giving a shorter, generally more benign illness.

Clinical features — cholinergic toxidrome

Most patients are symptomatic within **8 h** of ingestion and nearly all by **24 h**; onset is fastest with inhalation, slowest transdermally. Three receptor groups produce overlapping signs.

Receptor group	Mechanism	Clinical effects (mnemonic)
Muscarinic	Post-ganglionic parasympathetic + sweat glands	* DUMBELS — <i>Defecation, Urination, Miosis, Bradycardia/Bronchorrhoea/Bronchospasm (“Killer Bs”), Emesis, Lacrimation, Salivation. Also SLUDGE*</i> (Salivation, Lacrimation, Urination, Defecation, GI cramps, Emesis), sweating
Nicotinic	Autonomic ganglia, adrenal medulla, NMJ	Muscle fasciculations , cramps, weakness → paralysis (incl. diaphragm); mydriasis, pallor, tachycardia, hypertension
CNS	Central cholinergic receptors	Anxiety, restlessness, tremor, headache, confusion, delirium, seizures, coma

- ▶ *Either picture may dominate* — parasympathetic effects usually predominate, but severe poisoning may present with **nicotinic features first** (tachycardia, hypertension). Classic severe triad: **pinpoint pupils + excessive secretions/sweating + difficulty breathing**, often with a **garlic/hydrocarbon odour**.
- ▶ **Death is due to respiratory failure** — combination of bronchorrhoea, bronchospasm, respiratory-muscle paralysis and central respiratory depression; aspiration of gastric contents/hydrocarbon worsens it. Myocardial ischaemia and pancreatitis may occur.

Four recognised clinical syndromes (high-yield):

- ▶ **1. Acute cholinergic crisis** — minutes to hours; the muscarinic/nicotinic/CNS toxidrome above.

- ▶ **2. Intermediate syndrome** — 1–5 days after exposure (up to ~40% of ingestions); proximal limb, neck-flexor, cranial-nerve and **respiratory-muscle weakness** *without* cholinergic features; may need ventilation; usually resolves within ~7 days. **Not** reported with nerve-gas poisoning.
- ▶ **3. OP-induced delayed neuropathy (OPIDN)** — a **distal, symmetrical sensorimotor axonopathy** appearing ~1–3 weeks later (classically attributed to inhibition of *neuropathy target esterase, NTE*); leg cramps → weakness/paralysis mimicking **Guillain–Barré syndrome**; *not* reversed by atropine/oximes.
- ▶ **4. Chronic toxicity / neuropsychiatric sequelae** — with low-grade repeated exposure: cognitive/memory impairment, mood change, autonomic dysfunction, extrapyramidal signs.

Diagnosis / Investigations

- ▶ **Clinical** — diagnosis rests on history + the cholinergic toxidrome; **do not delay antidote** awaiting enzyme assays.
- ▶ **Cholinesterase assays** —
 - *Plasma BuChE* falls first; in poisoning, plasma/RBC cholinesterase is **<50% of normal**; BuChE normalises in **28–42 days** (if no oxime given).
 - *RBC AChE* is the better marker: reduced to **10–20%** of normal in moderate, **<10%** in severe poisoning; full recovery needs RBC turnover (up to **120 days**).
- ▶ **Cautions:** BuChE is low in liver disease, malnutrition, pregnancy, genetic variants and with certain drugs; RBC AChE is factitiously low with haemoglobinopathy, pernicious anaemia and antimalarials.
- ▶ **Ancillary:** ECG — sinus brady/tachycardia, **prolonged QT, ST/T changes, AV block**, torsades/VT; CXR — pulmonary oedema/aspiration; bloods — hyper-/hypoglycaemia, leucocytosis, amylase (pancreatitis); ABG. EMG can demonstrate NMJ dysfunction/intermediate syndrome.

Management

General principles: secure airway and ventilation, decontaminate, **adequate atropinisation**, and **early oxime** before aging — with intensive supportive care. Therapy must **not** be withheld pending cholinesterase results.

Step	Detail
Resuscitation	Airway, 100% O ₂ , suction secretions; intubate for coma/seizures/respiratory failure/bronchorrhoea. Use a non-depolarising relaxant if paralysis needed — avoid succinylcholine (prolonged apnoea, as it is hydrolysed by BuChE). IV crystalloid for hypotension.

Step	Detail
Decontamination	Staff wear nitrile/neoprene gloves, gown, face shield (latex is inadequate); remove all clothing as hazardous waste; wash skin/hair/nails with soap & water ; dilute 1:10 hypochlorite (bleach) decontaminates equipment. Gastric lavage only within 1 h of large ingestion after airway protection; activated charcoal, lavage and haemodialysis are of no proven benefit.
Atropine (<i>physiological antidote — muscarinic only</i>)	Bolus 1.2–3 mg IV (CMDT: 2 mg); double the dose every 5 min until atropinised — <i>clear chest on auscultation, HR >80/min, SBP >80 mmHg</i> . Tens-hundreds of mg may be needed. Then infusion at 10–20%/h of the total atropinising dose (~0.4–4 mg/h), titrated; watch for toxicity (absent bowel sounds, hyperthermia, delirium). Tachycardia and mydriasis are NOT contraindications/endpoints. <i>Glycopyrrolate</i> is an alternative without CNS effects.
Pralidoxime (2-PAM) (<i>enzyme reactivator — nicotinic + muscarinic; reverses muscle weakness if given before aging</i>)	WHO regimen: 30 mg/kg IV bolus over 5–10 min, then 8 mg/kg/h infusion for 24–48 h. (CMDT: 1–2 g IV load, then 200–500 mg/h.) Give as early as possible ; still worthwhile even 24–48 h post-exposure. Continue while signs of acetylcholine excess persist. Not for asymptomatic or pure-carbamate (carbaryl) poisoning.
Seizures	Benzodiazepines (IV) ; atropine may abort early cholinergic seizures.
Adjuncts (unproven)	Magnesium sulfate and calcium-channel blockers show some benefit but are not routine.

Organophosphate vs Carbamate — key contrasts

Feature	Organophosphate	Carbamate
Enzyme bond	Phosphorylation — irreversible, ages	Carbamylation — reversible, no aging
Duration	Prolonged (weeks for enzyme resynthesis)	Short — recovers in hours (spontaneous, usually <24 h)
CNS penetration / seizures	Yes (adults)	Poor in adults (less CNS toxicity, no seizures)
Pralidoxime	Indicated, early	Usually not needed ; avoid in single-agent carbaryl
Atropine	Yes	Yes — mainstay

Feature	Organophosphate	Carbamate
DIAGRAMS TO DRAW — IMAGE SUGGESTIONS ▶ Cholinergic synapse / mechanism schematic — label: <i>presynaptic neuron, acetylcholine (ACh) vesicles, synaptic cleft, acetylcholinesterase (AChE), postsynaptic muscarinic & nicotinic receptors, OP compound phosphorylating AChE (“aging”), pralidoxime reactivating AChE, atropine blocking muscarinic receptor.</i> ▶ “DUMBELS / SLUDGE + nicotinic + CNS” toxidrome figure — a body silhouette labelled: <i>miosis (pinpoint pupils), lacrimation, salivation, bronchorrhoea, bronchospasm, bradycardia, vomiting, diarrhoea, urination, sweating (muscarinic); fasciculations, weakness, mydriasis, tachycardia, hypertension (nicotinic); seizures/coma (CNS).</i>		

Clinical / Diagnostic significance

- ▶ **Bedside diagnostic clue:** pinpoint pupils + secretions + bradycardia + garlicky breath in a patient who may have agricultural access ⇒ treat empirically.
- ▶ **Atropine titration is the therapeutic art** — dose to the chest and haemodynamics, not the pupils; under-atropinisation kills via bronchorrhoea.
- ▶ **Watch for the intermediate syndrome** at days 1–5: recurrent respiratory failure after apparent recovery — keep ICU/ventilatory vigilance.
- ▶ **Fat-soluble agents** (fenthion, dimethoate) cause prolonged/relapsing illness needing days–weeks of atropine ± oxime infusion.
- ▶ Avoid succinylcholine, ester local anaesthetics and β -blockers, which may worsen toxicity.

High-yield exam pointers

- ▶ OP = irreversible AChE inhibitor; aging makes oximes ineffective — *soman ages in minutes.*
- ▶ RBC AChE more specific; plasma BuChE falls first/easier to measure; activity <50% normal in poisoning.
- ▶ Muscarinic = DUMBELS/SLUDGE + Killer Bs (bradycardia, bronchorrhoea, bronchospasm); Nicotinic = fasciculations, weakness, mydriasis, tachycardia, hypertension; CNS = seizures/coma.
- ▶ Death = respiratory failure (bronchorrhoea + respiratory-muscle paralysis + central depression).
- ▶ Atropine endpoints: clear chest, HR >80, SBP >80; pralidoxime (2-PAM) WHO dose 30 mg/kg bolus + 8 mg/kg/h.
- ▶ Atropine treats muscarinic effects only; pralidoxime reverses nicotinic (muscle) weakness — give both.
- ▶ **Four syndromes:** acute crisis → intermediate syndrome (1–5 d, respiratory/proximal weakness) → OPIDN (~1–3 wk, distal neuropathy, NTE) → chronic neuropsychiatric.

- ▶ **Carbamate** poisoning: reversible, no aging, shorter course, pralidoxime usually unnecessary (avoid in carbaryl).
- ▶ Nerve agents (sarin, soman, tabun, VX) are OP compounds; **do not** cause the intermediate syndrome.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Poisoning and Drug Overdose” (cholinergic/acetylcholinesterase-inhibitor toxidrome and antidote table).
- ▶ **Tintinalli's Emergency Medicine** — “Pesticides” (organophosphate pathophysiology, aging, four clinical syndromes, cholinesterase assays, atropine and pralidoxime regimens, carbamate contrasts) — principal depth source.
- ▶ **CMDT 2026** — “Poisoning: Pesticides — Cholinesterase Inhibitors” (atropine and pralidoxime dosing, decontamination).

Coverage note: The neuropathy-target-esterase (NTE) mechanism and classic 1–3-week timing of OPIDN, and the term “intermediate syndrome,” are universally accepted toxicology teaching; the corpus (Tintinalli) describes these syndromes in detail but frames the delayed/chronic neuropathies with slightly different labels — the standard timing/mechanism is presented here for exam completeness.



Paracetamol (Acetaminophen) Poisoning

Asked in: Paper IV Jul 2021 · Paper IV Nov 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — Paracetamol (acetaminophen, *N*-acetyl-*p*-aminophenol, APAP) is the most widely used over-the-counter analgesic–antipyretic and, in overdose, the commonest cause of drug-induced acute liver failure in the Western world (accounting for nearly half of all acute liver failure cases). Toxicity is a **dose-dependent direct hepatotoxicity** caused by the reactive metabolite ***N*-acetyl-*p*-benzoquinone-imine (NAPQI)**, which, once hepatic glutathione is depleted, binds covalently to **hepatocyte macromolecules producing** centrilobular (zone 3) hepatic necrosis*. *It is eminently treatable: the antidote N^{*}-acetylcysteine (NAC)*, if given early, is nearly 100% protective, making early recognition and the Rumack–Matthew nomogram central to management.

Pharmacology, metabolism and the basis of toxicity

- ▶ **Pharmacokinetics:** rapid GI absorption; peak therapeutic level at 30 min–2 h (≈ within 2 h after overdose, later with extended-release or anticholinergic/opioid co-ingestants); ~100% bioavailability, ~20% protein-bound, $V_d \approx 0.85 \text{ L/kg}$, elimination half-life ≈ 2.5 h.
- ▶ **Normal (therapeutic) metabolism:** mainly **glucuronidation (40–67%)** and **sulfation (20–46%)** to non-toxic conjugates; <5% excreted unchanged; only 5–15% oxidised by CYP450 (chiefly

CYP2E1) to the reactive electrophile **NAPQI**, which is immediately conjugated by **glutathione** to harmless mercapturic acid and renally excreted.

- ▶ **In overdose:** glucuronidation and sulfation pathways are **saturated**, diverting more drug through CYP2E1, so excess NAPQI is generated. When hepatic **glutathione falls below ~30% of normal**, unconjugated NAPQI **binds covalently to nucleophilic hepatocyte proteins** (“APAP–protein adducts”), causing **centrilobular hepatic necrosis** and hepatocyte death (lysis typically on day 2, releasing transaminases).
- ▶ **Massive ingestion** (>500 mg/kg, peak level >750 µg/mL [>5000 µmol/L]) can cause **early metabolic acidosis with raised lactate and altered sensorium** even before liver failure — due to glutathione-depletion-related 5-oxoproline accumulation and inhibition of mitochondrial respiration.

Toxic dose and risk factors

- ▶ **Toxic exposure (≥6 yr):** a single ingestion of >150–200 mg/kg or >10 g; a single dose of 10–15 g (occasionally less) may produce liver injury; **fatal fulminant disease usually with ≥25 g**.
- ▶ **Repeated supratherapeutic (“staggered”) ingestion:** >6 g/day or 150 mg/kg/24 h; ~8 g/day (twice the recommended maximum) over several days can readily cause liver failure, especially with opioid–acetaminophen combinations.
- ▶ **Factors increasing risk (low glutathione / induced CYP2E1):**

Mechanism	Examples
Glutathione depletion	Chronic alcohol use, malnutrition/starvation, prolonged fasting in febrile illness, AIDS
CYP2E1 / mixed-oxidase induction	Chronic alcohol, isoniazid, anti-tubercular & anticonvulsant drugs, rifampicin, phenobarbital
Underlying liver vulnerability	Hepatitis C co-infection

- ▶ In **chronic alcoholics**, the toxic threshold may fall to as low as **2 g**; the FDA-recommended maximum daily dose has been reduced from 4 g to **3 g** (lower still in heavy alcohol users), and the acetaminophen content of prescription opioid-combination tablets capped at **325 mg/tablet**.

Clinical features — the four stages

Stage	Timing	Clinical features	Laboratory
1	First 24 h	Often asymptomatic; anorexia, nausea, vomiting, malaise, pallor, diaphoresis	Usually normal
2	Days 2–3	GI symptoms improve; right-upper-quadrant	Rising AST/ALT; raised bilirubin & prolonged PT if severe

Stage	Timing	Clinical features	Laboratory
		pain & hepatic tenderness	
3	Days 3–4	Peak hepatotoxicity — recurrent vomiting, jaundice, encephalopathy, fulminant hepatic failure , metabolic acidosis, coagulopathy, AKI/anuria, $\pm$ pancreatitis	AST/ALT may exceed 10,000 IU/L (far higher than viral hepatitis); raised INR, lactate, creatinine; hypoglycaemia
4	After day 5	Recovery (clinical improvement over 7–8 days; complete hepatic regeneration in 1–3 months) or deterioration to multi-organ failure and death	Resolving vs worsening

- ▶ **Diagnostic biochemical signature:** strikingly **high aminotransferases with relatively low bilirubin** in a “hyperacute” picture should raise suspicion of paracetamol even without a clear history.
- ▶ **Acute kidney injury** occurs in up to ~75% of severe cases but is usually self-limited; rare extrahepatic effects include myocardial injury and pancreatitis.

Diagnosis and the Rumack–Matthew nomogram

- ▶ Measure a serum acetaminophen concentration in every patient with intentional overdose (history is unreliable; toxicity is delayed and treatable). Also send AST/ALT, bilirubin, PT/INR, creatinine, glucose, ABG/lactate, and a co-ingestant screen (salicylate level).
- ▶ **Rumack–Matthew nomogram** plots serum level against time since ingestion to predict hepatotoxicity. The **treatment line corresponds to a 4-hour level of 150 $\mu\text{g/mL}$ (1000 $\mu\text{mol/L}$)** (lowered from the original 200 $\mu\text{g/mL}$ line to widen the safety margin); levels **above the line warrant NAC**.
- ▶ Risk by 4-hour level: **>200 $\mu\text{g/mL}$ (>1300 $\mu\text{mol/L}$) $\approx$ 60% hepatotoxicity, ~5% mortality; >300 $\mu\text{g/mL}$ (>2000 $\mu\text{mol/L}$) $\approx$ 90% hepatotoxicity; <150 $\mu\text{g/mL}$ suggests injury is highly unlikely.**
- ▶ **Nomogram limitations** — **does NOT apply to:** levels drawn **<4 h or >24 h** after ingestion, **unknown time of ingestion**, **chronic/staggered ingestion**, **extended-release preparations**, or **IV acetaminophen overdose**. In these settings, treat empirically guided by detectable level (>10 $\mu\text{g/mL}$ [$>66 \mu\text{mol/L}$]) and/or rising transaminases.

Treatment

- ▶ **Resuscitation & supportive care:** secure airway/breathing/circulation; correct hypoglycaemia, electrolytes, acidosis and coagulopathy; manage cerebral oedema in fulminant failure.
- ▶ **GI decontamination:** a single dose of **activated charcoal** if presenting within 1–2 h of ingestion (charcoal's minor interference with oral NAC absorption is not clinically significant). Lavage/whole-bowel irrigation are generally unnecessary given rapid absorption.
- ▶ ****N-acetylcysteine (NAC) — the antidote:****
 - **Mechanism:** acts as a **glutathione precursor/substitute and sulfate precursor**, and can **directly reduce NAPQI** back to acetaminophen; in established toxicity it is also **antioxidant**, improves microcirculatory flow and oxygen delivery, and reduces neutrophil-mediated injury.
 - **Timing:** nearly **100% effective if started within 8 h** of ingestion; efficacy declines with delay but NAC still benefits even when given up to 24 h (and is used in established hepatotoxicity/late presentation).
 - **IV regimen (standard 21-hour):** 150 mg/kg over 1 h → 50 mg/kg over 4 h → 100 mg/kg over 16 h. The IV route is preferred for vomiting, hepatic failure or pregnancy.
 - **Oral regimen (72-hour):** loading 140 mg/kg, then 70 mg/kg every 4 h for 17 doses (with an antiemetic such as ondansetron for the disagreeable taste/nausea).
 - **Adverse effects:** anaphylactoid reactions in 4–17% of IV NAC (mostly in the first 2 h, more in asthmatics); manage by **slowing/temporarily stopping the infusion** and giving diphenhydramine, then resume at a slower rate.
 - **Massive overdose** (>30 g or level >2× the nomogram line): consider enhanced dosing (e.g., higher third-bag dose) and contact a poison centre.
- ▶ **Extracorporeal removal:** haemodialysis is **rarely indicated** — reserved for massive overdose with altered mental status, metabolic acidosis and very high levels; NAC is dialysable, so the dose is increased during dialysis.
- ▶ **Liver transplantation referral** if fulminant failure evolves despite NAC.

King's College Criteria for liver transplantation (paracetamol-induced acute liver failure)

- ▶ Arterial pH <7.30 (after fluid resuscitation), OR
- ▶ All three of: PT >100 s (INR >6.5) + serum creatinine >3.3 mg/dL (>292 µmol/L) + grade III/IV hepatic encephalopathy.
- ▶ Adjunct poor-prognosis markers: **arterial lactate >3.5 mmol/L** (Harrison) after resuscitation, hypoglycaemia, and rising serum phosphate.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Acetaminophen metabolism pathway:** Acetaminophen → branch to **Glucuronidation** (40–67%), **Sulfation** (20–46%), **Renal excretion of unchanged drug** (<5%), and **CYP2E1** (5–15%) → **NAPQI**. From NAPQI draw two arrows: (a) + **Glutathione** → **mercapturic acid** (APAP-mercaptate) → **renal excretion** (non-toxic); (b) **when glutathione <30% normal** → **covalent binding to hepatocyte proteins** → **centrilobular hepatic necrosis / cell death**.
Label: *NAPQI, glutathione, CYP2E1, centrilobular (zone 3) necrosis*.
- ▶ **Rumack–Matthew nomogram:** Y-axis = plasma acetaminophen (µg/mL and µmol/L, log scale), X-axis = hours after ingestion (4–24 h). Draw the **treatment line through 150 µg/mL at 4 h** (sloping down to ~37.5 µg/mL at 12 h); label zones “**Treatment recommended (above line)**” and “**Toxicity unlikely (below line)**”; mark “**take level ≥4 h after ingestion.**”

Clinical / Diagnostic significance

- ▶ A near-asymptomatic stage 1 with a potentially lethal stage 3 means **management is dictated by the level/nomogram and time, not by early symptoms** — never reassure on a “well-looking” patient.
- ▶ The **APAP level must be drawn at ≥4 h** post-ingestion; if the result will not be available within the 8-h window, start NAC **empirically** and reassess once the level returns.
- ▶ **Pregnancy:** treat exactly as in non-pregnant patients — NAC is safe and effective and crosses the placenta; delay in treatment is associated with fetal loss.
- ▶ Suspect paracetamol in any **acute liver failure with very high transaminases and low bilirubin**, and in unexplained early high-anion-gap metabolic acidosis after massive ingestion.
- ▶ All intentional-overdose patients need a **psychiatric evaluation**; report cases to the regional poison-control centre.

High-yield exam pointers

- ▶ Toxic metabolite = **NAPQI**, generated by **CYP2E1**; detoxified by **glutathione**; toxicity when glutathione <30% → **centrilobular (zone 3) necrosis**.
- ▶ **Toxic dose ≥150 mg/kg or >10 g**; fatal usually ≥25 g; alcoholic threshold may be as low as 2 g.
- ▶ **Four stages:** (1) <24 h GI/asymptomatic, (2) days 2–3 RUQ pain + rising LFTs, (3) days 3–4 fulminant hepatic failure, (4) after day 5 recovery or death.
- ▶ **Rumack–Matthew nomogram** treatment line = **150 µg/mL at 4 h**; not valid <4 h, >24 h, staggered, or extended-release ingestions.
- ▶ **NAC is ~100% effective if given within 8 h**; benefit up to 24 h and in established hepatotoxicity.
- ▶ **IV NAC:** 150 mg/kg/1 h → 50 mg/kg/4 h → 100 mg/kg/16 h (21-h protocol); **oral:** 140 then 70 mg/kg × 17 doses (72 h).

- ▶ **NAC anaphylactoid reactions 4–17%** — slow/stop infusion + antihistamine.
- ▶ **King's College Criteria:** pH <7.30 or (PT >100 s + creatinine >3.3 mg/dL + grade III/IV encephalopathy) → transplant referral.
- ▶ **Activated charcoal** only useful early (within 1–2 h); **haemodialysis** rarely needed (massive overdose).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Toxic and Drug-Induced Hepatitis” (acetaminophen mechanism, NAPQI/glutathione, toxic dose, stages, nomogram thresholds, NAC, lactate prognosis) and “Poisoning and Drug Overdose.”
- ▶ **Tintinalli's Emergency Medicine** — “Acetaminophen” (pharmacokinetics, metabolism figure, four-stage table, Rumack–Matthew nomogram, IV/oral NAC regimens and dosing table, anaphylactoid reactions, King's College Criteria, massive/IV/extended-release overdose).
- ▶ **CMDT 2026** — “Poisoning” (current management, activated charcoal timing, FDA-approved 21-hour IV acetylcysteine regimen, fomepizole as investigational adjunct, high-risk thresholds).



Russell's Viper Envenomation

Asked in: Paper IV Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Russell's viper envenomation is systemic and local poisoning after bite by *Daboia russelii*, an Old World viperid of major importance in South Asia. The dominant syndrome is **viperid cytotoxic-hemotoxic envenomation** with painful swelling, tissue injury, venom-induced consumptive coagulopathy, spontaneous bleeding, shock, and acute kidney injury; certain Indian Russell's vipers may also cause neurotoxicity. It is an emergency because antivenom reverses circulating venom best before fixed renal failure, established paralysis, and tissue necrosis have developed.

Epidemiology and species importance

- ▶ Russell's viper is a medically important Indian viperid and a classic rural/agricultural hazard; Brenner notes that snake bite in the Indian subcontinent commonly occurs when people work barefoot in fields.
- ▶ Harrison lists **Russell's vipers (Daboia russelii)** among snakes responsible for large numbers of deaths outside North America, together with cobras, saw-scaled/carpet vipers, large African vipers, lancehead pit vipers, and tropical rattlesnakes.
- ▶ In the Indian subcontinent, **AKI develops after viper-family bites**, especially Russell's viper, saw-scaled viper (*Echis carinatus*), and pit vipers.

- ▶ Brenner gives the incidence of AKI after Russell's viper or *E. carinatus* bites in India as 13-32%; a Sri Lankan series of unidentified viper bites reported AKI in 27%.
- ▶ Risk of severe disease rises with large venom load, bite on a vascular area or head/neck, delayed transport, traditional treatment before hospital care, lack of appropriate antivenom, shock, coagulopathy, and established renal injury.

Venom pathophysiology

- ▶ Snake venom is a variable mixture of **enzymes, polypeptides, glycoproteins, and other constituents**; venom composition varies by species, snake age, diet, and geography, so local protocols matter.
- ▶ **Local cytotoxic/vascular injury**: venom increases vascular permeability and damages tissues, causing pain, edema, ecchymosis, bullae, hemorrhagic blebs, necrosis, and later functional loss.
- ▶ **Hemotoxic/procoagulant effect**: viper venom activates and consumes clotting factors, fibrinogen, and platelets, producing **venom-induced consumptive coagulopathy** or a DIC-like state with prolonged clotting times, low fibrinogen, thrombocytopenia, high FDP/D-dimer, and bleeding.
- ▶ **Shock mechanisms**: early hypotension may reflect bradykinin-potentiating vasodilatation, systemic bleeding, hemolysis, and intravascular volume loss into swollen tissues.
- ▶ **Renal injury**: AKI is multifactorial: bleeding, hypotension, circulatory collapse, intravascular hemolysis, hemoglobinuria, DIC/microangiopathic hemolysis, myoglobinuria when present, and direct venom nephrotoxicity.
- ▶ **Renal pathology**: acute tubular necrosis is the predominant lesion in snakebite-associated AKI; cortical necrosis may occur and carries much poorer renal recovery.
- ▶ **Neurotoxicity**: Harrison specifically notes that certain Indian Russell's vipers can cause neurologic dysfunction with ptosis, dysphagia, peripheral weakness, diaphragmatic paralysis, aspiration, and respiratory failure.

Clinical features and severity

- ▶ **Local features**: fang marks, early severe pain, rapidly progressive swelling, tenderness, regional lymphadenopathy, ecchymosis, serum-filled or hemorrhagic bullae, cellulitis-like inflammation, and full-thickness necrosis in severe bites.
- ▶ Swelling may involve the whole limb; hand, forearm, and anterior leg bites require vigilance for compartment pressure, although true fasciotomy-requiring compartment syndrome is uncommon.
- ▶ **Bleeding/coagulopathy**: persistent oozing from fang marks or venipuncture sites, gum bleeding, epistaxis, hematuria, hematemesis, melena, hemoptysis, ecchymoses, muscle/fascial compartment bleeding, serous cavity bleeding, and rarely subarachnoid hemorrhage.

- ▶ **Systemic features:** nausea, vomiting, altered/metallic taste, mouth numbness or perioral tingling, generalized weakness, tachycardia or bradycardia, hypotension/shock, pulmonary edema, spontaneous hemorrhage, and altered sensorium in severe envenomation.
- ▶ **Renal features:** oliguria commonly develops within the first 24 h, but may be delayed 2-3 days; anuria or non-oliguric AKI may occur. Clues include gross or microscopic hematuria, hemoglobinuria, jaundice from intravascular hemolysis, and renal-angle pain preceding oliguria.
- ▶ **Neurologic features:** headache, paresthesias, ptosis, diplopia, dysphagia, bulbar weakness, peripheral motor weakness, respiratory muscle paralysis, and aspiration risk.
- ▶ Practical grading:

Grade	Definition
Dry / none	Fang marks only; no progressive swelling, systemic symptoms, or laboratory abnormality after observation
Mild	Local pain, ecchymosis, and nonprogressive swelling only
Moderate	Progressive swelling, systemic symptoms, or laboratory abnormality such as thrombocytopenia/prolonged clotting
Severe	Shock, major bleeding, severe coagulopathy, neurotoxicity, respiratory distress, AKI, pulmonary edema, or extensive local necrosis

Diagnosis and monitoring

- ▶ Diagnosis is clinical: compatible bite history plus local injury, hematologic abnormality, systemic toxicity, or renal/neurotoxic features. Do not wait for snake identification before treating a compatible syndrome.
- ▶ **Bedside assessment:** ABC, vital signs, mental status, respiratory effort, bulbar function, distal pulses, capillary refill, sensory-motor status, and urine output.
- ▶ Mark the leading edge of swelling/ecchymosis/tenderness; measure limb circumference at the bite site and at joints proximal/distal every 15 min until stable, then every 1-2 h.
- ▶ **Core investigations:** CBC with platelets, blood group and cross-match, PT/INR/aPTT, fibrinogen, FDP or D-dimer, renal function, electrolytes, liver tests, glucose, creatine kinase, urinalysis for blood/myoglobin, ECG, and chest radiograph/ABG when severe or respiratory compromise is suspected.
- ▶ **20-min whole-blood clotting test (20WBCT):** place 1-2 mL venous blood in a clean, dry glass tube, leave undisturbed for 20 min, then invert. Persistent liquid blood/no clot indicates clinically important coagulopathy when formal coagulation tests are unavailable.

- ▶ Repeat CBC/coagulation studies every **4 h** if initial tests are normal but envenomation remains possible; after antivenom, repeat about every **6 h** until swelling, vital signs, and coagulation are stable.
- ▶ Watch for recurrent coagulopathy because venom antigens may outlast antivenom; late bleeding can appear after apparent improvement.

Management: first aid, antivenom and ICU care

- ▶ **First aid:** move away from the snake, reassure, keep the patient still, remove rings/bangles/tight clothing, splint the bitten limb in a neutral position, and transport rapidly to a facility with antivenom, airway support, and laboratory testing.
- ▶ Clean with soap and water and cover with a sterile dressing if this does not delay transport. Do **not** incise, suck, apply electric shock, ice, alcohol, stimulants, tight tourniquets, or massage. Pressure-immobilization is not recommended for viperid/cytotoxic bites because it may worsen local tissue injury.
- ▶ **Initial hospital care:** secure airway and breathing; intubate early for face/neck swelling, bulbar weakness, falling ventilation, or respiratory insufficiency. Monitor ECG, oxygen saturation, blood pressure, urine output, and mental status.
- ▶ Establish two large-bore IV lines in unaffected limbs; minimize venipuncture and avoid noncompressible sites because coagulopathy may be profound.
- ▶ Treat shock with isotonic crystalloid **20-40 mL/kg IV**; if shock persists after fluids and antivenom, use vasopressors such as norepinephrine or epinephrine and reassess for venom or antivenom anaphylaxis.
- ▶ **Antivenom is the mainstay.** Use geographically appropriate antivenom that covers Russell's viper venom; in India this generally means locally supplied polyvalent anti-snake venom according to product and institutional protocol.
- ▶ Indications for antivenom: rapidly progressive swelling; swelling involving more than half the limb; severe pain, bruising, blistering, or necrosis; any systemic toxicity; positive 20WBCT or abnormal PT/INR/aPTT/fibrinogen; thrombocytopenia; active bleeding; shock; neurotoxicity; rhabdomyolysis; AKI; or pulmonary edema.
- ▶ Give antivenom **IV only**, start slowly with clinician at bedside, and increase if no reaction; skin testing is neither sensitive nor specific. Keep epinephrine and airway equipment ready.
- ▶ If acute antivenom reaction occurs, stop temporarily and treat with **IM epinephrine 0.01 mg/kg up to 0.5 mg**, IV antihistamine such as diphenhydramine **1 mg/kg up to 50 mg**, and hydrocortisone **2 mg/kg up to 100 mg**; restart slowly at **5-10 mL/h** if antivenom remains necessary.

- ▶ Blood products are reserved for life-threatening bleeding or dangerously low platelets and should be given **after adequate antivenom**, because early replacement can fuel ongoing consumptive coagulopathy.
- ▶ AKI care: maintain perfusion, avoid nephrotoxins, monitor potassium/acidosis/fluid overload, and involve nephrology early; hemodialysis or peritoneal dialysis is used when indicated. ATN is often reversible; cortical necrosis has a poor renal prognosis.

Complications, disposition and follow-up

- ▶ Major complications: shock, DIC-like coagulopathy, intracranial or gastrointestinal bleeding, pulmonary edema, neuromy paralysis, aspiration, AKI, hyperkalemia/acidosis, local necrosis, compartment syndrome, secondary infection, serum sickness, recurrent coagulopathy, chronic limb disability, and late pituitary insufficiency.
- ▶ Suspect compartment syndrome when severe compartment-localized pain is opioid-resistant with weakness, sensory change, cyanosis, or tense swelling. Measure pressure; if **>30-40 mmHg**, give additional antivenom and elevate. Fasciotomy is last resort after antivenom failure and surgical consultation.
- ▶ Provide wound care, tetanus prophylaxis, acetaminophen or opioids for pain, and avoid NSAIDs/salicylates. Routine prophylactic antibiotics are not required unless there is infection, incision, mouth suction, necrosis, or local protocol supports use.
- ▶ Debride necrotic tissue only after coagulopathy is corrected; intact blebs should usually be left undisturbed, ruptured blebs debrided aseptically, and physiotherapy started early after swelling stabilizes.
- ▶ Admit all envenomated patients for at least **24 h**; ICU is indicated for shock, respiratory/neurotoxic signs, severe coagulopathy/bleeding, AKI, pulmonary edema, head/neck bite, progressive findings despite antivenom, or antivenom anaphylaxis.
- ▶ At discharge, warn about recurrent bleeding/coagulopathy over **2-3 weeks**, serum sickness at **1-2 weeks**, wound infection, chronic functional loss, and symptoms of adrenal/pituitary insufficiency after Russell's viper bite. Arrange repeat CBC, PT/INR, and fibrinogen if coagulopathy occurred.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Russell's viper envenomation flowchart:** bite -> first aid/immobilization -> ABC -> local/systemic/renal/neuro assessment -> 20WBCT + labs -> antivenom indications -> IV antivenom -> monitor coagulation, urine output, swelling, respiration -> complications/follow-up.
- ▶ **Pathophysiology diagram:** *Daboia venom* -> local vascular injury/tissue necrosis; procoagulant VICC/DIC -> bleeding; capillary leak/hemolysis/shock -> AKI; neurotoxicity -> ptosis/bulbar weakness/respiratory failure; late pituitary insufficiency.

Clinical / Diagnostic significance

- ▶ A positive 20WBCT is a treatment-triggering bedside sign of viperid coagulopathy when formal PT/fibrinogen are delayed.
- ▶ Oliguria after Russell's viper bite is renal failure until proved otherwise; check creatinine, potassium, urine blood/myoglobin, acid-base status, and involve nephrology early.
- ▶ Ptosis or dysphagia after a viper bite is dangerous, because certain Indian Russell's vipers can cause neurotoxicity; monitor ventilation and intubate before respiratory arrest.
- ▶ Antivenom neutralizes circulating venom, not established ATN/cortical necrosis, fixed paralysis, or necrotic tissue; delay is the key preventable cause of poor outcome.
- ▶ Blood products before antivenom are a common error unless resuscitation is life-saving; replace components after venom neutralization when bleeding demands it.

High-yield exam pointers

- ▶ Russell's viper = **painful swelling + coagulopathy/bleeding + shock + AKI**; add neurotoxicity for certain Indian bites.
- ▶ Mention Indian renal data: AKI after Russell's viper/*Echis* bites 13-32%; oliguria often within 24 h, sometimes 2-3 days.
- ▶ Must write 20WBCT: 1-2 mL blood, clean dry glass tube, 20 min, no clot = coagulopathy.
- ▶ Antivenom indications: progressive local swelling, bleeding/coagulopathy, shock, neurotoxicity, rhabdomyolysis, AKI, pulmonary edema.
- ▶ Antivenom is **IV only**; no skin testing; keep epinephrine ready and restart slowly after treated reaction if still indicated.
- ▶ First aid: immobilize, remove constrictors, rapid transport; **no incision, suction, tourniquet, ice, alcohol, massage, or pressure-immobilization for viperid bites**.
- ▶ Blood products only after adequate antivenom except life-saving resuscitation; avoid NSAIDs and salicylates.
- ▶ Compartment syndrome is treated first with antivenom and pressure monitoring; fasciotomy is last resort.
- ▶ Follow up for **recurrent coagulopathy for 2-3 weeks**, serum sickness, renal recovery, limb function, and late pituitary insufficiency.

SOURCE & COVERAGE

Harrison 22e — “Disorders Caused by Venomous Snakebites and Marine Animal Exposures”; Tintinalli's Emergency Medicine — “Snakebite”; Brenner & Rector's The Kidney — “Indian Subcontinent”; CMDT 2026 — “Poisoning”. Coverage note: the corpus is strong for syndrome,

AKI, monitoring, and general antivenom principles, but does not provide India-specific Russell's viper ASV dosing; dosing should follow local antivenom product and institutional protocol.



Venomous snake bite poisoning

Asked in: Paper IV Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Venomous snake bite poisoning is local and/or systemic envenomation following injection of snake venom through fangs. It is a medical emergency because venom may cause progressive tissue necrosis, coagulopathy, shock, acute kidney injury, rhabdomyolysis, neuromuscular paralysis, and death from respiratory failure. Snakebite envenoming is the deadliest neglected tropical disease; Harrison estimates 1.2-5.5 million bites and 421,000-1,200,000 envenomations worldwide each year. In India, an exam answer should think syndromically: **viperid/cytotoxic-hemotoxic bite** versus **elapid/neuroparalytic bite**.

Epidemiology and important snakes

- ▶ Medically important venomous snakes belong mainly to **Viperidae** (Old World vipers and pit vipers) and **Elapidae** (cobras, kraits, coral snakes, sea snakes, Australian elapids); less common families include Lamprophiidae and venomous colubrids.
- ▶ Indian high-yield clinical pattern: **cobra/krait** bites usually suggest neuroparalysis; **Russell's viper** and **saw-scaled viper** bites suggest local swelling, bleeding/coagulopathy, shock, and renal injury.
- ▶ Harrison lists **cobras, carpet/saw-scaled vipers, Russell's vipers, large African vipers, lancehead pit vipers, and tropical rattlesnakes** among snakes causing large numbers of deaths globally.
- ▶ **Dry bite** means fang marks without venom effect. About **20-25% of pit viper bites** are dry; dry bites may be even more frequent with some snakes, including sea snakes.
- ▶ Risk of death rises with delayed transport, traditional treatment before hospital care, lack of correct antivenom, bites on head/neck, children, pregnancy, shock, respiratory paralysis, and established renal failure.
- ▶ Do not overdepend on colour or popular identification rules; a **safe photograph** may help, but attempted capture increases repeat bite risk.

Venom pathophysiology

- ▶ Snake venoms are complex mixtures of **enzymes, polypeptides, glycoproteins, and other constituents**; composition varies with species, age, diet, geography, and even within the same species.
- ▶ Major mechanisms:

Venom effect	Pathophysiology	Typical clinical result
Cytotoxic / local	Vascular permeability, tissue digestion, local necrosis	Pain, edema, ecchymosis, bullae, tissue loss
Hemotoxic / procoagulant	Fibrinogen and platelet consumption, fibrinolysis, endothelial injury	Bleeding, prolonged PT/INR/aPTT, low fibrinogen, DIC-like state
Neurotoxic	Pre- or postsynaptic neuromuscular blockade	Ptosis, ophthalmoplegia, dysphagia, respiratory paralysis
Myotoxic	Myolysis and rhabdomyolysis	Myalgia, myoglobinuria, hyperkalemia, AKI
Systemic vascular	Vasodilation, capillary leak, hemolysis, bleeding	Hypotension, shock, pulmonary edema

- ▶ Renal failure may follow hypotension, myoglobinuria, coagulopathy, hemolysis, or direct nephrotoxicity; it is often acute tubular necrosis but cortical necrosis is possible.
- ▶ Established presynaptic paralysis, renal failure, and rhabdomyolysis may not be reversed by antivenom; hence early recognition and early antivenom are crucial.

Clinical manifestations and severity

- ▶ **Local envenomation:** fang marks, immediate or delayed pain, progressive swelling, tenderness, ecchymosis, hemorrhagic or serum-filled vesicles/bullae, regional lymphadenopathy, cellulitis-like appearance, necrosis. Swelling may threaten airway after face/neck bites and function after hand/forearm bites.
- ▶ **Systemic viperid/cytotoxic syndrome:** nausea, vomiting, metallic or altered taste, perioral tingling, weakness, tachycardia or bradycardia, hypotension, spontaneous bleeding, thrombocytopenia, coagulopathy, hemolysis, pulmonary edema, AKI.
- ▶ **Neuroparalytic syndrome:** nausea/headache/paresthesias may precede cranial nerve signs; ptosis, diplopia, dysarthria, dysphagia, loss of facial expression, salivation, descending flaccid weakness, diaphragmatic paralysis, aspiration, and respiratory arrest. Symptoms may be delayed for 12 h or more after some elapid bites.
- ▶ **Myotoxic/sea-snake-like syndrome:** variable local pain, generalized myalgia, trismus, rhabdomyolysis, myoglobinuria, hyperkalemia, and progressive flaccid paralysis.
- ▶ Severity grading useful at bedside:

Grade	Practical definition
None / dry bite	Fang marks only; no local progression, systemic features, or laboratory abnormality
Mild	Local pain/ecchymosis/nonprogressive swelling only

Grade	Practical definition
Moderate	Clearly progressive swelling, systemic symptoms/signs, and/or laboratory abnormality
Severe	Neurologic dysfunction, respiratory distress, cardiovascular instability, or shock

First aid and prehospital care

- ▶ Move the patient away from the snake; keep calm and still; **immobilize the bitten limb** in a neutral position and arrange rapid transport to a facility with airway support, laboratory testing, and antivenom.
- ▶ Remove rings, bangles, anklets, footwear, and tight clothing before swelling progresses. Clean with soap and running water if this does not delay transport; cover with a sterile dressing and splint.
- ▶ **Avoid** incision, suction, electric shock, ice, alcohol, stimulants, tight tourniquets, massage, and attempts to capture the snake.
- ▶ Pressure-immobilization may delay systemic absorption in a reliably identified **primarily neurotoxic elapid bite without significant local cytotoxicity**; it is **not recommended for viperid/cytotoxic bites** because it may worsen local injury.
- ▶ If pressure-immobilization is used by a trained rescuer, Harrison gives approximate wrap pressures of **40-70 mmHg for upper limb** and **55-70 mmHg for lower limb**, with complete limb immobilization and carriage to hospital.

Hospital assessment and investigations

- ▶ Start with **ABC**: early endotracheal intubation for face/neck swelling, bulbar weakness, falling vital capacity, difficulty swallowing, or respiratory insufficiency.
- ▶ Monitor vital signs, cardiac rhythm, oxygen saturation, mental status, and **urine output**. Establish two large-bore IV lines in unaffected limbs; minimize venipuncture and avoid noncompressible sites because coagulopathy may develop.
- ▶ Record time of bite, first-aid methods used, progression of symptoms, comorbidities, drugs, pregnancy, and snake identification if safely available.
- ▶ Mark the leading edge of swelling/ecchymosis/tenderness; measure limb circumference at three points every **15 min** until stable, then every **1-2 h**.
- ▶ Laboratory work-up: CBC with platelets, blood group and cross-match, PT/INR/aPTT, fibrinogen, FDP or D-dimer, renal and hepatic function, electrolytes, glucose, creatine kinase, urinalysis for blood/myoglobin; ECG/chest radiograph in severe envenomation or major comorbidity; ABG if respiratory compromise.

- ▶ **20-min whole-blood clotting test (20WBCT):** place 1-2 mL venous blood in a clean dry glass tube, leave undisturbed for **20 min**, then invert. Persistent liquid blood/no clot indicates coagulopathy when laboratory coagulation tests are unavailable.
- ▶ If initial labs are normal, repeat CBC and coagulation tests every **4 h** until systemic envenomation is excluded; after antivenom, recheck about every **6 h** until clinical stability.

Treatment: antivenom and supportive care

- ▶ **Specific antivenom is the mainstay** for significant envenomation. Use the geographically appropriate monovalent or polyvalent antivenom; in India this means locally available polyvalent anti-snake venom as per institutional protocol and manufacturer instructions.
- ▶ Indications for antivenom:
 - progressive local injury: rapidly spreading swelling, swelling involving more than half the limb, extensive bruising/blistering, or severe pain;
 - any systemic feature: hypotension, shock, vomiting not controlled, bleeding, neurotoxicity, rhabdomyolysis, AKI, cardiac collapse;
 - any significant laboratory abnormality: thrombocytopenia, prolonged clotting times, low fibrinogen, positive 20WBCT, rising CK, renal injury.
- ▶ Give antivenom **IV only**; do not inject IM or into a digit. Start slowly with the clinician at bedside, then increase if no reaction. Skin testing is not sensitive or specific and is not useful.
- ▶ Treat acute antivenom reaction by stopping the infusion temporarily and giving **IM epinephrine 0.01 mg/kg up to 0.5 mg**, IV antihistamine such as **diphenhydramine 1 mg/kg up to 50 mg**, and glucocorticoid such as **hydrocortisone 2 mg/kg up to 100 mg**; restart slowly at **5-10 mL/h** if antivenom remains necessary.
- ▶ Resuscitate shock with isotonic crystalloid **20-40 mL/kg IV**; if shock persists after fluids and antivenom, use vasopressors such as norepinephrine or epinephrine.
- ▶ Neurotoxic paralysis: secure airway early; ventilatory support may be needed for days to weeks. In objective postsynaptic neurotoxicity, a trial of acetylcholinesterase inhibitor may be used: atropine **0.6 mg IV**, then neostigmine **0.02 mg/kg IV/IM**; if objective improvement occurs, neostigmine **0.5 mg** every 1 h as needed with atropine cover. This never replaces intubation or antivenom.
- ▶ Blood products are rarely needed and, if essential for life-threatening bleeding or dangerously low platelets, should be given **after adequate antivenom** to avoid fueling consumptive coagulopathy.
- ▶ Wound care: soap-water cleansing, sterile dressing, splintage with padding between digits, tetanus prophylaxis, acetaminophen/opioids for pain, avoid salicylates/NSAIDs, and avoid routine prophylactic antibiotics unless infection, incision, or mouth suction occurred.

Complications, disposition and follow-up

- ▶ Important complications: shock, airway edema, aspiration, respiratory paralysis, DIC-like coagulopathy, recurrent coagulopathy, AKI, rhabdomyolysis, hyperkalemia, tissue necrosis, compartment syndrome, secondary infection, serum sickness, and chronic disability.
- ▶ Suspect compartment syndrome with severe compartment-localized pain resistant to opioids, weakness, sensory change, cyanosis, or apparent pulselessness. Measure pressure; **>30-40 mmHg** indicates additional antivenom and elevation. Fasciotomy is a last resort after antivenom, because fasciotomy is needed in **<1%** of cases in modern series and may increase morbidity.
- ▶ Observe any envenomated patient in hospital for at least **24 h**. An apparently dry viperid bite needs **8-12 h** observation; coral snake/other elapid/sea snake bites need at least **24 h** because systemic toxicity may be delayed.
- ▶ ICU admission: head/neck bite, progressive findings despite initial antivenom, respiratory or cardiovascular instability, severe neurotoxicity, severe coagulopathy/bleeding, renal failure, or acute hypersensitivity to antivenom.
- ▶ Discharge only when swelling is improving, coagulopathy is corrected, pain is controlled, and the patient is ambulatory. Warn about recurrence of bleeding/coagulopathy over **2-3 weeks**, serum sickness at **1-2 weeks**, wound infection, and need for repeat CBC/PT/fibrinogen if coagulopathy occurred.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Flowchart: snakebite management** — Bite -> ABC and immobilization -> classify dry/mild/moderate/severe -> labs including 20WBCT -> antivenom indications -> IV antivenom -> monitor swelling/coagulation/respiration -> complications and follow-up.
- ▶ **Limb monitoring diagram** — fang marks, leading edge of swelling, ecchymosis, bullae, three circumference measurement levels, distal pulse/capillary refill, sensory-motor status, compartment-pressure site.

Clinical / Diagnostic significance

- ▶ Ptosis after snakebite is respiratory failure until proved otherwise; do not wait for cyanosis before intubating or ventilating.
- ▶ 20WBCT is a bedside triage test, not a substitute for PT/INR/aPTT/fibrinogen where available; persistent liquid blood after 20 min is clinically significant.
- ▶ Antivenom reverses circulating venom, not established necrosis, renal failure, or fixed presynaptic paralysis; delay is the main preventable cause of poor outcome.
- ▶ Recurrent coagulopathy occurs because venom antigens may outlast antivenom; repeat labs and counsel against trauma/elective surgery for 2-3 weeks after acute coagulopathy.
- ▶ Routine antibiotics, routine fasciotomy, incision/suction, and tight tourniquets are common harmful errors in exam and practice.

High-yield exam pointers

- ▶ Write the two syndromes first: **hemotoxic/cytotoxic viper bite** and **neuromuscular elapid bite**.
- ▶ First aid mantra: **reassure, immobilize, remove constrictors, rapid transport; no incision, suction, ice, alcohol, or tourniquet**.
- ▶ Must mention **ABC**, early intubation for bulbar/respiratory signs, and mechanical ventilation when needed.
- ▶ Must write investigations: CBC/platelet, PT/INR/aPTT, fibrinogen, FDP/D-dimer, renal function, CK, urine myoglobin, and **20WBCT**.
- ▶ Antivenom indications: progressive swelling, systemic toxicity, neurotoxicity, coagulopathy, rhabdomyolysis, renal failure, shock.
- ▶ Antivenom is **IV only**; manage anaphylaxis with epinephrine and restart slowly if benefit outweighs risk.
- ▶ Blood products only after adequate antivenom; NSAIDs and salicylates are avoided.
- ▶ Compartment syndrome is diagnosed by pressure and treated first with antivenom; fasciotomy is last resort.
- ▶ Observe dry bite 8-12 h, envenomation at least 24 h, and warn about serum sickness and recurrent coagulopathy.

SOURCE & COVERAGE

Harrison 22e — “Disorders Caused by Venomous Snakebites and Marine Animal Exposures”; Tintinalli’s Emergency Medicine — “Snakebite”; CMDT 2026 — “Poisoning”.



What are the risk factors, clinical features and treatment of lead toxicity?

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — Lead (Pb) is a *xenobiotic* heavy metal with **no physiological role and no safe threshold of exposure** — it is theoretically toxic at any level. Toxicity (*plumbism / saturnism*) usually results from **chronic, repeated low-level exposure** rather than a single ingestion, and predominantly injures the **nervous system, haematopoietic system, gastrointestinal tract and kidneys**. Because absorbed lead is ~95–99% sequestered in red cells and bone (bone half-life >20 years), it accumulates silently and causes both acute encephalopathic crises and insidious chronic organ damage.

Risk factors and sources of exposure

- ▶ **Occupational (the dominant adult risk)**: manufacture and recycling of automobile/storage batteries, smelting, soldering, plumbing, demolition or sanding of lead-painted houses and

bridges, stained-glass making, ceramic/pottery glazing, radiator repair, and firing ranges (inhalation of bullet dust).

- ▶ **Environmental / domestic:** ingestion of **paint chips and house dust in homes built before ~1975**, lead-contaminated soil, drinking water from **lead pipes and plumbing/solder**, food or drink from **improperly glazed ceramics or lead-contaminated cookware**, and historic combustion of **leaded gasoline** (now globally phased out) plus electronic-waste recycling.
- ▶ **Ingested / cultural sources:** **contaminated spices, traditional herbal and folk remedies (Ayurvedic medicines, Latino azarcon/greta), contaminated candies, and retained lead bullet fragments lodged in or near a joint** (synovial fluid corrodes the metal → chronic toxicity).
- ▶ **Organic lead** (e.g., *tetraethyl lead* in older fuels) is additionally **absorbed dermally** and is highly neurotoxic.
- ▶ **Host susceptibility factors:** **young children** (hand-to-mouth/pica behaviour, higher fractional GI absorption, immature blood–brain barrier, developing CNS); **nutritional deficiency of iron, calcium and zinc** (enhances GI lead absorption); **pregnancy and lactation** (bone lead is mobilised into blood and crosses the placenta and into breast milk); and genetic polymorphisms (e.g., *ALAD* variants) modifying handling and effect.

Toxicokinetics and mechanism of toxicity

- ▶ **Absorption** via ingestion or inhalation (organic lead also dermally); in blood **95–99% is bound to red cells**, so lead must be measured in **whole blood, not serum**.
- ▶ **Distribution:** soft-tissue half-life ~30 days; ~15% of a dose is deposited in **bone (half-life >20 years)**, the major cumulative reservoir reflected by *KXRF bone-lead* measurement. Excreted mainly in **urine**, also in breast milk.
- ▶ **Molecular toxicity:** interferes with **mitochondrial oxidative phosphorylation**, ATPases and **calcium-dependent second messengers**; binds **sulphydryl groups**; enhances oxidative stress and apoptosis; and substitutes for calcium/zinc in metalloproteins.
- ▶ **Haem-synthesis block (key for exam):** lead **inhibits δ -aminolevulinic acid dehydratase (ALA-dehydratase, ALAD)** and **ferrochelatase** → accumulation of **ALA and coproporphyrin III** in urine and a rise in **free erythrocyte / zinc protoporphyrin (FEP/ZPP)**, with impaired haem formation causing anaemia. Lead intoxication is a recognised differential of *ALA-dehydratase-deficient porphyria*. Inhibition of **pyrimidine-5'-nucleotidase** leaves ribosomal RNA aggregates producing **basophilic stippling** of red cells.

Clinical features

System	Acute / high-level exposure	Chronic / subclinical exposure
CNS (children)	Lead encephalopathy — convulsions, coma, death	Impaired IQ, developmental & neurobehavioural delays,

System	Acute / high-level exposure	Chronic / subclinical exposure
	(BPb >80–120 µg/dL); raised ICP	language/motor/balance/hearing/behaviour & school-performance deficits (BPb 25–60 µg/dL; <i>no safe threshold</i>)
CNS / PNS (adults)	Headache, irritability, lethargy; severe → encephalopathy	* <i>Demyelinating peripheral neuropathy, mainly motor</i> → wrist drop (<i>radial nerve</i>)*, foot drop; slowed reaction time, impaired short-term memory, declining cognition, depression, loss of libido
GI	Lead colic — colicky abdominal pain, anorexia, constipation , nausea	<i>Burton's line</i> — bluish-grey lead line at the gingiva–tooth border
Haematological	Anaemia, impaired haematopoiesis	Anaemia with basophilic stippling ; microcytic in children, normocytic–normochromic in adults; elevated FEP/ZPP
Renal	Proximal tubular dysfunction → Fanconi syndrome , pyuria, azotaemia	Chronic interstitial nephritis and chronic renal failure; hyperuricaemia → saturnine gout
Other	—	Hypertension, ECG conduction delays, ↑cardiovascular morbidity/mortality, reduced sperm counts , spontaneous abortion

- ▶ **Blood-lead severity bands (CMDT/Harrison):** *subclinical* neurodevelopmental effects even at 1–25 µg/dL; 25–60 µg/dL — headache, irritability, subclinical neuropathy, anaemia (children); 60–80 µg/dL — moderate toxicity, impaired neurotransmission; >80–100 µg/dL — severe poisoning/encephalopathy.

Diagnosis / Investigations

- ▶ **Venous whole-blood lead level (BPb)** is the *diagnostic gold standard*. The **CDC blood-lead reference value** is 3.5 µg/dL — exceeding it triggers source investigation; OSHA mandates worker removal at BPb >40 µg/dL (newer proposals: keep <10 µg/dL, remove >20 µg/dL).
- ▶ **Peripheral smear:** normocytic/normochromic (adults) or microcytic (children) anaemia with basophilic stippling.
- ▶ **Biochemical markers of haem-pathway block:** elevated **free erythrocyte / zinc protoporphyrin (FEP/ZPP)**, raised **urinary ALA and coproporphyrin III**.
- ▶ **Imaging:** long-bone x-rays show dense **metaphyseal “lead lines”** in children; abdominal radiograph may reveal radiopaque ingested lead (paint chips, fishing weight, retained bullet).
- ▶ **Bone-lead by KXRF** estimates cumulative body burden (research/specialist).

- ▶ **Screening:** CDC recommends screening US children when they begin to crawl (~6 months).

Treatment

- ▶ **First and most important step — identify and remove the source of exposure (occupational hygiene, abatement of lead paint/water, report to public-health authority); chelation is reserved for symptomatic and/or high-level toxicity*.*
- ▶ **Decontamination:** for recent ingestion of a retained lead object (e.g., fishing weight) visible on x-ray, use **whole-bowel irrigation, endoscopy or surgical removal** (activated charcoal does **not** bind lead).
- ▶ **Supportive care:** secure airway, treat seizures and coma; manage raised ICP in encephalopathy.
- ▶ **Chelation agents** (consult a toxicologist / poison centre, 1-800-222-1222):

Severity	First-line chelation (per CMDT 2026)
Severe — encephalopathy or BPb >70–100 µg/dL	Edetate calcium disodium (CaEDTA) ~50 mg/kg/day (1500 mg/m ² /day) in 4–6 divided doses or continuous IV infusion, + dimercaprol (BAL) 4–5 mg/kg IM every 4 h × 5 days for encephalopathy
Moderate — symptomatic / BPb 45–69 µg/dL	CaEDTA (as above) or oral succimer (DMSA) 10 mg/kg every 8 h × 5 days, then every 12 h × 2 weeks
Mild–moderate, ambulatory	Oral succimer (DMSA) is preferred

- ▶ **Sequencing pearl:** in encephalopathy give **dimercaprol (BAL)** first/with CaEDTA — CaEDTA alone can redistribute lead into the CNS and *worsen encephalopathy*.
- ▶ **Adjuncts:** correct **iron, calcium, magnesium and zinc deficiency** to reduce further lead absorption; **calcium supplementation (1200 mg)** lowers blood lead and limits bone-lead mobilisation in pregnancy; vitamin C is only a weak natural chelator.
- ▶ **Evidence caveats:** a large RCT of chelation in **asymptomatic children (BPb 20–40 µg/dL)** showed **no improvement in IQ**; benefit of chelation for chronic adult cardiovascular outcomes remains unproven (TACT-2 negative).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Haem-synthesis pathway showing the two lead-blocked enzymes.** Labels: *Glycine + Succinyl-CoA* → ALA synthase → δ -ALA → ALA-dehydratase (**BLOCKED by lead**) → Porphobilinogen → ... → Protoporphyrin IX → Ferrochelatase (**BLOCKED by lead**) + Fe^{2+} → Haem; annotate “↑urinary ALA & coproporphyrin III”, “↑FEP/ZPP”, “anaemia”.
- ▶ **Clinical signs schematic of plumbism.** Labels: *Burton’s (gingival) lead line, basophilic stippling on smear, wrist drop (motor neuropathy), lead colic / constipation, metaphyseal lead lines on x-ray, encephalopathy*.

Clinical / Diagnostic significance

- ▶ Suspect lead in any patient with **unexplained abdominal colic + anaemia + peripheral motor neuropathy**, or a child with developmental regression/encephalopathy and a relevant exposure history (old housing, occupation, folk remedies).
- ▶ **Basophilic stippling + microcytic anaemia + raised ZPP** strongly suggests plumbism and helps separate it from iron-deficiency and sideroblastic anaemia.
- ▶ Lead is a **reportable / notifiable** exposure in many jurisdictions; OSHA-style biological monitoring and medical removal protect occupational cohorts.
- ▶ Chronic low-level lead is now an established risk factor for **hypertension, resistant hypertension, chronic kidney disease and cardiovascular mortality** — relevant to the internist beyond overt poisoning.

High-yield exam pointers

- ▶ **No safe blood-lead level**; CDC reference value = 3.5 µg/dL. Measure lead in **whole blood, not serum**.
- ▶ Lead **inhibits ALA-dehydratase and ferrochelatase** → ↑urinary ALA/coproporphyrin, ↑FEP/ZPP, anaemia.
- ▶ **Basophilic stippling** (pyrimidine-5'-nucleotidase inhibition) is the classic smear clue.
- ▶ **Burton's line** = gingival lead line; **wrist drop** = motor (radial) neuropathy; **lead colic** = abdominal pain with constipation.
- ▶ **Children get metaphyseal “lead lines”** on x-ray and are most vulnerable (pica, ↑absorption, developing brain).
- ▶ Encephalopathy appears at BPb >80–120 µg/dL.
- ▶ **Treatment hierarchy**: remove source → supportive care → chelation. **Severe/encephalopathy** → CaEDTA + dimercaprol (BAL given first); **moderate/oral** → succimer (DMSA).
- ▶ Iron/calcium/zinc repletion reduces lead absorption; **calcium 1200 mg** curbs bone-lead mobilisation in pregnancy.
- ▶ **Saturnine gout** = lead nephropathy with hyperuricaemia/gout.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Heavy Metal Poisoning” (lead sources, toxicokinetics, blood-lead toxicity bands, diagnosis, chelation) and “The Porphyrrias” (lead inhibition of ALA-dehydratase; raised urinary ALA/coproporphyrin III); smear chapter on basophilic stippling in lead poisoning.
- ▶ **CMDT 2026** — “Poisoning” chapter, *Lead* section (clinical findings, blood-lead severity ranges, CaEDTA / dimercaprol / succimer regimens and doses, decontamination, source removal).

Coverage note: The spec lists no dedicated toxicology subspecialty textbook; grounding is from Harrison 22e + CMDT 2026, which cover this topic comprehensively. *Burton's line*, *saturnine gout*, ferrochelatase inhibition and the BAL-before-EDTA sequencing pearl are universally accepted standard internal medicine added for exam completeness; the corpus explicitly supports the gingival “lead line”, ALA-dehydratase inhibition, raised protoporphyrin, and the chelation regimens.



Hematology & oncology



Apoptosis pathways and role in cancer

Asked in: Paper I Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — *Apoptosis* is the genetically programmed, energy-dependent, **non-inflammatory** form of regulated cell death that culls aged, terminally differentiated, or irreparably damaged cells and so maintains tissue homeostasis. It is executed by a conserved family of cysteine-aspartate proteases (**caspases**) triggered through two principal routes — the **extrinsic (death-receptor)** pathway and the **intrinsic (mitochondrial)** pathway — that converge on common executioner caspases. Because the net cell number in a tissue reflects the balance between proliferation and death, *evasion of apoptosis* is a core enabling hallmark of malignancy: it lets cells carrying oncogenic mutations and genetic instability survive, expand clonally, and resist chemotherapy and radiation.

Regulated cell death — apoptosis and its alternatives

- ▶ The cell can respond to lethal stress by several distinct programmes: **apoptosis**, **autophagy** (lysosomal degradation of proteins/organelles), and irreversible growth arrest (**senescence**), plus newer caspase-variant deaths.
- ▶ Other regulated death modes (roles in cancer still being defined): **pyroptosis** — caspase-1-dependent, cleaves *gasdermins* to form plasma-membrane pores; **ferroptosis** — iron- and reactive-oxygen-species-dependent lipid peroxidation; **necroptosis** — caspase-independent, with cell rupture causing inflammation and tissue damage.
- ▶ Apoptosis is morphologically defined: cell shrinkage, chromatin condensation and nuclear fragmentation (pathologists' *karyorrhexis*, “nucleus bursting”), lamin and cytoskeletal cleavage, internucleosomal DNA degradation, and membrane blebbing into apoptotic bodies that are phagocytosed **without an inflammatory response** — contrasting with necrosis.

Feature	Apoptosis	Necrosis
Trigger	Physiologic or pathologic, programmed	Severe injury/ischaemia
Energy (ATP)	Required (active)	Not required (passive)
Cell volume	Shrinkage	Swelling
DNA	Internucleosomal cleavage ("ladder")	Random smear
Membrane	Intact; apoptotic bodies	Early rupture
Inflammation	Absent	Present

The extrinsic (death-receptor) pathway

- ▶ Activated by cross-linking of **TNF-receptor-superfamily** death receptors by their ligands: **CD95 (Fas)** by Fas ligand, and **DR4/DR5** by **TRAIL** (TNF-related apoptosis-inducing ligand).
- ▶ Ligation recruits the adaptor **FADD** (Fas-associated death domain) and **procaspase-8** to the receptor's cytoplasmic death domains, forming the death-inducing signalling complex (DISC).
- ▶ **Caspase-8** is autoactivated and directly cleaves the executioner **caspases-3 and -7**, producing the morphologic features of apoptosis.
- ▶ Physiologic brake: **FLIP**, which competes with caspase-8 for FADD; *decoy receptors* also blunt TRAIL signalling. Normal cells often express these inhibitors while tumour cells may not — the basis for therapeutic TRAIL/agonist-antibody selectivity.

The intrinsic (mitochondrial) pathway and the Bcl-2 family

- ▶ Initiated by **mitochondrial outer-membrane permeabilisation (MOMP)** in response to *DNA damage, oncogene-induced proliferation, loss of attachment to extracellular matrix, growth-factor deprivation, hypoxia, chemotherapy and radiation*.
- ▶ MOMP releases **cytochrome c** and **SMAC/DIABLO** from the mitochondrial intermembrane space. Cytochrome c associates with **dATP**, **procaspase-9** and the adaptor **APAF-1** to assemble the **apoptosome**, which activates **caspase-9** and then the effector caspases.
- ▶ **SMAC** binds and neutralises **inhibitor-of-apoptosis proteins (IAPs)** — e.g. **XIAP** — which otherwise restrain caspase activation.
- ▶ MOMP is governed by the **Bcl-2 family**, whose relative levels at the mitochondrial membrane set the apoptotic threshold:

Class	Members	Action
Anti-apoptotic (guardians)	Bcl-2, Bcl-XL, Mcl-1	Anchor to outer membrane; sequester pro-apoptotic proteins via a hydrophobic BH (Bcl-2-homology) pocket

Class	Members	Action
Pro-apoptotic effectors	Bax, Bak	Oligomerise to form outer-membrane pores → cytochrome c release
BH3-only activators/sensitisers	Bad, Bim, Bid, Puma, Noxa	Neutralise anti-apoptotic members and/or activate Bax/Bak

- ▶ If BH3-only proteins are mopped up by Bcl-2/Bcl-XL/Mcl-1, pores do not form and apoptosis is averted; when they predominate, Bax/Bak oligomerise and the cell dies. The **mitochondrion** is thus the central regulatory organelle of intrinsic apoptosis.

Convergence, executioner caspases and survival signalling

- ▶ **Initiator caspases** (-8, -9, -10) sit atop each pathway; **executioner/effector caspases** (-3, -6, -7) are the common downstream blades that cleave structural and regulatory substrates (caspase-activated DNase, lamins, cytoskeletal proteins).
- ▶ **Cross-talk:** caspase-8 cleaves the BH3-only protein **Bid** to truncated tBid, amplifying the death signal through the mitochondrial pathway — linking extrinsic and intrinsic routes.
- ▶ **p53 — “guardian of the genome”:** on DNA damage, ATM/ATR and Chk1/Chk2 phosphorylate p53 and MDM2, freeing p53 from MDM2-mediated degradation; oncogene stress induces **p14ARF**, which binds MDM2 and likewise stabilises p53. p53 then transactivates cell-cycle arrest (p21) or, if damage is severe, apoptosis via the pro-apoptotic BH3-only members **Puma and Noxa**.
- ▶ **Pro-survival pathways subverted in cancer:** the **PI3K/Akt** axis (Akt phosphorylates and inactivates BAD and FOXO/FKHR), **NF-κB** (held inactive by IκB; IKK phosphorylation → proteasomal IκB degradation → NF-κB-driven survival genes), and epigenetic silencing of **APAF-1** and caspase-8.

Apoptosis evasion as a hallmark of cancer

- ▶ **Bcl-2 overexpression** from the t(14;18) translocation underlies *follicular lymphoma*; Bcl-2 is also high in chronic lymphocytic leukaemia (CLL) and in prostate, breast, lung cancers and melanoma.
- ▶ **p53 inactivation** (the most frequent mutation in human cancer, chromosome 17p; germline loss = **Li-Fraumeni syndrome**; aflatoxin gives the codon-249 arginine→serine signature mutation in hepatocellular carcinoma) removes the damage-triggered death programme. **HPV E6** degrades p53 (and E7 inactivates Rb).
- ▶ Up-regulation of **IAPs/XIAP**, expression of **decoy death receptors** and **FLIP**, loss of **APAF-1/caspase-8**, and constitutive **PI3K-Akt / NF-κB** signalling all raise the apoptotic threshold.

- ▶ **Anoikis** — apoptosis normally triggered by loss of ECM contact — is suppressed in cells that invade and metastasise. **Cancer stem cells** further resist therapy through high anti-apoptotic Bcl-2 levels combined with ABC/P-glycoprotein (MDR) drug-efflux pumps.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Two-pathway apoptosis schematic.** Left **extrinsic limb**: FasL/TRAIL → *Fas* / *DR4* / *DR5* → *FADD* → *procaspase-8* → *caspase-8*. Right **intrinsic limb**: death stimuli (DNA damage, growth-factor withdrawal, chemo/radiation) → *BH3-only proteins* → *Bax/Bak* pore in mitochondrial outer membrane → release of *cytochrome c* + *SMAC*; *cytochrome c* + *APAF-1* + *dATP* + *procaspase-9* → *apoptosome* → *caspase-9*; *Bcl-2/Bcl-XL/Mcl-1* shown blocking *Bax/Bak*; *SMAC* inhibiting *IAP/XIAP*. Both converge on *executioner caspases-3/-7* → substrate cleavage → DNA degradation, chromatin condensation, lamin cleavage (apoptosis). Show *caspase-8* → *tBid* arrow linking the two limbs. Label drug targets: **venetoclax/BH3-mimetic** → *Bcl-2*, **SMAC-mimetic** → *IAP*, **bortezomib** → **proteasome/NF-κB**.
- ▶ **Bcl-2 rheostat bar**: anti-apoptotic (*Bcl-2*, *Bcl-XL*, *Mcl-1*) on one side versus pro-apoptotic (*Bax*, *Bak*, *BH3-only*) on the other, balance point = apoptotic threshold.

Clinical / Diagnostic significance

- ▶ **BH3 mimetics**: **venetoclax (ABT-199)**, an oral BCL-2 inhibitor, is approved for relapsed/refractory CLL with 17p deletion and is active in AML (e.g. with azacitidine/hypomethylating agents); the tool compound **ABT-737** is synergistic with docetaxel preclinically — proof of “targeting the dependence.”
- ▶ **Restoring the death signal**: recombinant TRAIL and agonist DR4/DR5 antibodies kill tumour (not normal) cells in preclinical work; **SMAC mimetics** lower the apoptotic threshold by neutralising IAPs; **HDAC inhibitors** up-regulate death receptors (DR4/5, FAS) and down-regulate XIAP.
- ▶ **Indirect pro-apoptotic agents**: **proteasome inhibitors** (bortezomib) prevent IκB destruction and block NF-κB survival signalling; **PI3K/Akt** and **BTK inhibitors** sensitise cells to apoptosis; **PARP inhibitors** exploit defective DNA-damage repair (BRCA-mutant tumours) to drive lethal DNA damage; **taxanes** stabilise microtubules and phosphorylate Bcl-2.
- ▶ **Diagnostic readouts**: apoptosis is detected by **annexin-V** (phosphatidylserine externalisation), TUNEL assay, caspase-3 activation, and the DNA “ladder” — used in tissue prognostication and as pharmacodynamic markers of drug response.
- ▶ **Therapeutic principle**: tumours “addicted” to anti-apoptotic proteins may be *more* vulnerable than normal cells to agents that re-engage apoptosis — the rationale for the whole BH3-mimetic class.

High-yield exam pointers

- ▶ Two pathways: **extrinsic** (Fas/DR4/DR5 → FADD → caspase-8) and **intrinsic** (mitochondrial: cytochrome c + APAF-1 + procaspase-9 → **apoptosome** → caspase-9); both converge on **executioner caspases-3/-7**.
- ▶ **Bcl-2 family rheostat**: anti-apoptotic **Bcl-2/Bcl-XL/Mcl-1** vs effectors **Bax/Bak** vs **BH3-only** (**Bad, Bim, Bid, Puma, Noxa**) sets MOMP.
- ▶ **SMAC/DIABLO** neutralises **IAP/XIAP**; **FLIP** blocks caspase-8 at the DISC; **caspase-8** → **tBid** cross-links the pathways.
- ▶ **p53** (“guardian of the genome”) drives apoptosis via **Puma/Noxa**; most-mutated cancer gene; germline loss = **Li-Fraumeni**.
- ▶ Apoptosis evasion = **hallmark of cancer**: Bcl-2 overexpression via **t(14;18)** in follicular lymphoma; loss of anoikis aids metastasis.
- ▶ **Venetoclax** (**BH3 mimetic, anti-BCL-2**) — CLL with 17p deletion, AML — is the flagship clinical translation.
- ▶ Apoptosis is **ATP-dependent, non-inflammatory**; necrosis is passive and inflammatory.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Cancer Cell Biology” (apoptosis pathways, Bcl-2 family, extrinsic/intrinsic mechanisms, p53/MDM2/p14ARF checkpoint, evasion of apoptosis, cancer stem cells, *Figs. 77-1 and 77-5*) and “Cancer Genetics.”
- ▶ **DeVita, Hellman & Rosenberg’s Cancer: Principles & Practice of Oncology, 12e** — apoptosis-directed therapeutics: BH3 mimetics (**ABT-737, ABT-199/venetoclax**), taxane-induced Bcl-2 phosphorylation and caspase-8 scaffolding, venetoclax–azacitidine in AML.
- ▶ Coverage note: Harrison provides the full mechanistic and clinical content; DeVita’s full text in this corpus is treatment-weighted, so it was used chiefly for the apoptosis-targeting drug detail. Apoptosis-versus-necrosis morphology, initiator/executioner caspase numbering, annexin-V/TUNEL detection, and the Bid→tBid cross-talk are standard, universally accepted internal-medicine content included for completeness.



Causes and management of Aplastic anemia

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — Aplastic anemia is **pancytopenia accompanied by a hypocellular (“empty,” fat-replaced) bone marrow**, with no abnormal infiltrate and no marrow fibrosis. It results from quantitative and qualitative failure of the pluripotent **haematopoietic stem cell (HSC)**, most often through immune-mediated (T-cell) destruction, less often from direct chemical/physical injury or an

inherited stem-cell defect. It is distinguished from peripheral cytopenias (haemolysis, ITP, hypersplenism) by the *deficient production* of cells. Incidence is **2 per million/year in Europe and Israel** and **5–7 per million in Thailand and China**, with a **biphasic age distribution** (major peak in the teens–twenties, second peak in older adults) and equal sex incidence.

Classification & Causes (Aetiology)

Aplastic anemia is broadly **acquired** (~80%, usually immune/idiopathic) or **inherited/constitutional** (inherited bone marrow failure syndromes, IBMFS). The major recognised associations:

Category	Specific causes
Idiopathic (immune)	Most common; T-cell–mediated autoimmune HSC destruction
Radiation	Marrow aplasia is a major acute sequela; accidental/occupational/therapeutic
Chemicals	Benzene (best-substantiated), toluene, insecticides
Drugs — regular (dose-dependent)	Cytotoxic chemotherapy: alkylators, antimetabolites, antimetotics
Drugs — idiosyncratic	Chloramphenicol , gold salts, sulfonamides, phenylbutazone/NSAIDs, anticonvulsants (phenytoin, carbamazepine, felbamate), antithyroid drugs (methimazole, PTU, carbimazole), penicillamine, allopurinol, quinacrine, tolbutamide
Viruses / infection	Seronegative (non-A, non-B, non-C) hepatitis (~5%, young men, very severe), EBV (infectious mononucleosis), parvovirus B19, CMV, HIV-1
Immune disorders	Eosinophilic fasciitis, SLE, thymoma/thymic carcinoma, hypogammaglobulinaemia, transfusion-associated GVHD, large granular lymphocytosis (LGL)
Clonal / other	Paroxysmal nocturnal haemoglobinuria (PNH); pregnancy (resolves with delivery)
Inherited (constitutional)	Fanconi anemia (AR; <i>FANCA</i> commonest; short stature, café-au-lait spots, thumb/radius & GU anomalies); Dyskeratosis congenita / telomere biology disorders (<i>DKC1</i> X-linked; <i>TERC/TERT</i> AD; <i>TINF2</i> shelterin); Shwachman-Diamond (<i>SBDS</i> ; neutropenia + pancreatic insufficiency); GATA2 deficiency , RUNX1 familial platelet disorder

- *Pearl*: “Association is not causation” — an incriminated drug may have merely been given to treat the *first* symptom of marrow failure (e.g., NSAIDs for petechiae, antibiotics for fever).

Pathophysiology

- ▶ **Immune destruction (the dominant mechanism in acquired disease):** activated, oligoclonal cytotoxic CD8 T cells and Type-1 cytokines (chiefly interferon- γ and TNF) suppress and kill CD34⁺ progenitors. IFN- γ induces Fas on CD34 cells $\rightarrow$ Fas/FasL-mediated apoptosis. The stem-cell pool falls to $\leq 1\%$ of normal in severe disease; CD34⁺ cells and committed progenitors are virtually absent. Response to anti-thymocyte globulin proves the immune basis.
- ▶ **Constitutional defect:** intrinsic stem-cell flaw — defective DNA inter-strand cross-link repair (Fanconi, FANCD2 mono-ubiquitination pathway), defective telomere maintenance/shelterin (telomere disorders), or impaired transcriptional regulation (GATA2, RUNX1) $\rightarrow$ limited proliferative capacity and genomic instability.
- ▶ **Chemical/drug injury:** generation of reactive electrophilic intermediates (e.g., benzene hydroquinones/quinolones) that bind cellular macromolecules; genetically determined detoxification differences explain idiosyncratic susceptibility.
- ▶ **Clonal escape:** PNH clones (PIG-A mutation) and somatic myeloid mutations may emerge, reflecting immune selection and explaining later clonal evolution.

Clinical features & Laboratory diagnosis

- ▶ **History/exam:** insidious or abrupt onset. **Bleeding is the commonest early symptom** (bruising, gum oozing, epistaxis, menorrhagia, petechiae); anaemic symptoms (fatigue, dyspnoea); infection is an *unusual* presenting feature (unlike agranulocytosis). Patients often “look well.” **Lymphadenopathy and splenomegaly are atypical** and should prompt another diagnosis. Look for IBMFS clues: short stature/café-au-lait (Fanconi), nail dystrophy/leukoplakia (dyskeratosis congenita), premature greying/pulmonary or hepatic fibrosis (telomere disorder), warts/unusual infections (GATA2).
- ▶ **Blood:** pancytopenia; normochromic, often macrocytic (raised MCV) RBCs; reticulocytopenia; no immature/abnormal forms (their presence suggests leukaemia/MDS).
- ▶ **Bone marrow:** aspirate dilute; trephine biopsy (>1 cm) hypocellular with haematopoietic cells <25%, mostly fat; megakaryocytes greatly reduced/absent; residual cells morphologically normal. MRI spine shows fatty marrow.
- ▶ **Ancillary / aetiological work-up:** chromosome breakage test (diepoxybutane / mitomycin C) in children & young adults for Fanconi; leucocyte telomere length for telomere disorders; flow cytometry for a PNH clone (CD55/CD59, FLAER); marrow cytogenetics (abnormal favours MDS); serology (EBV, HIV, hepatitis); next-generation sequencing germline + myeloid panels to separate inherited and clonal disease.

Severity grading (Camitta criteria) — guides treatment

Grade	Criteria
Severe aplastic anemia (SAA)	Marrow cellularity <25% plus any two of three: ANC <500/ μ L, platelets <20,000/ μ L, corrected reticulocyte count <1% (absolute reticulocytes <60,000/ μ L)
Very severe (VSAA)	As SAA but ANC <200/ μ L
Non-severe / moderate	Cytopenias not meeting SAA thresholds

- ▶ Better modern predictors of treatment response: **absolute reticulocytes >25,000/ μ L** and **lymphocytes >1000/ μ L**; presence of a PNH clone or small somatic mutations also informs prognosis.

Management

General principles: stop any suspected drug/chemical; glucocorticoids are **not effective as primary therapy**; spontaneous recovery is rare, so treat early in SAA. Choice between transplant and immunosuppression hinges on **age, donor availability and depth of neutropenia**. HLA-type early and **avoid family-member transfusions** in transplant candidates (sensitisation). Use **leucodepleted, irradiated** blood products.

1. Haematopoietic stem cell (bone marrow) transplantation — definitive/curative

- ▶ **First choice for the younger patient (<40 yr) with an HLA-matched sibling donor.** Long-term survival in children $\approx$ 90%; CMTD quotes **>80% under age 20** and **$\sim$ 65–70% in those 20–50**, dropping 10–15% with matched-unrelated donors.
- ▶ Matched-unrelated-donor transplant: initial option in children, salvage in adults failing immunosuppression. **Haploidentical** transplant with **post-transplant cyclophosphamide (PT-Cy)** is increasingly used as a donor is almost always available; cord blood for children.
- ▶ Radiation is generally omitted from conditioning (except some alternative-donor protocols) to reduce late malignancy.

2. Immunosuppressive “triple therapy” — for those without a donor or aged >40 yr

- ▶ **Standard of care (FDA-approved 2018): horse ATG + ciclosporin + eltrombopag**, achieving haematologic response in **70–80%** (CMTD cites up to $\sim$ 90%; complete responses $\sim$ 50%).
- ▶ **Equine (horse) ATG 40 mg/kg/day IV for 4 days** — *superior to rabbit ATG* (better response/survival); give with **methylprednisolone/prednisone 1–2 mg/kg/day for $\sim$ 1 week then taper over 2 weeks** to prevent infusion reactions and **serum sickness** (occurs $\sim$ day 10).
- ▶ **Ciclosporin 6 mg/kg PO twice daily**, level-adjusted, generally continued **$\sim$ 2 years**; toxicities — **nephrotoxicity, hypertension, seizures** (tacrolimus is an alternative).
- ▶ **Eltrombopag (TPO-receptor mimetic) 150 mg PO once daily for 6 months** then stop in responders; stimulates the HSC; main toxicity **hepatotoxicity**. Romiplostim is an alternative.

- ▶ Response usually within **1–3 months** (assessed at ~4 months); responses are often partial. **Relapse** occurs in up to one-third (often on tapering ciclosporin/eltrombopag) and usually responds to re-treatment. Patients failing immunosuppression can be salvaged by later transplant.

3. **Androgens** — fluoxymesterone 10–20 mg/day or **danazol 200 mg PO twice daily**; modest, unproven benefit; useful in **moderate disease and telomere disorders** (up-regulate telomerase).

4. Supportive care (essential to survive to definitive therapy)

- ▶ **Infection:** neutropenic fever is an emergency — **prompt empirical broad-spectrum parenteral antibiotics**; suspect **fungal** disease (*Candida*, *Aspergillus*) with persistent fever and add antifungals; granulocyte transfusions for refractory infection.
- ▶ **Platelets:** prophylactic transfusion to keep count **>10,000/μL**; HLA-matched/single-donor units if alloimmunised; suppress menstruation; avoid aspirin/NSAIDs.
- ▶ **Red cells:** transfuse to Hb ~70 g/L (**90 g/L if cardiac/pulmonary disease**); add iron chelation (**deferoxamine/deferasirox**) around the **50th transfusion** to prevent secondary haemochromatosis.
- ▶ **Not useful:** EPO and G-CSF are **ineffective** in aplastic anemia; reverse isolation and gut decontamination do not reduce mortality.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology schematic of aplastic anemia (after Harrison Fig 107-1):** three aetiologic arrows — *Physical/chemical damage*, *Immune (T-cell) destruction*, *Constitutional genetic defect* — converging on “**empty bone marrow replaced by fat**”, with treatment boxes beneath each: *HGF/Support + BMT*; *IST + BMT + Eltrombopag*; *Sex hormones + BMT*. Labels: HSC, CD34⁺ cell, cytotoxic T cell, IFN-γ, Fas/FasL, apoptosis, fatty marrow.
- ▶ **Treatment algorithm:** Confirm SAA → assess age & HLA-matched sibling → *Young + matched sibling* → **Allogeneic HSCT**; *No donor / >40 yr* → **Horse ATG + Ciclosporin + Eltrombopag (triple therapy)** → response → taper; no response → **MUD/haploidentical transplant** or second IST. Side panel: **supportive care** (antibiotics, platelets >10k, RBC to Hb 70, chelation).

Clinical / Diagnostic significance

- ▶ **Differentiate from hypoplastic MDS** (favoured by dysplasia, increased blasts, clonal cytogenetics, spliceosome/cohesin mutations) and from **hypocellular hairy cell leukaemia** (splenomegaly, hairy cells) — both are pancytopenia mimics.
- ▶ A **PNH clone** at diagnosis supports an immune mechanism and predicts immunosuppression-responsiveness; it may later expand to clinical haemolytic PNH.

- ▶ Clonal evolution to MDS/AML or PNH occurs in ~10–15% (up to one-quarter at 10 years) after immunosuppression — long-term marrow surveillance is mandatory.
- ▶ Recognising IBMFS (Fanconi, telomere disorders, GATA2) changes management: avoid standard high-dose conditioning, screen relatives, and counsel on malignancy risk.

High-yield exam pointers

- ▶ Triad = pancytopenia + reticulocytopenia + hypocellular (fatty) marrow with no organomegaly.
- ▶ Commonest acquired cause = idiopathic (immune, T-cell mediated); classic toxins = benzene and chloramphenicol; ~5% follow seronegative hepatitis in young men.
- ▶ Camitta SAA: marrow <25% + 2 of (ANC <500, platelets <20,000, retic <1%); VSAA = ANC <200.
- ▶ Cure = HLA-matched sibling allogeneic transplant (first choice in young patients).
- ▶ No donor / older → triple therapy = horse ATG + ciclosporin + eltrombopag (~70–90% response); horse ATG > rabbit ATG.
- ▶ Eltrombopag = TPO mimetic, 150 mg/day × 6 months, hepatotoxicity; ciclosporin continued ~2 years.
- ▶ Glucocorticoids, EPO and G-CSF are NOT primary therapy.
- ▶ Platelets transfused to keep >10,000/μL; RBC to Hb 70 g/L; iron chelation from ~50th unit.
- ▶ Always exclude Fanconi anemia (DEB/mitomycin C chromosome breakage) and telomere disorders in young patients.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia” (Neal S. Young & Emma M. Groarke) — primary source for definition, classification/aetiology, pathophysiology, Camitta severity, transplant and triple-therapy (ATG/ciclosporin/eltrombopag), androgens and supportive care.
- ▶ **CMDT 2026** — “Blood Disorders” (Aplastic Anemia) — current severity definition, drug regimens/doses (equine ATG 40 mg/kg × 4 days, ciclosporin 6 mg/kg BID, eltrombopag 150 mg/day, danazol/fluoxymesterone) and survival figures.
- ▶ **Coverage note:** The dedicated specialty text for this spec, *DeVita's Cancer (Principles & Practice of Oncology)*, is an oncology/haematologic-malignancy reference and addresses aplastic anemia only peripherally (as a differential of hypoplastic MDS and via the eltrombopag-immunosuppression trial); the substantive grounding here is therefore Harrison 22e (authored by the world authority on the disease) and CMDT 2026. The

VSAA threshold (ANC <200) is universally accepted Camitta-criteria internal medicine and is included as standard.



Cell cycle and regulation

Asked in: Paper I Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — The **cell division cycle** is the ordered, tightly regulated sequence of events by which a cell duplicates its genome and divides into two daughter cells. It comprises four active phases — **G1** (growth/preparation for DNA synthesis), **S** (DNA synthesis), **G2** (preparation to divide) and **M** (mitosis) — together with a quiescent out-of-cycle state, **G0**. Orderly progression is driven by **cyclin–cyclin-dependent kinase (CDK) complexes** and policed at a series of **checkpoints** that verify genomic integrity before allowing the cell to advance. Loss of this control — through activation of positive regulators (oncogenes such as *Ras*, *Myc*, cyclin D) or inactivation of negative regulators (tumour-suppressors *Rb* and *p53*) — produces the deregulated proliferation that is the defining feature of cancer.

Phases of the cell cycle

- ▶ **G1 (gap 1)**: the cell grows, senses growth-factor and nutrient signals, and takes “inventory” — Is the DNA-repair machinery in place? Are nucleotides, replicating enzymes and energy adequate? A late-G1 point of no return, the **restriction (R) point**, commits the cell irreversibly to division; beyond it the cell no longer needs external mitogens.
- ▶ **S (synthesis)**: semiconservative replication; each segment of DNA must be copied **once and only once**.
- ▶ **G2 (gap 2)**: the cell confirms faithful, complete duplication and synthesises the mitotic spindle and proteins needed to produce two daughter cells.
- ▶ **M (mitosis)**: prophase → metaphase → anaphase → telophase + cytokinesis; chromosomes segregate to opposite poles.
- ▶ **G0 (quiescence)**: a reversible resting state outside the cycle, maintained by signals including **Notch** and **STING** pathways; cells can be recalled into G1 by appropriate mitogenic/tissue-repair signals (e.g., hepatocytes after partial hepatectomy).

The molecular engine — cyclins, CDKs and CDK inhibitors

- ▶ **CDKs** are serine/threonine kinases that are catalytically inert until bound by their regulatory **cyclin** partner; the cyclin level oscillates (“cyclic”) through the cycle while CDK protein is constant. Sequential cyclin–CDK activation phosphorylates downstream substrates to push the cell forward.
- ▶ Activity is opposed by two families of **CDK inhibitors (CKIs)**:

- **INK4 family** — $p16^{INK4a}$ and $p15^{INK4b}$ — specifically inhibit CDK4/6.
- **CIP/KIP family** — $p21^{Cip1/Waf1}$, $p27^{Kip1}$, $p57^{Kip2}$ — broadly inhibit cyclin-CDK complexes; $p21$ is the principal transcriptional effector of p53.

Phase / transition	Cyclin	CDK partner	Key action
Mid-late G1	Cyclin D	CDK4 / CDK6	Initial phosphorylation (inactivation) of Rb
G1 → S	Cyclin E	CDK2	Completes Rb inactivation; fires the R point
S	Cyclin A	CDK2	Drives/limits DNA replication
G2 → M	Cyclin A / B	CDK1 (Cdc2)	Triggers mitotic entry

Cell-cycle checkpoints — the quality-control machinery

Checkpoints are surveillance circuits that arrest the cycle until prerequisites are met; the critical proteins controlling them are frequently the **tumour-suppressor genes** mutated in cancer.

- ▶ **G1/S (restriction) checkpoint:** decides whether the cell is fit to replicate. When ready, cyclin D-CDK4/6 then cyclin E-CDK2 **phosphorylate Rb**, releasing the transcription factor **E2F/DP1**, which switches on S-phase genes. If not ready, CKIs ($p21$, $p16$, $p27$) block the CDKs. *Nearly every cancer has a defect in the G1 checkpoint.*
- ▶ **Intra-S checkpoint:** slows replication when DNA damage is sensed, allowing repair.
- ▶ **G2/M checkpoint:** verifies that DNA is fully and accurately replicated before mitosis. DNA damage activates the **ATM/ATR → Chk1/Chk2 → p53** axis (and WEE1 kinase, which restrains CDK1); damaged cells are held in G2.
- ▶ **M-phase spindle (spindle-assembly) checkpoint:** ensures every chromosome is correctly attached to the mitotic spindle before anaphase. Failure permits **aneuploidy** (abnormal chromosome number), a frequent feature of cancers.

The two master tumour-suppressors — Rb and p53

- ▶ **Retinoblastoma protein (Rb)** is the molecular “brake” at G1/S. In its hypophosphorylated state it sequesters E2F/DP1; CDK-mediated hyperphosphorylation releases E2F and licenses S-phase entry. Rb is inactivated in cancer by mutation/deletion (RB1 on **13q14**), by CDK4/6 hyperactivity, by loss of $p16^{INK4a}$, or by viral oncoproteins. Per **Knudson’s two-hit hypothesis** (derived from inherited vs sporadic retinoblastoma), **both alleles** of a tumour-suppressor must be inactivated; germline carriers inherit one “hit” and need only one somatic event, explaining earlier and multiple tumours.

- ▶ **p53** — “guardian of the genome” — a transcription factor normally kept at very low levels by MDM2 (an E3 ubiquitin ligase that both blocks p53 transactivation and targets it for proteasomal degradation). Two activating circuits:
 - **DNA-damage checkpoint:** ATM/ATR and Chk1/Chk2 **phosphorylate p53 and MDM2**, dissociating them; stabilised p53 then drives **cell-cycle arrest** (via *p21*), **DNA repair**, or, if damage is irreparable, **apoptosis** (via pro-apoptotic Bcl-2 members *Noxa* and *Puma*). Inducers include hypoxia, ionising/UV radiation, chemotherapy, ribonucleotide depletion and telomere shortening.
 - **Oncogene checkpoint:** hyperproliferative oncogenes (*Myc*, *E2F*) induce **p14^{ARF}**, which binds MDM2 and rescues p53 — eliminating “renegade” cells by senescence or apoptosis.
- ▶ **Clinical correlates of p53:** *TP53* on 17p is among the most commonly mutated genes in human cancer; germline mutation causes **Li–Fraumeni syndrome**; aflatoxin produces a signature **codon 249 Arg→Ser** mutation in hepatocellular carcinoma; HPV E6 degrades p53 and HPV E7 inactivates Rb — together required for epithelial transformation.

Replicative senescence, telomeres and loss of apoptosis

- ▶ Normal somatic cells divide only ~25–50 population doublings, then enter **replicative senescence** (irreversible growth arrest, cells remaining viable) — a tumour-protective mechanism mediated by the **Rb, p16^{INK4a} and p53** pathways.
- ▶ Each S phase fails to copy chromosome tips, so **telomeres** (tandem TTAGGG repeats; ~15–20 kb at birth, forming a protective T-loop) shorten progressively; critically short telomeres trigger a p53-dependent damage response. **>90% of human cancers re-express telomerase** (catalytic subunit **hTERT** + RNA template) to maintain telomeres and achieve replicative immortality. *Germline telomerase defects cause dyskeratosis congenita.*
- ▶ Cancer cells also subvert **programmed cell death**: the **intrinsic (mitochondrial)** pathway — cytochrome c/SMAC release, APAF-1/caspase-9 activation, governed by the **Bcl-2 family** balance — and the **extrinsic (death-receptor)** pathway — Fas/DR4/DR5 → FADD → caspase-8. Overexpression of antiapoptotic **Bcl-2** or loss of p53 lets genetically damaged cells survive and accumulate further mutations.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Circular cell-cycle map:** draw the ring G1 → S → G2 → M with **G0** branching off G1. Label the **restriction point** in late G1; mark the **G1/S, intra-S, G2/M and M (spindle)** checkpoints; annotate each segment with its cyclin–CDK pair (**Cyclin D–CDK4/6**, **Cyclin E–CDK2**, **Cyclin A–CDK2**, **Cyclin B–CDK1**) and the CKIs (**INK4**, **CIP/KIP**).
- ▶ **Rb/p53 control circuit:** boxes for **Cyclin D–CDK4/6 → P-Rb → release of E2F/DP1 → S-phase genes**, with *p16* inhibiting CDK4/6; and a parallel limb **DNA damage → ATM/ATR**

→ Chk1/Chk2 → p53 ⊣ MDM2 → p21 (arrest) / Noxa-Puma (apoptosis), with *p14ARF* linking oncogenes to MDM2.

Clinical / Diagnostic significance

- ▶ **Therapeutic exploitation:** CDK4/6 inhibitors — *palbociclib*, *ribociclib*, *abemaciclib* — combined with endocrine therapy markedly improve progression-free survival in **ER-positive/HER2-negative metastatic breast cancer** (e.g., palbociclib + letrozole in PALOMA-2); intact **RB1** is required for response, and *RB1* loss confers resistance.
- ▶ **Disease associations:** Cyclin D1 (*CCND1*) overexpression from t(11;14) defines **mantle cell lymphoma**; *CDKN2A* (*p16*) deletion/methylation is common across many tumours; **CDK4 amplification** characterises well-/de-differentiated liposarcoma.
- ▶ **Checkpoint as a drug target:** **WEE1 inhibitors** (e.g., adavosertib) are synthetically lethal in *TP53*-deficient tumours (which rely on the G2/M checkpoint); **PARP inhibitors** exploit DNA-repair defects (*BRCA1/2*); proteasome inhibitors (bortezomib) raise p21/p27 and induce arrest/apoptosis in myeloma.
- ▶ **Proliferation markers:** **Ki-67** indexes the growth fraction; tumours grow by **Gompertzian kinetics** (growth fraction falls from 100% to <5% by presentation), explaining chemoresponsiveness and dose-limiting marrow/gut toxicity.

High-yield exam pointers

- ▶ Four active phases **G1–S–G2–M** + quiescent **G0**; commitment occurs at the **restriction point** in late G1.
- ▶ **Cyclins** (oscillating) activate **CDKs** (constant); pairs: D–CDK4/6, E–CDK2, A–CDK2, B–CDK1.
- ▶ **CKIs:** **INK4** (p16, p15) inhibit CDK4/6; **CIP/KIP** (p21, p27, p57) inhibit broadly; **p21** is the p53 effector.
- ▶ Checkpoints: G1/S (**Rb–E2F**), intra-S, G2/M (p53, ATM/ATR–Chk, WEE1), M **spindle-assembly** (prevents aneuploidy).
- ▶ **Rb** = G1/S brake; phosphorylation releases **E2F/DP1**. **Knudson two-hit** for tumour-suppressors (*RB1* 13q14).
- ▶ **p53** = “guardian of the genome” (17p); MDM2-regulated; ATM/ATR–Chk activate it → *p21* arrest, repair, or *Noxa/Puma* apoptosis; **p14^{ARF}** = oncogene checkpoint.
- ▶ **HPV E6** → **p53 degradation**; **HPV E7** → **Rb inactivation**; **Li–Fraumeni** = germline *TP53*; aflatoxin **codon 249**.
- ▶ **Telomere shortening** (TTAGGG) limits division; **telomerase/hTERT** reactivated in >90% of cancers → immortality.

- ▶ Therapeutics: CDK4/6 inhibitors (palbo/ribo/abemaciclib) in ER+ breast cancer; WEE1 and PARP inhibitors exploit checkpoint/repair defects.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Cancer Cell Biology” (cell-cycle phases and checkpoints, Rb–E2F, p53/MDM2/p14ARF, ATM/ATR–Chk, spindle checkpoint, senescence/telomerase, apoptosis) and “Cancer Genetics” (Knudson two-hit hypothesis, tumour-suppressor biallelic inactivation).
- ▶ **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — CDK4/6–cyclin D–RB1–E2F axis, *CDKN2A/CCND1/CCNE1*, Cyclin E–CDK2/Cyclin B–CDK1, CDK4/6 inhibitors (palbociclib/ribociclib/abemaciclib, PALOMA-2), WEE1 inhibition and synthetic lethality, mantle-cell t(11;14).
- ▶ **Coverage note:** The corpus is rich on checkpoint and Rb/p53 biology. The full per-phase cyclin–CDK pairing table (Cyclin A–CDK2, Cyclin B–CDK1) is standard, universally-accepted cell biology; the corpus explicitly names cyclins A, B, D, E and CDK1/2/4/6 and the Cyclin D–CDK4/6, Cyclin E–CDK2 pairings, but does not tabulate every pairing. *p57^Kip2* is included as a standard CIP/KIP member though the corpus names principally p21 and p27.



Coagulation Cascade

Asked in: Paper I Jul 2020 · Paper I Nov 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — The **coagulation cascade** is the sequence of reactions in which inactive plasma clotting factors (zymogens) are converted, in an amplifying, enzyme-driven chain, into active serine proteases that culminate in **thrombin** generation and the conversion of soluble **fibrinogen** to an insoluble **fibrin** clot. Originally described as a *waterfall* or *cascade* (Macfarlane; Davie & Ratnoff, 1964) with separate **extrinsic** and **intrinsic** limbs converging on a **common pathway**, it is now understood that *in vivo* coagulation is initiated by **tissue factor** (TF) exposure with critical amplification through intrinsic-pathway elements. It operates on activated, phospholipid (anionic) cell membranes, requires **calcium** (**factor IV**), and is one arm of secondary hemostasis (fibrin formation), distinct from primary hemostasis (platelet plug).

Classification of clotting factors

- ▶ **Nomenclature:** Factors are numbered I–XIII (Roman numerals); the activated form carries the suffix “a” (e.g., factor Xa). There is no factor VI.
- ▶ **Functional groups:**

Group	Factors	Key feature
Fibrinogen / thrombin-sensitive group	I (fibrinogen), V (<i>proaccelerin</i> , labile), VIII (<i>antihemophilic factor</i>), XIII (<i>fibrin-stabilising factor</i>)	Consumed in clotting; V & VIII are cofactors activated by thrombin
Prothrombin / vitamin K-dependent group	II (prothrombin), VII (<i>proconvertin</i>), IX (<i>Christmas factor</i>), X (<i>Stuart-Prower factor</i>)	Need vitamin K for γ -carboxylation; also anticoagulant proteins C, S, Z
Contact group	XII (<i>Hageman</i>), XI, prekallikrein (PK), high-molecular-weight kininogen (HMWK)	Initiate intrinsic limb <i>in vitro</i>
Cofactors	Tissue factor (III), Ca^{2+} (IV), V, VIII	Accelerate but are not enzymes

- ▶ **Vitamin K dependence:** Factors II, VII, IX, X and the natural anticoagulants **protein C**, **protein S**, **protein Z** require vitamin K-dependent γ -glutamyl carboxylation of glutamic acid residues ($\rightarrow$ Gla residues), a step essential for Ca^{2+} -mediated binding to phospholipid surfaces. Warfarin inhibits **vitamin K epoxide reductase (VKORC1)**, depleting reduced vitamin K (Fig. 121-3).
- ▶ All coagulation factors are **synthesised in the liver** (TF and VWF are extrahepatic); hepatic failure $\rightarrow$ combined factor deficiencies.

The cascade: extrinsic, intrinsic & common pathways

- ▶ **Extrinsic (TF) pathway — physiologic initiator:** Vascular injury exposes blood to **tissue factor**, constitutively expressed on subendothelial smooth-muscle cells/fibroblasts (also on circulating microparticles). TF binds **factor VIIa**; the TF/VIIa complex activates **factor X $\rightarrow$ Xa** directly, and also activates **factor IX $\rightarrow$ IXa** (indirect route). Tested by the PT.
- ▶ **Intrinsic (contact) pathway:** *In vitro* begins with **factor XII, prekallikrein, HMWK** on a negatively charged surface $\rightarrow$ XIIa $\rightarrow$ activates XI $\rightarrow$ XIa $\rightarrow$ IXa (with VIIIa cofactor) $\rightarrow$ Xa. Tested by the aPTT. *In vivo* the contact factors are dispensable — **factor XII deficiency causes a long aPTT but NO bleeding**; physiologically **factor XI is activated chiefly by thrombin** (positive feedback), so XIa amplifies/propagates rather than initiates.
- ▶ **Common pathway:** **Factor Xa**, with cofactor **Va** on phospholipid (the *prothrombinase complex*), converts **prothrombin (II) $\rightarrow$ thrombin (IIa)**. Thrombin then cleaves **fibrinogen $\rightarrow$ fibrin monomer**, which polymerises; **factor XIIIa** (activated by thrombin) covalently **cross-links** fibrin to a stable clot. Tested by aPTT and PT; the fibrinogen $\rightarrow$ fibrin step by the **thrombin time (TT)**.
- ▶ **Thrombin — the pivotal protease (central amplifier):** Beyond cleaving fibrinogen, thrombin feeds back to activate **FV $\rightarrow$ Va**, **FVIII $\rightarrow$ VIIIa**, **FXI $\rightarrow$ XIa**, and **FXIII $\rightarrow$ XIIIa**, hugely amplifying its own generation; it also activates platelets and protein C.
- ▶ **Modern in vivo (cell-based) view** — three overlapping phases on cell surfaces:

- ▶ **Initiation:** TF/VIIa on TF-bearing cells generates small amounts of Xa and thrombin.
- ▶ **Amplification:** Trace thrombin activates platelets and cofactors V, VIII, XI on the platelet surface.
- ▶ **Propagation:** The “tenase” (IXa/VIIIa) and “prothrombinase” (Xa/Va) complexes assemble on activated platelet phospholipid → a **thrombin burst** → robust fibrin clot.
- ▶ **Key insight (Harrison):** Once TF/VIIa/Xa forms, **TFPI shuts off the TF/VIIa trigger**, making sustained coagulation dependent on the **amplification loop via factors XI, IX and VIII** — explaining why severe FVIII/FIX deficiency (haemophilia) bleeds despite an intact extrinsic start.

Natural anticoagulant (antithrombotic) mechanisms

Physiologic inhibitors localise clotting to the site of injury and preserve fluidity:

- ▶ **Antithrombin (AT):** Major plasma inhibitor of **thrombin and other serine proteases** (Xa, IXa, XIa, XIIa); forms a 1:1 covalent complex. Its rate is accelerated **several-thousand-fold** by **heparin / endothelial heparan sulfate** — the basis of heparin action. Deficiency → lifelong VTE risk.
- ▶ **Protein C – protein S system:** Thrombin bound to endothelial **thrombomodulin** (with **endothelial protein C receptor, EPCR**) activates **protein C** → **activated protein C (APC)**; APC, with cofactor **protein S**, proteolytically **inactivates FVa and FVIIIa** (Fig. 69-3). A point mutation at the APC cleavage site in FVa (**factor V Leiden**) confers **APC resistance** and a hypercoagulable state.
- ▶ **Tissue factor pathway inhibitor (TFPI):** Inhibits the TF/VIIa/Xa complex, switching off extrinsic initiation; partly released from endothelium by heparin.
- ▶ **Endothelial antithrombotic products:** prostacyclin (PGI₂), nitric oxide, ecto-ADPase/CD39 (inhibit platelets), plus heparan proteoglycans and thrombomodulin.

The fibrinolytic system

- ▶ **Plasmin** is the key fibrinolytic protease, generated from **plasminogen** by **tissue plasminogen activator (tPA)** and **urokinase (uPA)**, which cleave the **Arg560-Val561** bond.
- ▶ **Fibrin specificity:** Lysine-binding sites let plasminogen and tPA bind fibrin, forming a ternary (fibrin–plasminogen–tPA) complex that localises and accelerates plasmin generation on the clot.
- ▶ **Products:** Plasmin digests fibrin → **fibrin degradation products (FDPs)**; lysis of *cross-linked* fibrin releases **d-dimers** (specific marker of clot turnover; used to exclude DVT/PE; rises with age → age-adjusted cut-offs).
- ▶ **Regulation (three levels):** (1) **PAI-1 and PAI-2** inhibit tPA/uPA; (2) **TAFI** (thrombin-activatable fibrinolysis inhibitor) removes terminal lysines and limits lysis; (3) **α₂-antiplasmin** inactivates free plasmin.

Laboratory assessment of the cascade

Test	What it measures	Prolonged in
PT / INR	Extrinsic + common: I, II, V, VII, X	FVII deficiency, warfarin , early vitamin K deficiency, liver disease, direct Xa inhibitors (may be normal on apixaban)
aPTT	Intrinsic + common: XII, XI, IX, VIII, X, V, II, I, PK, HMWK	Haemophilia A/B, heparin , lupus anticoagulant, FXI/XII deficiency, vWD
Thrombin time (TT)	Fibrinogen → fibrin	Heparin, direct thrombin inhibitors (dabigatran, argatroban, bivalirudin) , dys-/afibrinogenaemia
Reptilase time	Fibrinogen → fibrin (heparin-insensitive)	Dysfibrinogenaemia (normal with heparin)
Clot solubility	Fibrin cross-linking	Factor XIII deficiency

- ▶ $INR = (PT_{\text{patient}} / PT_{\text{mean-normal}})^{ISI}$, where ISI = International Sensitivity Index; standardises warfarin monitoring across thromboplastins.
- ▶ **Mixing study:** Patient plasma + normal plasma 1:1. **Corrects** → factor deficiency; **fails to correct** → inhibitor (e.g., lupus anticoagulant, acquired FVIII inhibitor — the latter prolongs further on 37 °C incubation).
- ▶ Anti-Xa assay monitors LMWH/UFH and direct Xa inhibitors; **bleeding time is no longer recommended** for predicting bleeding risk.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — The coagulation cascade (Y-shaped scheme).** Left limb labelled *Intrinsic (contact) pathway*: XII → XIIa (with PK, HMWK) → XI → XIa → IX → IXa; right limb *Extrinsic pathway*: Tissue factor + VIIa. Both converge on X → Xa (*common pathway*); show VIIIa (tenase cofactor) and Va (prothrombinase cofactor) on a **phospholipid + Ca²⁺** surface; then **Prothrombin (II) → Thrombin (IIa) → Fibrinogen (I) → Fibrin → (XIIIa) cross-linked fibrin clot**. Bracket the aPTT over the intrinsic+common limbs and the PT over the extrinsic+common limbs; mark TT at the fibrinogen→fibrin step.
- ▶ **Diagram 2 — Natural anticoagulant loops.** Label TFPI (on TF/VIIa/Xa), **antithrombin + heparin** (on thrombin & Xa), and the **thrombomodulin–EPCR → APC + protein S** loop inactivating FVa/FVIIIa.

Clinical / Diagnostic significance

- ▶ **Pattern recognition:** Isolated ↑PT → FVII deficiency/early warfarin; isolated ↑aPTT → haemophilia A/B or FXI deficiency (or heparin/lupus anticoagulant); **both** ↑ → deficiency of II, V, X or fibrinogen, late vitamin K deficiency, liver disease, **DIC**.
- ▶ **Haemophilia A (FVIII) & B (FIX):** X-linked; severity by factor level — **severe** <1%, **moderate** 1–5%, **mild** 6–30%; hallmark **haemarthrosis** and deep-muscle bleeds; treat with factor concentrates, **emicizumab** (bispecific FIXa/FX antibody mimicking FVIIIa), or gene therapy.
- ▶ **Acquired coagulopathies:** liver disease (combined deficiency + thrombocytopenia), **vitamin K deficiency/warfarin** (factors II, VII, IX, X), and **DIC** (consumption → ↑PT/aPTT, ↓fibrinogen, ↓platelets, ↑d-dimer).
- ▶ **Reversal/replacement:** **4-factor PCC** (II, VII, IX, X + proteins C & S) for warfarin reversal; **FFP**, **cryoprecipitate** (fibrinogen, VIII, XIII, VWF); **FXIII concentrate** for FXIII deficiency.
- ▶ **Thrombophilia:** Factor V Leiden, prothrombin **G20210A**, and deficiencies of **antithrombin**, **protein C**, **protein S** predispose to VTE; test only when results change management, in steady state off anticoagulants.

High-yield exam pointers

- ▶ **Thrombin (IIa)** is the central enzyme — converts fibrinogen→fibrin, activates V, VIII, XI, XIII, platelets and protein C.
- ▶ *In vivo* the cascade is **TF-initiated**; the intrinsic limb chiefly **amplifies** — hence **FXII deficiency = long aPTT but no bleeding**.
- ▶ **Vitamin K-dependent factors:** II, VII, IX, X + **proteins C, S, Z** (mnemonic “1972 → 2,7,9,10”).
- ▶ FVII has the **shortest half-life** → PT/INR is the earliest test to prolong with warfarin/vitamin K deficiency.
- ▶ **PT = extrinsic; aPTT = intrinsic; both = common pathway; TT = fibrinogen→fibrin.**
- ▶ **Factor XIII** is *not* detected by PT/aPTT — diagnose by **clot solubility (urea)**.
- ▶ **APC resistance = factor V Leiden** is the commonest inherited thrombophilia.
- ▶ **d-dimer** = lysis of cross-linked fibrin; sensitive for excluding VTE, not specific.
- ▶ **Mixing study corrects** = deficiency; **does not correct** = inhibitor.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “*Bleeding and Thrombosis*” (steps of haemostasis, the TF-initiated cascade with intrinsic amplification, antithrombotic mechanisms, fibrinolytic system, and laboratory evaluation incl. PT/aPTT/TT/INR and mixing studies) and “*Coagulation Disorders*” (Fig. 121-1 cascade with aPTT/PT/TT mapping, vitamin K cycle Fig. 121-3, factor groups, haemophilia, PCC composition).
- ▶ **CMDT 2026** — *Blood Disorders* (current laboratory/management framing).

- *Coverage note:* The Harrison corpus presents the cascade physiology, natural anticoagulants and fibrinolysis in full; classical factor **eponyms/synonyms** (Christmas, Stuart-Prower, Hageman, etc.) and the **three-phase cell-based model** (**initiation/amplification/propagation**) are universally accepted standard haematology nomenclature added for completeness, consistent with Harrison's TF-initiation-plus-amplification description. The spec's DeVita reference (heme malignancies) is peripheral to cascade physiology and was not required.



Describe Erythropoiesis. Write briefly on Polycythaemia rubra vera

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Erythropoiesis is the regulated process of red cell production within the **erythron** — the dynamic “organ” comprising the rapidly proliferating pool of marrow erythroid precursors plus the large mass of circulating red cells. It begins with the pluripotent **haematopoietic stem cell** (HSC) and is driven principally by the hormone **erythropoietin** (EPO) so that tissue oxygen delivery is matched to demand. **Polycythaemia rubra vera** (PV) — polycythaemia *vera* — is a clonal HSC (myeloproliferative) neoplasm in which phenotypically normal red cells, granulocytes and platelets accumulate **in the absence of a recognisable physiologic stimulus**, almost always driven by a *JAK2* mutation.

Erythropoiesis — lineage, cell sequence and kinetics

- **Haematopoiesis** produces all formed elements from the HSC, which can generate red cells, all granulocytes, monocytes, platelets and immune cells. Erythroid cells arise from a **common erythroid/megakaryocytic progenitor** whose development requires the transcription factors **GATA-1** and **FOG-1** (friend of GATA-1).
- After lineage commitment, progenitors fall progressively under the control of growth factors/hormones; **EPO is the primary regulatory hormone**. EPO maintains committed erythroid progenitors, which **undergo apoptosis (programmed cell death) in its absence**.
- The first morphologically recognisable erythroid precursor is the **pronormoblast (proerythroblast)**; it undergoes **four to five cell divisions**, yielding **16–32 mature red cells** per pronormoblast.
- The mature red cell is **8 µm, anucleate, biconcave/discoid** and highly pliable; the biconcave disc maximises surface area for oxygen exchange and membrane integrity is sustained by **intracellular ATP**.

- ▶ **Kinetics:** normal production replaces 0.8–1% of circulating red cells daily, since the average red cell survives 100–120 days. Marrow cellularity is expressed as the **myeloid:erythroid (M:E) ratio**, normally ~2.5:1 (range 2:1–5:1).
- ▶ The **reticulocyte** (residual ribosomal RNA, seen as *polychromasia* on Wright–Giemsa) is the youngest red cell released; the **reticulocyte count is the clinical marker of effective erythropoiesis** — high with haemolysis/blood loss, low/inappropriate with hypoproliferative marrow.

Erythropoietin and oxygen-sensing regulation (HIF axis)

- ▶ EPO is a **glycoprotein hormone** produced and released by **peritubular capillary lining (interstitial) cells of the kidney**, with a small contribution from **hepatocytes**.
- ▶ The **fundamental stimulus is oxygen availability** for tissue metabolism. The master regulator is **hypoxia-inducible factor-1 α (HIF-1 α)**:
 - In **normoxia**, HIF-1 α is **hydroxylated at a key proline**, ubiquitinated and degraded by the **proteasome** → low EPO.
 - In **hypoxia**, hydroxylation fails → HIF-1 α partners with other proteins, **translocates to the nucleus and upregulates the EPO gene**.
- ▶ Impaired renal O₂ delivery (and hence ↑EPO) results from **decreased red cell mass (anaemia)**, **impaired O₂ loading of haemoglobin/hypoxaemia**, a **high-O₂-affinity haemoglobin**, or **reduced renal blood flow** (e.g., renal artery stenosis).
- ▶ Normal plasma EPO is **10–25 U/L**; when haemoglobin falls below **100–120 g/L (10–12 g/dL)**, EPO rises logarithmically in proportion to anaemia severity. EPO **half-life is 6–9 h**.
- ▶ EPO binds receptors on marrow erythroid precursors → proliferation and maturation; with stimulation, **red cell output can increase 4–5 fold over 1–2 weeks**, but only if substrate is adequate.
- ▶ An effective erythron therefore requires (1) normal renal EPO production, (2) a functioning erythroid marrow, and (3) adequate substrate — **iron, vitamin B12 and folate**.

Polycythaemia — definition and classification

- ▶ **Polycythaemia** = haemoglobin above normal; *erythrocytosis* strictly implies a **documented increase in red cell mass**. A rise may be **real (absolute)** or **apparent (relative/spurious)** from plasma volume contraction.
- ▶ Thresholds prompting concern: **Hb >17 g/dL (men) / >15 g/dL (women)**; **Hct >50% (men)/>45% (women)** may be abnormal; **Hct >60% (men)/>55% (women)** almost invariably reflects a raised red cell mass. Red cell mass **<36 mL/kg (men) / <32 mL/kg (women)** indicates spurious polycythaemia.

Category	Mechanism	Examples
Relative / spurious	↓ plasma volume, normal red cell mass	Dehydration, diuretics, alcohol/tobacco; Gaisböck's syndrome (stress erythrocytosis)
Primary	Intrinsic clonal marrow defect; EPO low/normal	Polycythaemia vera; EPO-receptor mutation; familial polycythaemia
Secondary — appropriate EPO	Tissue hypoxia → physiologic ↑EPO	High altitude, chronic lung disease, sleep apnoea, cyanotic heart disease, CO poisoning ("smoker's polycythaemia"), high-O ₂ -affinity haemoglobinopathy
Secondary — inappropriate EPO	Autonomous/ectopic EPO; HIF-pathway defects	Renal cysts/artery stenosis, post-transplant; tumours — hypernephroma, hepatoma, cerebellar haemangioblastoma, uterine myoma, pheochromocytoma; Chuvash polycythaemia (VHL), PHD2/EGLN1, HIF-2α/EPAS1 mutations; exogenous androgens, recombinant EPO, SGLT2 inhibitors

Polycythaemia rubra vera — pathogenesis and clinical features

- ▶ **Pathogenesis:** PV is the **commonest myeloproliferative neoplasm**, incidence ~2.5/100,000 (rising with age to >10/100,000). The central lesion is a mutation (V617F — valine→phenylalanine) in the **autoinhibitory pseudokinase domain of JAK2**, causing constitutive kinase activation**.
- ▶ JAK2 is the cognate non-receptor tyrosine kinase for the **EPO and thrombopoietin receptors**. Constitutive activation produces **EPO hypersensitivity, EPO-independent erythroid colony formation, ↑Bcl-XL and apoptosis resistance**.
- ▶ >95% of PV patients carry JAK2 V617F; most of the remainder carry **exon 12 mutations**. JAK2 lies on chromosome 9p; uniparental disomy causing **homozygosity for V617F** occurs in ~60% of PV. Non-random cytogenetic changes (del 20q, del 13q, trisomy 9) occur in up to 30%.
- ▶ **Clinical features** — PV is a *panmyelopathy*; presentation is often an **incidental high Hb/Hct/red cell count**:
 - **Hyperviscosity:** vertigo, tinnitus, headache, visual disturbance, TIAs; systolic hypertension; *ruddy* (plethoric) complexion.

- **Thrombosis (arterial & venous)** — the dominant complication; cerebral, cardiac and mesenteric vessels; **Budd–Chiari (hepatic vein) thrombosis**, classically in young women (the only thrombosis specifically linked to JAK2 V617F); **portal vein thrombosis** commoner in men.
- **Bleeding**: easy bruising, epistaxis, GI haemorrhage; extreme thrombocytosis ($>900,000/\mu\text{L}$) causes **acquired von Willebrand's disease**.
- **Erythromelalgia** (erythema, burning, pain of digits $\pm$ infarction), **aquagenic pruritus**, splenomegaly, peptic ulcer disease, and **hyperuricaemia** $\rightarrow$ **secondary gout / uric acid stones**.

PV — diagnosis

- ▶ Diagnosis is straightforward when **erythrocytosis coexists with leukocytosis, thrombocytosis or splenomegaly**. With isolated red cell elevation it is harder, because in PV the **plasma volume expands and can mask a raised red cell mass** (especially in women) — true erythrocytosis cannot be reliably separated from plasma contraction unless **Hb ≥ 20 g/dL (Hct $\geq 60\%$)**.
- ▶ **Serum EPO** is the pivotal screening test: **low/unmeasurable EPO favours PV**, whereas an **elevated EPO points to a secondary cause**.
- ▶ **Quantitative JAK2 V617F / exon 12 assay by next-generation sequencing is now the confirmatory test and has superseded surrogate tests. Supportive findings: leukocytosis, raised absolute basophil count, thrombocytosis*.*
- ▶ Only **three causes** produce a **microcytic erythrocytosis**: **β -thalassaemia trait, hypoxic erythrocytosis and PV** (the latter two via associated iron deficiency, with raised RDW). Bone marrow aspirate/biopsy is **non-specific** (may resemble ET/PMF).
- ▶ *Standard add (WHO 2016 criteria, not detailed in the provided text):* Hb >16.5 g/dL (men)/ >16.0 g/dL (women) or raised red cell mass + trilineage marrow panmyelosis + JAK2 mutation, with **subnormal serum EPO** as a minor criterion.

PV — management

- ▶ PV is **indolent** (course measured in decades); **thrombosis from erythrocytosis is the most significant complication**, so red cell mass control is mandatory.

Modality	Role / target
Phlebotomy	First-line; maintain Hct $<45\%$ (men)/ $<42\%$ (women) [Hb ≤ 14 / ≤ 12 g/dL]; induces iron deficiency limiting re-expansion — usually only every ~3 months once iron-deplete
Low-dose aspirin (salicylate)	Reduces thrombosis — only if red cell mass is controlled ; risk of bleeding (esp. age >60) if uncontrolled

Modality	Role / target
Anticoagulation	After a thrombotic event; newer oral anticoagulants preferred (no monitoring)
Hydroxyurea	Cytoreduction; does not target the malignant HSC and is mutagenic/leukemogenic — short-course
Pegylated interferon- α	Targets involved HSC, non-mutagenic; ~20% complete haematologic/molecular remission
Ruxolitinib (JAK1/2 inhibitor)	Refractory pruritus, symptomatic splenomegaly (replaces splenectomy)
Anagrelide	Lowers platelets (PDE inhibitor); marrow-sparing but cardiotoxic/nephrotoxic in elderly
Allopurinol	Hyperuricaemia when cytoreduction is used; tranexamic/ ϵ -aminocaproic acid for vWD-related bleeding

- ▶ Avoid alkylating agents and radioactive ^{32}P — strongly leukaemogenic.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Erythropoiesis pathway (vertical flow):** HSC $\rightarrow$ common myeloid progenitor $\rightarrow$ BFU-E $\rightarrow$ CFU-E $\rightarrow$ Pronormoblast $\rightarrow$ basophilic normoblast $\rightarrow$ polychromatophilic normoblast $\rightarrow$ orthochromatic normoblast $\rightarrow$ Reticulocyte $\rightarrow$ Mature RBC. **Side-label:** EPO acting at CFU-E/pronormoblast; GATA-1/FOG-1** at commitment; “16–32 RBC per pronormoblast”; “lifespan 100–120 days”.
- ▶ **Diagram 2 — Renal O_2 -sensing/EPO feedback loop:** labels Tissue hypoxia $\rightarrow$ Kidney (peritubular cells) $\rightarrow$ HIF-1 α stabilised $\rightarrow$ $\uparrow$ EPO $\rightarrow$ Erythroid marrow $\rightarrow$ $\uparrow$ Red cell mass $\rightarrow$ $\uparrow$ O_2 delivery $\rightarrow$ (negative feedback) $\rightarrow$ HIF-1 α hydroxylated/degraded.

Clinical / Diagnostic significance

- ▶ Serum EPO + JAK2 mutation together separate PV (low EPO, JAK2+) from secondary polycythaemia (high EPO) — order both simultaneously.
- ▶ A “normal” Hct in a PV patient with massive splenomegaly should be assumed to mask a raised red cell mass until proven otherwise.
- ▶ Suspect PV in any patient (esp. a young woman) with Budd–Chiari/splanchnic vein thrombosis, aquagenic pruritus or erythromelalgia.
- ▶ The reticulocyte count triages anaemia (high = haemolysis/blood loss; low = hypoproliferative) and reflects EPO-driven erythropoiesis — the mirror image of the polycythaemia work-up.

High-yield exam pointers

- ▶ EPO source = renal peritubular interstitial cells; master switch = HIF-1 α (degraded in normoxia via proline hydroxylation).
- ▶ Pronormoblast $\rightarrow$ 4–5 divisions $\rightarrow$ 16–32 RBCs; RBC lifespan 100–120 days; daily turnover 0.8–1%; normal M:E ratio 2.5:1.
- ▶ Normal EPO 10–25 U/L; rises once Hb <10–12 g/dL; half-life 6–9 h.
- ▶ PV = JAK2 V617F (>95%), exon 12 in most others; low/absent serum EPO is the hallmark.
- ▶ Hct targets: <45% men / <42% women; phlebotomy + low-dose aspirin are first-line.
- ▶ Budd–Chiari is the thrombosis specifically tied to JAK2 V617F.
- ▶ Only 3 causes of microcytic erythrocytosis: β -thalassaemia trait, hypoxic erythrocytosis, PV.
- ▶ Avoid ^{32}P / alkylators (leukaemogenic); hydroxyurea is short-course; pegIFN- α and ruxolitinib target the disease clone.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 66 “Anemia and Polycythemia” (erythropoiesis, EPO/HIF regulation, definition and classification of polycythaemia) and Ch 108 “Polycythemia Vera and Other Myeloproliferative Neoplasms” (PV pathogenesis, clinical features, diagnosis, treatment). *Coverage note:* the intermediate erythroid maturation stages (BFU-E/CFU-E, basophilic $\rightarrow$ orthochromatic normoblast) and the explicit WHO 2016 diagnostic criteria are universally accepted standard haematology added for completeness — they are not spelled out verbatim in the provided chapters (which name only the *pronormoblast* and *reticulocyte*, and present a JAK2/EPO-based diagnostic algorithm).



Describe Vitamin B12 metabolism. Write briefly about the Neurological manifestations of Vitamin B12 deficiency

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Vitamin B12 (cobalamin) is a water-soluble cobalt-containing vitamin synthesised solely by micro-organisms; humans obtain it only from animal foods. It is the obligatory cofactor for just two human enzymatic reactions, yet its deficiency produces both a **megaloblastic anaemia** (defective DNA synthesis) and a distinctive **neurological syndrome** (demyelination), the latter often dominating the picture in the non-anaemic patient. Understanding its metabolism — structure, dietary source, intrinsic-factor-dependent absorption, plasma transport and intracellular function — explains why deficiency develops slowly, why pernicious anaemia is the commonest cause, and how the neuropathy arises.

Structure and biochemical forms

- ▶ All cobalamins have a **cobalt atom at the centre of a corrin ring**. They differ only in the upper axial ligand.
- ▶ **Adenosylcobalamin (2-deoxyadenosyl / ado-cobalamin)** — the main natural form, located in **mitochondria**; cofactor for **L-methylmalonyl-CoA mutase**.
- ▶ **Methylcobalamin** — the predominant form in **human plasma and cell cytoplasm**; cofactor for **methionine synthase**.
- ▶ Minor amounts of **hydroxocobalamin** are present; methyl- and ado-cobalamin are converted to it rapidly on exposure to light (relevant to the therapeutic forms used).

Dietary sources, requirement and body stores

Parameter	Value (Harrison 22e)
Source	Synthesised only by micro-organisms; for humans, animal origin only — meat, fish, dairy. Plant foods free of B12 unless bacterially contaminated
Dietary content (Western diet)	5–30 µg/day
Daily loss / requirement	1–3 µg/day (~0.1% of body stores); body cannot degrade cobalamin
Body stores	2–3 mg, sufficient for 3–4 years if intake stops

- ▶ Because stores are large and an enterohepatic circulation conserves cobalamin, dietary deficiency (strict vegans) develops only after years; in contrast, **malabsorption** depletes stores faster because biliary reabsorption is also lost.

Absorption (intrinsic-factor pathway)

- ▶ Two mechanisms exist: a **passive** route (through buccal, duodenal and ileal mucosa; rapid but very inefficient — <1% of an oral dose) and the physiological **active** route (ileal, **intrinsic-factor dependent**, efficient for small doses).
- ▶ Sequential steps of active absorption:

Step	Event
1	Dietary B12 released from protein in stomach/duodenum/jejunum by acid and enzymes
2	Binds salivary haptocorrin (HC) in the stomach
3	Pancreatic trypsin digests HC in the intestine; B12 transferred to intrinsic factor (IF)
4	IF (gene at chromosome 11q13) is secreted by gastric parietal cells (fundus/body); secretion parallels HCl

Step	Event
5	IF-B12 complex reaches the ileum and binds the receptor cubilin on enterocyte microvilli; cubilin traffics via amnionless (AMN)
6	Complex is endocytosed; IF is destroyed; after ~6 h B12 enters portal blood bound to transcobalamin II

- ▶ 0.5–5 µg of B12 enters bile daily, binds IF and is largely **reabsorbed (enterohepatic circulation)** together with B12 from sloughed cells.

Plasma transport and cellular uptake

- ▶ Two plasma transport proteins each bind B12 one-to-one:
 - **Transcobalamin I (TC I / haptocorrin)** — gene *TCN1* (chr 11); derived mainly from **neutrophil granules**; normally ~two-thirds saturated; does **not** deliver B12 to tissues but carries analogues to the **liver for biliary excretion**.
 - **Transcobalamin II (TC II)** — gene on **chromosome 22q11–q13.1**; synthesised by liver, macrophages, ileum and vascular endothelium; carries only 20–60 ng/L but is the **functional delivery protein**, readily giving up B12 to marrow, placenta and other tissues.
- ▶ Cellular uptake of TC II–B12 is by **receptor-mediated endocytosis** via the **TC II receptor** and **megalín (LRP-2 gene)** through clathrin-coated pits; the complex is degraded and free B12 exported via an ABC transporter.

Intracellular biochemical functions (the two B12-dependent reactions)

- ▶ **Reaction 1** — Methylmalonyl-CoA → succinyl-CoA (methylmalonyl-CoA mutase, needs **adocobalamin**). Block raises **methylmalonic acid (MMA)** — the basis of the MMA diagnostic test and a contributor to neuropathy.
- ▶ **Reaction 2** — Homocysteine → methionine (methionine synthase, needs **methylcobalamin** + 5-methyl-THF). This is the first step that regenerates intracellular **tetrahydrofolate (THF)** and produces **methionine** → **S-adenosylmethionine (SAM)**, the universal methyl donor for >100 methyltransferase reactions (including myelin lipids, myelin basic protein and DNA).
- ▶ **Methylfolate trap (“THF starvation”)**: in B12 deficiency, 5-MTHF cannot be demethylated, so it accumulates in plasma while intracellular folate falls — explaining the **megaloblastic anaemia** and why it partially responds to large doses of folic acid (which must not be given alone, as it masks anaemia while neuropathy progresses).

Neurological manifestations of B12 deficiency (brief)

- ▶ Cobalamin is required for **myelination of the CNS**; deficiency causes demyelination.

- ▶ **Subacute combined degeneration (SCD) of the spinal cord** is the hallmark: **demyelination of the posterior (dorsal) columns and lateral (pyramidal) tracts** of the cervical and thoracic cord; MRI may show “spongy” degeneration.
- ▶ **Bilateral peripheral neuropathy** — symmetrical glove-and-stocking **paraesthesiae**, often the earliest symptom.
- ▶ **Posterior-column signs**: loss of **vibration and proprioception (position) sense**, **positive Romberg sign**, **Lhermitte sign**, sensory ataxia.
- ▶ **Pyramidal (lateral-column) signs**: spastic, ataxic gait with **hyperreflexia** and extensor plantars (a combination of upgoing toes with absent ankle jerks is classic).
- ▶ **Autonomic involvement**: postural hypotension, **impotence**, urinary/faecal incontinence.
- ▶ **Cerebral / cranial**: **dementia**, depression, psychotic symptoms, cognitive impairment (“megaloblastic madness”), **optic atrophy**, and **anosmia / loss of taste**; cranial-nerve involvement is less frequent.
- ▶ **Infancy**: poor brain and intellectual development, feeding difficulty, lethargy, coma, convulsions and myoclonus.
- ▶ Patients are **more often male** and may present with neurological disease **before or without anaemia** — the non-anaemic patient with neuropsychiatric features and a low/borderline serum B12 is an important clinical trap.
- ▶ **Proposed mechanism**: the neuropathy correlates with the **defect in homocysteine→methionine conversion**; accumulation of **S-adenosylhomocysteine** in brain inhibits transmethylation, and failure of SAM-dependent methylation of biogenic amines (e.g., dopamine), proteins and phospholipids is implicated (the exact biochemical basis “remains obscure”). Importantly, neuropathy can occur **without** methylmalonic aciduria (as in TC II deficiency).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — B12 absorption & transport pathway (flow diagram)**: Label — *Dietary B12 (animal food) → Stomach: acid/enzymes + Haptocorrin (HC) → Duodenum: pancreatic trypsin → Intrinsic factor (IF) from gastric parietal cells → IF-B12 complex → Ileum: cubilin-amnionless receptor → enterocyte endocytosis → portal blood → Transcobalamin II (TC II) → tissues (marrow, CNS) via TC II receptor / megalin (LRP-2). Side branch: Bile → enterohepatic recirculation.*
- ▶ **Diagram 2 — Spinal cord cross-section in SCD**: Label — *Posterior (dorsal) columns — fasciculus gracilis & cuneatus (demyelinated), Lateral corticospinal (pyramidal) tracts (demyelinated), Anterior columns spared, grey matter butterfly; annotate “cervical & thoracic cord, bilateral, symmetrical.”*

Clinical / Diagnostic significance

- ▶ **Causes of deficiency: pernicious anaemia** (gastric atrophy, anti-IF / anti-parietal-cell antibodies) — commonest; total gastrectomy, ileal resection/Crohn's disease, **strict vegetarianism/veganism**, fish tapeworm (*Diphyllobothrium*), tropical sprue, stagnant-loop syndrome, and drugs — **metformin, proton-pump inhibitors / H2-blockers**.
- ▶ **Investigations: serum B12** by ELISA/CBLA (normal $\approx 160\text{--}1000$ ng/L; deficiency usually <100 ng/L; **false-normal in up to 50% of PA** when anti-IF antibodies interfere). **Serum MMA and homocysteine** are raised and are sensitive early markers (homocysteine alone rises in folate deficiency too; **MMA is specific to B12**). Peripheral film: **oval macrocytes**, **MCV >100 fL**, **hypersegmented neutrophils (>5 lobes)**. PA work-up: **anti-IF and anti-parietal-cell antibodies**, raised serum gastrin, low pepsinogen I, endoscopy.
- ▶ **Treatment: parenteral hydroxocobalamin (UK) or cyanocobalamin (US)**. Replenishment: **six 1000- μg IM hydroxocobalamin injections at 3–7 day intervals**; maintenance **1000 μg IM every 3 months** (hydroxocobalamin) or **1000 μg cyanocobalamin IM monthly**. High-dose oral cyanocobalamin (**1000–2000 $\mu\text{g}/\text{day}$**) exploits passive absorption. More frequent dosing is used if neuropathy is present.
- ▶ **Pearls: never treat suspected B12 deficiency with folate alone** (precipitates/worsens SCD). Neurological recovery depends on early treatment — long-standing cord signs may be irreversible. Watch for **hypokalaemia and thrombocytosis** during early response; give aspirin if platelets rise $>800 \times 10^9/\text{L}$. Screen for coexisting **iron deficiency** in pernicious anaemia (occurs in 15–20% of those >60 y).

High-yield exam pointers

- ▶ B12 = **cobalt in a corrin ring**; only two human reactions need it — **methylmalonyl-CoA mutase (ado-B12)** and **methionine synthase (methyl-B12)**.
- ▶ **Body stores 2–3 mg last 3–4 years** $\rightarrow$ deficiency is slow; faster in malabsorption than in vegans (loss of enterohepatic recycling).
- ▶ Absorption chain to memorise: HC $\rightarrow$ **trypsin** $\rightarrow$ **IF (parietal cell)** $\rightarrow$ **cubilin/amnionless (ileum)** $\rightarrow$ **TC II**.
- ▶ **TC II** is the functional delivery protein; **TC I (haptocorrin)** carries analogues for biliary excretion.
- ▶ **Methylfolate trap** links B12 deficiency to megaloblastic anaemia and the folate response.
- ▶ **SCD = demyelination of dorsal columns + lateral pyramidal tracts** of cervical/thoracic cord.
- ▶ Classic sign-set: **absent ankle jerks + extensor plantars**, positive Romberg and Lhermitte, loss of vibration/position sense.
- ▶ **MMA specific for B12; homocysteine raised in both B12 and folate deficiency**.
- ▶ **Never give folate alone** — masks anaemia, worsens neuropathy.

- ▶ Neuropathy can precede anaemia and may occur with **normal serum B12** (use MMA/homocysteine).

SOURCE & COVERAGE

Harrison 22e — Ch 104 “Megaloblastic Anemias” (cobalamin structure, dietary source, IF-dependent absorption, TC I/TC II transport, the two B12-dependent reactions, methylfolate trap, neurologic manifestations, diagnosis and treatment) + Ch 344 “Vitamin and Trace Mineral Deficiency and Excess” (B12 deficiency clinical features — loss of vibratory/position sense, abnormal gait, dementia, impotence, bladder/bowel involvement, ↑homocysteine/↑MMA — and causes). *Coverage note:* The eponymous physical signs (Romberg, Lhermitte) and the “absent ankle jerks with extensor plantars” combination, plus the explicit term *subacute combined degeneration* and the standard PA causes/drug list, are universally accepted textbook internal medicine used here to satisfy the exam ask; Harrison Ch 104 describes the underlying tract demyelination, positive Romberg/Lhermitte signs and hyperreflexia, and Ch 344 lists the deficiency features verbatim.



Diagnosis and management of chronic Myeloid Leukemia

Asked in: Paper IV May 2022 — RGUHS MD General Medicine

Definition / Introduction — Chronic myeloid leukemia (CML) is a clonal hematopoietic myeloproliferative *stem-cell* neoplasm driven by the **BCR::ABL1** chimeric gene, which encodes a constitutively active tyrosine kinase. It arises from a balanced reciprocal translocation between the long arms of chromosomes 9 and 22, *t(9;22)(q34.1;q11.2)*, cytogenetically recognised as the **Philadelphia (Ph) chromosome**. Untreated, the course is biphasic/triphasic — an indolent **chronic phase**, followed by an **accelerated phase** and a terminal **blastic phase**. The introduction of BCR::ABL1 **tyrosine kinase inhibitors (TKIs)** in 2000 transformed CML from a fatal disease (pre-TKI median survival 3–7 years; 10-year survival ≤30%) to one with a 10-year survival >85%, approaching that of an age-matched population.

Epidemiology and pathophysiology

- ▶ CML accounts for ~15% of all leukemias; male:female 1.6:1; median age at diagnosis 55–65 years; only ~3% are <20 years. Annual incidence ~2 per 100,000. No familial association; the only established risk factor is **ionizing radiation** exposure.
- ▶ The **t(9;22)** is present in >90% of classical CML and occurs in hematopoietic cells but not stromal cells. ABL1 (chr 9) is juxtaposed to the **major breakpoint cluster region (M-BCR)** of BCR (chr 22), generating the hybrid oncogene.

- ▶ Breakpoint determines transcript and oncoprotein: **M-BCR (e13/e14)** → e13a2 (b2a2)/e14a2 (b3a2) → **p210** (commonest in CML); **m-BCR (e1a2)** → **p190** (two-thirds of Ph-positive ALL; rare in CML; *worse outcome*); **μ-BCR (e19a2)** → **p230** (indolent course).
- ▶ p210 has **constitutive kinase activity** → increased proliferation, reduced apoptosis, and growth advantage, suppressing normal hematopoiesis. Signalling proceeds via **RAS, MAP kinases, STAT, PI3K and MYC** through adapter proteins (GRB-2, CRK, CRK-L, SHC). Most TKIs bind the **ATP-binding domain**; **asciminib** uniquely binds the **myristoyl pocket** (*STAMP* — Specifically Targeting the ABL1 Myristoyl Pocket).
- ▶ Transformation is associated with **additional chromosomal abnormalities** (double Ph, trisomy 8, isochromosome 17/17p loss of TP53, 3q26) and mutations (*TP53, RBL, RUNX1, ASXL1*). >100 **ABL1 kinase-domain mutations** drive TKI resistance; **T315I** is the “gatekeeper” mutation conferring resistance to imatinib and all second-generation TKIs.

Clinical features and phases

- ▶ ~90% present in **chronic phase**. In settings with screening, 50–60% are diagnosed incidentally on a routine blood count with minimal symptoms (fatigue).
- ▶ Symptomatic disease reflects **anemia and splenomegaly**: fatigue, malaise, weight loss, early satiety, left-upper-quadrant pain. **Splenomegaly is the commonest physical sign** (20–70%); hepatomegaly 5–10%, lymphadenopathy 5%.
- ▶ Less common: leukostasis/hyperviscosity from extreme leukocytosis or thrombocytosis (priapism, visual disturbance, MI, CVA, dyspnea); basophilia-related histamine excess (pruritus, flushing, diarrhea, GI ulcers).
- ▶ **Phase definitions (key marks):**

Phase	Defining features (Harrison 22e)
Chronic	Blasts ≤5%; controllable counts; >90% present here
Accelerated	≥15% peripheral blasts; ≥30% blasts + promyelocytes; ≥20% peripheral basophils; cytogenetic clonal evolution (ACAs other than Ph); platelets <100 × 10 ⁹ /L (therapy-unrelated)
Blastic	≥30% blasts in peripheral blood or marrow, or sheets of blasts in extramedullary disease

- ▶ Blastic phase is **myeloid in ~60%** and **lymphoid in ~25%** (lymphoblasts TdT-positive, peroxidase-negative; CD10/19/20/22, often co-express myeloid markers). The newest WHO classification proposes eliminating “accelerated phase,” reclassifying such patients as **high-risk CML**.

Diagnostic approach and investigations

- ▶ **Peripheral blood:** leukocytosis ($10\text{--}500 \times 10^9/\text{L}$), left-shifted granulocytosis with all maturation stages and blasts usually $\leq 5\%$; **basophilia/eosinophilia**; thrombocytosis common (thrombocytopenia suggests acceleration). **Low leukocyte alkaline phosphatase (LAP)** score; high vitamin B₁₂, uric acid, LDH and lysozyme.
- ▶ **Bone marrow:** hypercellular with myeloid hyperplasia, **myeloid:erythroid ratio 15–20:1**, blasts $\leq 5\%$; reticulin fibrosis (grade 3–4 in 30–40%).
- ▶ **Cytogenetics/molecular — confirm the diagnosis:** the diagnosis depends on documenting **t(9;22)** by **G-banding** (positive in $\sim 90\%$). **FISH** quantifies Ph-positive cells; **RT-PCR** detects/quantifies BCR::ABL1 transcripts (can be done on peripheral blood). Diagnosis should rest on a **marrow with routine cytogenetics** (detects ACAs that FISH misses); the **transcript type must be documented at diagnosis** to avoid spuriously “undetectable” follow-up PCR. $\sim 10\%$ have complex/variant or “masked” Ph; $\sim 5\text{--}10\%$ have additional chromosomal abnormalities.
- ▶ **Response milestones (standardised on the International Scale, IS) — the basis of monitoring:**

Response	Definition
Partial cytogenetic	$\leq 35\%$ Ph-positive metaphases ($\approx \text{IS } \leq 10\%$)
Complete cytogenetic (CCyR / MR2)	0% Ph-positive ($\approx \text{IS } \leq 1\%$)
Major molecular (MMR / MR3)	BCR::ABL1 (IS) $\leq 0.1\%$ ($\geq 3\text{-log}$ reduction)
Deep molecular (DMR / MR4)	BCR::ABL1 (IS) $\leq 0.01\%$
MR4.5	BCR::ABL1 (IS) $\leq 0.0032\%$ ($\geq 4.5\text{-log}$ reduction)

- ▶ **Resistance** = BCR::ABL1 (IS) $> 10\%$ at 6 months or $> 1\%$ at ≥ 12 months. Pre-TKI prognostic scores (Sokal, Hasford, EUTOS) have lost much impact; **achievement of CCyR/MR2** is now the key prognostic endpoint, while MMR/DMR reduces relapse and enables treatment-free remission.

Management — frontline TKI therapy

The goal of management is durable disease control with TKIs; **achievement of CCyR by 12 months** is the principal therapeutic endpoint. Six oral BCR::ABL1 TKIs are FDA-approved.

TKI (brand)	Generation / indication	Frontline dose	Notable toxicities
Imatinib (Gleevec/Glivec)	1st; all phases	400 mg once daily	Fluid retention, periorbital edema, myelosuppression, rashes, cramps
Dasatinib (Sprycel)	2nd; all phases	100 mg daily (50 mg as effective, less toxic)	Pleural/pericardial effusions, pulmonary hypertension, myelosuppression

TKI (brand)	Generation / indication	Frontline dose	Notable toxicities
Nilotinib (Tasigna)	2nd; all phases except blastic	300 mg twice daily (empty stomach)	Hyperglycemia, pancreatitis, arterio-occlusive events , hypertension, QT/hyperbilirubinemia
Bosutinib (Bosulif)	2nd; all phases	400 mg daily (with dose escalation)	Diarrhea/colitis, liver and renal toxicity
Ponatinib (Iclusig)	3rd; T315I, failure of ≥ 2 TKIs	45 mg daily (reduce to 15–30 mg on response)	Highest arterio-occlusive events , hypertension (50–60%), pancreatitis
Asciminib (Scemblix)	3rd (STAMP inhibitor); third-line, T315I	40 mg twice daily or 80 mg daily; T315I 200 mg twice daily	Generally well tolerated

- ▶ **All four of imatinib, dasatinib, bosutinib and nilotinib are acceptable frontline.** Second-generation TKIs give faster/deeper molecular responses (ENESTnd, DASISION, BFORE) and lower early transformation, but **no overall-survival advantage** over imatinib. Choice is individualised by: (1) **treatment aim** (survival vs treatment-free remission, linked to age); (2) **cost/affordability** (generic imatinib ~US\$500/year); (3) **comorbidities** — avoid dasatinib with lung disease, nilotinib with diabetes/pancreatitis/vascular disease, bosutinib with hepatic/renal/GI disease. If survival is the aim, **generic imatinib** is appropriate; if TFR is the aim, a **second-generation TKI** (e.g., dasatinib) is preferred, as in high-risk disease.
- ▶ **Omacetaxine mepesuccinate, hydroxyurea (0.5–10 g/day, cytoreductive bridge), low-dose cytarabine, decitabine and leukapheresis** (for leukostasis) are adjuncts; **interferon- α** is used in pregnancy.

Resistance, transformation, transplant and treatment-free remission

- ▶ **Resistance:** before switching, perform BCR::ABL1 kinase-domain mutation analysis (Sanger sequencing; ~50% of resistant patients have mutations). Mutation-guided salvage: Y253H, E255K/V, F359V/C/I → **dasatinib or bosutinib**; V299L, T315A, F317L → **nilotinib**; T315I → **ponatinib or asciminib** and consider allogeneic HSCT.
- ▶ **TKI toxicity management:** in patients already in good molecular response, **dose reduction** (rather than switching) is acceptable for reversible toxicity; switch for prohibitive toxicities (recurrent pleural effusion/dasatinib; vaso-occlusive events/ponatinib, nilotinib; pulmonary hypertension; pancreatitis; immune-mediated pneumonitis/myocarditis/hepatitis treated with steroids).

- ▶ **Allogeneic HSCT** — the only proven *curative* modality, now a **later-line** option: indicated for resistance to a second-generation TKI, **T315I** disease, or advanced phase. Chronic-phase long-term survival 50–70% (1-year mortality 5–30%); accelerated phase cure 30–50%; **blastic phase** ≤20%.
- ▶ **Accelerated/blastic phase**: TKIs (2nd/3rd generation) ± chemotherapy to reduce burden, **bridging to allogeneic HSCT**. **Lymphoid blast crisis** — anti-ALL chemotherapy (**hyper-CVAD**) + TKI (CR ~70%, median survival ~3 years); **myeloid blast crisis** — anti-AML chemotherapy + TKI (CR 30–50%).
- ▶ **Treatment-free remission (TFR)**: discontinuation after durable **DMR (MR4)** for >2–3 years yields TFR in 40–60% (≥5 years DMR → 80%+). Eligibility: low/intermediate Sokal risk, first chronic phase, quantifiable transcripts (e13a2/e14a2), ≥5 years of TKI, sustained DMR >2–5 years; restart the TKI only if BCR::ABL1 (IS) rises >0.1% (confirmed twice).
- ▶ **Pregnancy**: TKIs are teratogenic (malformations 2–10%); **discontinue immediately** on confirmed pregnancy and manage with leukapheresis/hydroxyurea (and interferon-α if needed).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **The Philadelphia chromosome / BCR::ABL1 fusion**. Labels: *Chromosome 9 — ABL1 locus (q34.1); Chromosome 22 — BCR gene (q11.2); Reciprocal translocation t(9;22); Derivative 22q = Philadelphia chromosome; Fusion BCR::ABL1 gene → p210 oncoprotein (constitutive tyrosine kinase).*
- ▶ **Natural history / phase flow with response monitoring**. Labels: *Chronic phase (blasts ≤5%) → Accelerated phase (≥15% blasts / clonal evolution) → Blastic phase (≥30% blasts); alongside, the response ladder Hematologic → Cytogenetic (CCyR/MR2) → Molecular (MMR/MR3 → DMR/MR4 → MR4.5).*

Clinical / Diagnostic significance

- ▶ Sustained unexplained **leukocytosis with splenomegaly and a low LAP score** should prompt marrow examination and cytogenetics — the screen that uncovers CML.
- ▶ Demonstrating **BCR::ABL1** (G-banding/FISH/RT-PCR) is both diagnostic and the substrate for monitoring; **quantitative RT-PCR on the International Scale** drives every therapeutic decision (response, resistance, TFR).
- ▶ A “**masked Ph**” (morphologic CML, Ph not seen on karyotype) still responds to TKIs if FISH/PCR confirm BCR::ABL1 — do not exclude CML on G-banding alone.
- ▶ TKIs have made **CCyR achievement** the dominant prognostic factor, displacing the older Sokal/Hasford/EUTOS scores.

High-yield exam pointers

- ▶ **Hallmark**: Ph chromosome, t(9;22)(q34.1;q11.2), **BCR::ABL1** → p210 tyrosine kinase.

- ▶ **Diagnostic triad:** neutrophilic leukocytosis with full myeloid spectrum + basophilia, **low LAP**, splenomegaly; confirm with cytogenetics/FISH/PCR.
- ▶ **Three phases:** chronic ($\leq 5\%$ blasts) $\rightarrow$ accelerated ($\geq 15\%$ blasts / clonal evolution) $\rightarrow$ blastic ($\geq 30\%$ blasts).
- ▶ **Frontline:** imatinib 400 mg OD, dasatinib 100 mg OD, nilotinib 300 mg BD, bosutinib 400 mg OD — all acceptable; second-gen = deeper responses, no survival edge.
- ▶ **T315I** = gatekeeper mutation $\rightarrow$ only **ponatinib** / **asciminib** ($\pm$ allo-HSCT) work.
- ▶ **Asciminib** = **STAMP inhibitor** (myristoyl pocket); ponatinib inhibits VEGFR $\rightarrow$ hypertension.
- ▶ **Monitoring milestones:** CCyR/MR2 (IS $\leq 1\%$), MMR/MR3 (IS $\leq 0.1\%$), DMR/MR4 (IS $\leq 0.01\%$). Resistance: IS $> 10\%$ at 6 mo or $> 1\%$ at 12 mo.
- ▶ **Allo-HSCT** = only curative option, reserved for TKI failure / T315I / advanced phase.
- ▶ **TFR** possible after durable DMR ≥ 2 years; **stop TKIs in pregnancy** (teratogenic).

SOURCE & COVERAGE

Harrison 22e — Ch 110 “Chronic Myeloid Leukemia” (Kantarjian & Jabbour). Fully covered by the provided chapter; no coverage gap. Standard textbook adjuncts (LAP score, hyper-CVAD regimen composition) are corroborated by the chapter text.



Coagulation Cascade and Disseminated Intravascular Coagulation (DIC)

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — The **coagulation cascade** is the sequence of reactions in which inactive plasma serine-protease zymogens are sequentially activated on phospholipid (activated platelet) surfaces, culminating in **thrombin** generation and conversion of soluble **fibrinogen to an insoluble cross-linked fibrin clot**. It functions as one limb of the hemostatic system, balanced against natural anticoagulants and fibrinolysis. **Disseminated intravascular coagulation (DIC)** is, per the ISTH (2001), “an acquired syndrome characterised by intravascular activation of coagulation with loss of localisation arising from different causes that can originate from and cause damage to the microvasculature, which, if sufficiently severe, can produce organ dysfunction” — i.e., uncontrolled thrombin generation causing simultaneous microvascular thrombosis and consumptive bleeding.

Steps of Normal Haemostasis

- ▶ **Primary haemostasis (platelet plug):** vascular injury exposes subendothelial collagen; **von Willebrand factor (VWF)** acts as molecular glue mediating platelet adhesion under high shear; adhesion via Gp Ib-IX-V and collagen receptors triggers activation, the release reaction (ADP,

serotonin, thromboxane A₂), and aggregation through the **Gp IIb/IIIa (αIIbβ₃)** receptor binding fibrinogen/VWF (≈50,000 sites/platelet).

- ▶ **Secondary haemostasis (fibrin formation):** the coagulation cascade stabilises the platelet plug with fibrin.
- ▶ **Fibrinolysis & remodelling:** plasmin degrades fibrin to restore vessel patency once bleeding is arrested.

The Coagulation Cascade — Cell-Based (“Waterfall”) Model

Originally described as **extrinsic (tissue factor)** and **intrinsic (contact)** pathways converging on a **common pathway**; the modern view is that coagulation is *initiated* by tissue factor with *amplification* through intrinsic elements. All reactions require **calcium (Ca²⁺)** and occur on activated phospholipid surfaces.

- ▶ **Initiation (extrinsic):** vascular damage exposes **tissue factor (TF)**, constitutively expressed on subendothelial smooth muscle/fibroblasts and on circulating microparticles. TF binds **factor VIIa**; the TF/VIIa complex activates **FX→FXa** (directly) and **FIX→FIXa** (indirectly).
- ▶ **Amplification (intrinsic loop):** **Tissue factor pathway inhibitor (TFPI)** rapidly switches off the TF/VIIa/FXa complex, making sustained coagulation dependent on the amplification loop — **thrombin** feeds back to activate **FXI, FVIII and FV**. **FXIa** is thus important in *propagation/amplification*, not initiation.
- ▶ **Common pathway:** **FXa**, with cofactor **FVa** on phospholipid, converts **prothrombin (FII)→thrombin (FIIa)** — the pivotal protease. Thrombin converts **fibrinogen→fibrin** and activates **FXIII→FXIIIa**, which covalently cross-links fibrin to stabilise the clot.
- ▶ **Note:** **FXII, prekallikrein and high-molecular-weight kininogen (HMWK)** (contact phase) prolong the aPTT but cause *no bleeding*, because thrombin can directly activate **FXI** — explaining why **FXII** deficiency is asymptomatic.

Pathway	Key factors	Screening test
Extrinsic	TF, FVII	PT
Intrinsic (contact)	FXII, FXI, FIX, FVIII, PK, HMWK	aPTT
Common	FX, FV, FII (prothrombin), fibrinogen (FI)	PT + aPTT
Fibrin formation	thrombin → fibrinogen; FXIII cross-link	Thrombin time (TT)

Natural Anticoagulants and the Fibrinolytic System

- ▶ **Antithrombin (AT):** major plasma inhibitor of thrombin and other proteases; activity accelerated several-thousand-fold by **heparin/heparan sulfate**. Deficiency → lifelong VTE risk.

- ▶ **Protein C / Protein S pathway:** thrombin bound to endothelial **thrombomodulin** (with the endothelial **protein C receptor, EPCR**) activates **protein C**; **activated protein C (APC)** with cofactor **protein S** cleaves and inactivates **FVa and FVIIIa**. Resistance to APC due to **Factor V Leiden** causes a hypercoagulable state.
- ▶ **TFPI:** inhibits the TF/FVIIa/FXa initiation complex.
- ▶ **Fibrinolysis:** **tPA** and **urokinase (uPA)** convert **plasminogen**→**plasmin**, which digests fibrin to fibrin degradation products (FDPs); complete lysis of cross-linked fibrin releases **D-dimer** (a specific marker of clot formation/breakdown). Regulated by **PAI-1/PAI-2** (inhibit tPA/uPA), **α2-antiplasmin** (inhibits plasmin), and **TAFI** (thrombin-activatable fibrinolysis inhibitor).

DIC — Aetiology and Pathophysiology

DIC is always **secondary** to an underlying trigger; common causes (ISTH/Harrison):

Category	Examples
Sepsis/infection	Gram-negative bacilli, staph/strep/pneumococci/meningococci; viral, fungal, parasitic, rickettsial
Trauma/tissue injury	Brain injury, extensive burns, fat embolism, rhabdomyolysis
Obstetric	Abruptio placentae, amniotic-fluid embolism, dead-fetus (retained), septic abortion, HELLP
Malignancy	Mucin-producing adenocarcinoma (prostate, pancreas), acute promyelocytic leukaemia (APL/M3)
Vascular	Giant haemangioma (Kasabach-Merritt), large-vessel/aortic aneurysm
Others	Snake/insect envenomation , acute haemolytic transfusion reaction, transplant rejection/GVHD, fulminant hepatic failure, shock, ARDS, massive transfusion

- ▶ **Central mechanism — uncontrolled thrombin generation.** Inflammatory activation (sepsis) → increased **TF expression**, neutrophil/monocyte activation, cytokine release, **neutrophil extracellular traps (NETs)** and polyphosphates → **thrombo-inflammation** and excess thrombin.
- ▶ Simultaneous **loss of endothelial antithrombotic properties** and disrupted natural anticoagulants + abnormal fibrinolysis.
- ▶ → **Systemic fibrin deposition** in small/midsize vessels → microvascular thrombosis → **ischaemic multi-organ damage** (lung→ARDS, kidney, liver, brain) and **microangiopathic haemolysis** (schistocytes).

- ▶ → Consumption of platelets and clotting factors + secondary hyperfibrinolysis (late) → diffuse bleeding.
- ▶ **Purpura fulminans**: severe DIC with extensive cutaneous thrombosis, in children after viral/bacterial infection and in **homozygous protein C deficiency** neonates.

DIC — Clinical Features and Diagnosis

- ▶ **Bleeding**: petechiae, ecchymoses, oozing from venepuncture/catheter/incision sites, GI/pulmonary/CNS haemorrhage; **purpura fulminans**.
- ▶ **Thrombosis**: microvascular occlusion → organ failure; large-vessel thrombosis, cerebral embolism; cancer-associated DIC may present chiefly as thrombosis (**Trousseau syndrome**).
- ▶ **Acute DIC**: haemodynamic instability/shock; mortality **30 to >80%**, largely determined by the underlying disease.
- ▶ **Laboratory hallmark**: ↓platelets, **prolonged PT and aPTT**, **low/falling fibrinogen**, **raised D-dimer/FDPs**, schistocytes on smear. Serial testing (every 6–8 h) is essential as values evolve.

ISTH scoring system for overt DIC (validated; uses platelet count, D-dimer, PT prolongation, fibrinogen):

Parameter	Value	Points
Platelets	>100 ×10 ⁹ /L / >50–<100 / <50	0 / 1 / 2
D-dimer	Normal / Moderate ↑ / Severe ↑	0 / 2 / 3
PT prolongation	<3 s / 3–<6 s / >6 s	0 / 1 / 2
Fibrinogen	>1 g/L / <1 g/L	0 / 1

- ▶ **Score ≥5** → **overt DIC** (repeat labs daily); **<5** → **non-overt/low-grade DIC** (repeat every 1–2 days). *Not to be used in pregnancy* (a separate obstetric tool exists).
- ▶ **Chronic (compensated) DIC**: giant haemangioma, metastatic carcinoma, late fetal demise; D-dimer/FDP elevated but PT/aPTT/fibrinogen often normal, mild/no thrombocytopenia.
- ▶ **Differential: severe liver disease** (similar abnormalities but change slowly, not rapidly) and **TTP** (acute thrombocytopenia + schistocytes + organ failure, but distinguished by **ADAMTS13 deficiency/inhibitor**).

DIC — Management

- ▶ **Treat the underlying cause** — this is the cornerstone (antimicrobials for sepsis, chemotherapy, surgery, evacuation of uterus/delivery for obstetric DIC).
- ▶ **Blood-product support for active bleeding / high bleeding risk** (not merely to correct numbers):
 - **Platelets** for count <10,000–20,000/μL (goal >20 ×10⁹/L; >50 ×10⁹/L for serious/intracranial bleeding).

- Cryoprecipitate or fibrinogen concentrate to keep fibrinogen >100–150 mg/dL (correct fibrinogen *before* giving FFP for prolonged PT/aPTT).
- FFP for prolonged PT/aPTT *with* bleeding (target PT/aPTT <1.5× normal).
- Vitamin K should be given.
- ▶ **Heparin** (low-dose continuous infusion, e.g., 5–10 U/kg/h, **no bolus**): for **low-grade/chronic** DIC with solid tumour or APL, for recognised thrombosis, and for **purpura fulminans**. *Aggravates bleeding in acute haemorrhagic DIC*; contraindicated if platelets cannot be kept >20,000–30,000/μL, in CNS/GI bleeding, placental abruption, or imminent surgery. No proven survival benefit in severe DIC.
- ▶ **Antifibrinolytics** (tranexamic acid/EACA): only in **primary hyperfibrinolytic** DIC with severe bleeding (e.g., APL, giant haemangioma) — use cautiously (thrombosis risk), often with heparin and only with haematology input.
- ▶ **Antithrombin / thrombomodulin concentrates**: post-hoc benefit suggested in sepsis-associated DIC; require further study. (Recombinant activated protein C was withdrawn.)
- ▶ **Special situations**: APL-associated DIC needs immediate treatment (start ATRA early) within ~24 h; **Trousseau syndrome** is treated with **heparin/LMWH** (warfarin less effective); **HELLP** requires delivery/evacuation of the uterus.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Cell-based coagulation cascade**: vessel injury → TF + FVIIa → activate FIX→FIXa and FX→FXa; cofactors FVIIIa and FVa; **prothrombin (FII)→thrombin (FIIa)**; **fibrinogen→fibrin**; **FXIIIa cross-linking**; thrombin feedback arrows to FXI, FVIII, FV; TFPI inhibiting TF/FVIIa/FXa. Bracket-label the PT (**extrinsic**), aPTT (**intrinsic**) and **common pathway**.
- ▶ **DIC pathophysiology flowchart**: *Trigger* → **Uncontrolled thrombin generation** → branch 1: **fibrin deposits in microcirculation** → ischaemic tissue damage + RBC damage/haemolysis + multi-organ failure; branch 2: **consumption of platelets & clotting factors** → **diffuse bleeding**; with **secondary fibrinolysis** → ↑FDP/D-dimer.

Clinical / Diagnostic significance

- ▶ **PT** screens the extrinsic/common pathway (FVII, X, V, II, fibrinogen) and underpins the **INR** for warfarin monitoring and liver-disease assessment; **aPTT** screens the intrinsic/common pathway and monitors unfractionated heparin.
- ▶ **Mixing studies** distinguish factor deficiency (corrects) from an inhibitor/lupus anticoagulant (fails to correct).
- ▶ **D-dimer** is a sensitive marker to *exclude* DVT/PE (age-adjusted thresholds) and is raised in DIC.

- ▶ A combined prolonged PT + aPTT with falling fibrinogen, thrombocytopenia, raised D-dimer and schistocytes in a sick patient is the classic DIC signature — always search for the underlying trigger.

High-yield exam pointers

- ▶ Coagulation is initiated by tissue factor, amplified by the intrinsic loop, occurs on phospholipid surfaces, and needs Ca^{2+} ; thrombin is the pivotal enzyme.
- ▶ FXII deficiency → long aPTT but no bleeding; FXIII deficiency → normal PT/aPTT but abnormal clot solubility and bleeding.
- ▶ Vitamin K-dependent factors = II, VII, IX, X + protein C and S.
- ▶ DIC is always secondary; commonest triggers = sepsis, trauma, obstetric complications, malignancy (APL, mucinous adenocarcinoma).
- ▶ ISTH overt-DIC score ≥ 5 (platelets, D-dimer, PT, fibrinogen).
- ▶ Schistocytes in 10–20%; D-dimer/FDP raised, fibrinogen low.
- ▶ HELLP = severe peripartum DIC variant; Trousseau = cancer DIC presenting as thrombosis; Kasabach-Merritt = haemangioma-associated.
- ▶ Treat the cause first; products only if bleeding; low-dose heparin for thrombotic/chronic DIC and purpura fulminans, *not* for acute haemorrhagic DIC.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Bleeding and Thrombosis" (coagulation cascade physiology, natural anticoagulants, fibrinolysis, PT/aPTT correlation) and "Coagulation Disorders" (DIC definition, causes, pathophysiology, ISTH scoring, management; differential vs liver disease and TTP).
- ▶ CMDT 2026 — "Disorders of Hemostasis, Thrombosis & Antithrombotic Therapy" (DIC essentials of diagnosis, management table, HELLP, Trousseau syndrome, APL-associated DIC, heparin thresholds).
- ▶ Coverage note: The DeVita oncology text was screened for the APL/malignancy-associated DIC angle; the substantive exam-grade DIC detail is fully covered by Harrison and CMDT, which were used as the primary sources.



Megaloblastic Anaemia

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Megaloblastic anaemias are a group of disorders characterised by a distinctive morphological abnormality of the developing red cells in the bone marrow (megaloblasts), arising from defective DNA synthesis with relatively preserved RNA and cytoplasmic (haemoglobin)

maturation — i.e. **nuclear–cytoplasmic asynchrony**. The marrow is typically hypercellular, yet the anaemia results from **ineffective erythropoiesis** (intramedullary death of haemopoietic precursors by apoptosis). The overwhelming majority are due to deficiency of **cobalamin (vitamin B12)** or **folate (vitamin B9)**, or to drugs/genetic defects impairing their metabolism or DNA synthesis directly.

Etiology

Cobalamin (B12) deficiency	Folate deficiency	Independent of B12/folate
Nutritional: strict vegans (large at-risk Indian/Hindu vegetarian population)	Nutritional (commonest): old age, infancy, poverty, alcoholism, chronic invalids; scurvy/kwashiorkor	Antimetabolite drugs: cytarabine, hydroxyurea, 6-mercaptopurine, AZT
Pernicious anaemia (PA) — commonest severe cause in the West; autoimmune gastric atrophy with IF lack	Malabsorption: tropical sprue, coeliac (gluten-induced enteropathy), specific folate malabsorption (PCFT mutation)	Methotrexate / antifolates (DHF-reductase inhibitors)
Gastric: total/partial gastrectomy, congenital IF deficiency	Increased utilisation/loss: pregnancy & lactation, prematurity, chronic haemolysis (sickle cell, spherocytosis), myelofibrosis, malignancy, exfoliative dermatitis, haemodialysis	Orotic aciduria (responds to uridine)
Intestinal: stagnant/blind-loop syndrome, ileal resection (≥ 1.2 m) or Crohn's, tropical sprue, fish tapeworm (<i>Diphyllobothrium latum</i>), Imerslund-Gräsbeck syndrome	Antifolate/anticonvulsant drugs: phenytoin, primidone, barbiturates, sulfasalazine; alcohol	Thiamine-responsive (<i>SLC19A2</i>), myelodysplasia, acute myeloid leukaemia
Metabolic: transcobalamin (TC) II deficiency; N2O inactivation of methylcobalamin		

- ▶ **B12 stores** are 2–3 mg (3–4 years' reserve); deficiency develops slowly. **Folate stores** are only ~10 mg (3–4 months' reserve), so folate deficiency develops rapidly.
- ▶ B12 is **synthesised only by microorganisms**; human source is food of animal origin (meat, fish, dairy). Folate is abundant in liver, yeast and green vegetables but is **destroyed by cooking**.

Pathogenesis — biochemical basis

- ▶ The common final lesion is **impaired conversion of deoxyuridine monophosphate (dUMP) → deoxythymidine monophosphate (dTMP)**, the rate-limiting step of DNA synthesis, which requires **5,10-methylene-tetrahydrofolate (THF)** as coenzyme (thymidylate synthase). The

shortage of dTTP slows DNA replication; replicons fail to join, producing single-stranded breaks
→ **megaloblastic change and apoptotic intramedullary cell death.**

- ▶ **Only two reactions in humans require cobalamin:**
- ▶ **Methionine synthase** (uses **methylcobalamin** + 5-methyl-THF): homocysteine → methionine; methionine → **S-adenosyl-methionine (SAM)**, the universal methyl donor.
- ▶ **L-methylmalonyl-CoA mutase** (uses **adenosyl-cobalamin**): methylmalonyl-CoA → succinyl-CoA.
- ▶ **Methylfolate trap (THF starvation):** In B12 deficiency, methionine synthase fails, so folate is trapped as 5-methyl-THF in plasma (high serum folate) and cannot be converted to THF/polyglutamates inside the cell (low cell folate). This explains why B12 deficiency produces a **functional intracellular folate deficiency** and why the anaemia partly responds to large doses of folic acid (which bypass the trap) — but giving folate alone allows the **neuropathy to progress.**
- ▶ **Neuropathy** is attributed to defective methionine/SAM synthesis (impaired methylation of myelin), not to the megaloblastic process; methylmalonic acid (MMA) accumulates only with the mutase (B12) defect, not with TC II deficiency or N2O exposure.

Clinical features

- ▶ **General/anaemia:** insidious pallor, fatigue; “lemon-yellow” tint from combined pallor and mild **unconjugated jaundice** (ineffective erythropoiesis); anorexia, weight loss, low-grade fever; mild splenomegaly may occur.
- ▶ **Epithelial/GI:** **glossitis** (beefy-red, sore tongue), **angular cheilosis/stomatitis**, diarrhoea or constipation; reversible **melanin skin hyperpigmentation**; cervical smear abnormalities.
- ▶ **Neurological (B12 only)** — **subacute combined degeneration (SCD) of the cord:** symmetrical demyelination of the **posterior (dorsal) and lateral (pyramidal) columns** of the cervico-thoracic cord. Presents (more often in males) with **distal paraesthesiae**, loss of **vibration and proprioception**, positive **Romberg** and **Lhermitte** signs, ataxic-spastic gait with **hyperreflexia and extensor plantars**. Also peripheral neuropathy, optic atrophy, autonomic dysfunction (postural hypotension, incontinence, impotence). **Crucially, neuro-psychiatric features can occur with a normal CBC/MCV.**
- ▶ **Neuropsychiatric:** dementia, depression, psychosis, cognitive impairment, anosmia/loss of taste (“megaloblastic madness”).
- ▶ **Reproductive/obstetric:** infertility (both sexes); maternal folate deficiency → prematurity, recurrent fetal loss and **neural-tube defects (NTDs)**.
- ▶ **Infantile B12 deficiency** (B12-deficient mother, breast-fed): megaloblastic anaemia at 3–6 months with growth retardation, hypotonia and delayed myelination.

Haematological & laboratory findings / Diagnosis

- ▶ **Peripheral smear:** oval macrocytes, marked anisopoikilocytosis, **MCV usually >100 fL** (often 110–140 fL); **hypersegmented neutrophils (>5 lobes)** — an early, characteristic sign. Mild leucopenia and thrombocytopenia in severe cases (pancytopenia possible).
- ▶ **Reticulocyte count** is low/inappropriately normal (ineffective erythropoiesis).
- ▶ **Bone marrow:** hypercellular; **megaloblasts** with open, sieve-like (“stippled”) nuclear chromatin despite haemoglobinised cytoplasm (nuclear-cytoplasmic dissociation); **giant metamyelocytes/giant bands** and hypersegmented megakaryocytes.
- ▶ **Ineffective erythropoiesis markers:** raised **unconjugated bilirubin** and **serum LDH** (often markedly), raised urine urobilinogen, **reduced haptoglobin** (may mimic haemolysis/AIHA).
- ▶ **Vitamin assays:** serum B12 deficient if <74 pmol/L (~100 ng/L) — symptomatic patients <100 pg/mL; serum/RBC folate low (RBC folate <150 ng/mL is diagnostic, and reflects stores better). **Note:** serum folate is *high* in B12 deficiency (methylfolate trap).
- ▶ **Metabolite confirmation (for borderline values):** **MMA raised in B12 deficiency only;** **homocysteine raised in both B12 and folate deficiency.** (MMA also rises in renal failure.)
- ▶ **Establish the cause of B12 deficiency (PA work-up):** anti-**intrinsic-factor antibody** (specific; blocking type I ~55%, binding type II ~35%), anti-**parietal-cell antibody** (sensitive ~90%, less specific), raised **serum gastrin**, low **pepsinogen I**, gastric endoscopy/biopsy (body-fundus atrophy). The Schilling test is now obsolete.

Complications

- ▶ **Neurological:** irreversible SCD/peripheral neuropathy and dementia if B12 deficiency is untreated or if folate is given alone.
- ▶ **Obstetric/fetal:** NTDs (anencephaly, meningomyelocele, spina bifida), cleft lip/palate, prematurity, fetal loss.
- ▶ **Vascular:** hyperhomocysteinaemia → increased risk of arterial and **venous thrombosis** (including unusual sites e.g. cerebral venous sinus); severe homocystinuria causes premature vascular disease.
- ▶ **Malignancy:** PA carries an increased long-term risk of **gastric carcinoma** (and gastric carcinoid).
- ▶ **Haematological:** symptomatic anaemia, high-output failure; risk of severe **hypokalaemia and thrombocytosis** during early treatment.

Management / Treatment

- ▶ **Principle:** identify and treat the *correct* deficiency. In a critically ill patient, take samples for B12/folate (± marrow) and then treat with **both** vitamins; **never give folate alone until B12 deficiency is excluded/corrected** (precipitates/worsens neuropathy).
- ▶ **Cobalamin replacement (PA / B12 deficiency):**

- **Hydroxocobalamin** 1000 µg IM × 6 doses at 3–7 day intervals to replenish stores; **maintenance 1000 µg IM every 3 months**, usually lifelong. (Cyanocobalamin needs higher/more frequent dosing, e.g. monthly, due to poorer retention.)
 - CMDT regimen: 100–1000 µg IM/SC daily for 1 week, weekly for a month, then monthly.
 - **High-dose oral cyanocobalamin 1000–2000 µg/day** is effective even in PA (≈1% absorbed passively, IF-independent); ensure compliance. Parenteral preferred where neuropathy or severe anaemia is present.
 - Give B12 routinely after total gastrectomy or ileal resection; screen patients on long-term PPIs/metformin or after bariatric surgery.
- **Folate replacement: oral folic acid 1–5 mg daily** (Harrison: 5–15 mg/day; CMDT: 1 mg/day), continued ~4 months (until folate-deficient cells are replaced) or long-term if the cause is irreversible (haemolysis, dialysis). **Folinic acid (5-formyl-THF)** is the antidote to methotrexate/antifolates.
- **Response & monitoring:** sense of well-being within days; **reticulocytosis at 5–7 days**; haematology normalises in ~2 months. Watch for **hypokalaemia** (give K⁺ supplements) and a rebound thrombocytosis — consider antiplatelet therapy if platelets rise >800 × 10⁹/L. Transfusion is rarely needed and is hazardous (precipitates failure); if essential give packed cells slowly, 1–2 units, with diuretic cover.
- **Prophylaxis:** periconceptional **folic acid 400 µg/day** (5 mg/day in previous NTD, diabetes, sickle cell, on antiepileptics) reduces NTDs by ~80%; routine folate in chronic dialysis, prematurity, chronic haemolysis; food fortification programmes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Methylfolate trap / one-carbon metabolism loop** — label: *dietary folate* → 5-methyl-THF (plasma); *methionine synthase (methylcobalamin)*; *homocysteine* → *methionine* → SAM; *THF* → 5,10-methylene-THF; *dUMP* → *dTMP (thymidylate synthase)* → DNA; *L-methylmalonyl-CoA* → *succinyl-CoA (adenosyl-cobalamin)*; arrows showing the block in B12 deficiency trapping folate as 5-methyl-THF.
- **Peripheral smear & marrow montage** — label: *oval macrocyte*, *hypersegmented neutrophil (>5 lobes)*, *megaloblast with open/stippled chromatin (nuclear-cytoplasmic asynchrony)*, *giant metamyelocyte*. Optional cord cross-section labelling *posterior columns* and *lateral (pyramidal) tracts* for subacute combined degeneration.

Clinical / Diagnostic significance

- **MCV + smear + hypersegmented neutrophils** give a rapid bedside diagnosis; confirm with B12/folate and, if borderline, **MMA (B12-specific) and homocysteine**.

- ▶ A **normal CBC does not exclude B12 neuropathy** — measure B12/MMA in any unexplained myelopathy, dementia or peripheral neuropathy.
- ▶ Distinguish from **non-megaloblastic macrocytosis** (alcohol, liver disease, hypothyroidism, MDS, reticulocytosis) — these lack megaloblastic marrow and hypersegmentation.
- ▶ Coexistent **iron deficiency** (common in PA from atrophic gastritis) can mask macrocytosis (“dimorphic” picture) — check iron studies.
- ▶ PA mandates a **single endoscopy** (atrophic gastritis, gastric carcinoma/carcinoid surveillance) and screening for associated autoimmune disease (thyroid, type 1 DM, Addison’s, vitiligo).

High-yield exam pointers

- ▶ Hallmark = **nuclear-cytoplasmic asynchrony** from defective DNA synthesis; anaemia is from **ineffective erythropoiesis** in a *hypercellular* marrow.
- ▶ **Two B12-dependent enzymes:** methionine synthase (methyl-B12) and methylmalonyl-CoA mutase (adenosyl-B12). MMA ↑ → B12; homocysteine ↑ → both.
- ▶ **Methylfolate trap** explains high serum folate + low cell folate in B12 deficiency.
- ▶ **Hypersegmented neutrophil (>5 lobes)** = earliest, most characteristic peripheral clue.
- ▶ **Never treat with folate alone** before excluding B12 — risk of subacute combined degeneration.
- ▶ **Pernicious anaemia:** elderly, anti-IF (specific) + anti-parietal-cell (sensitive) antibodies, ↑gastrin, ↓pepsinogen I; gastric carcinoma risk.
- ▶ Treatment response: **reticulocytosis day 5–7**; beware **hypokalaemia** and rebound **thrombocytosis** early.
- ▶ **Folic acid 400 µg periconception (5 mg high-risk)** prevents neural-tube defects.
- ▶ B12 store lasts **3–4 years**; folate store only **3–4 months**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Megaloblastic Anemias” (A.V. Hoffbrand): aetiology tables, cobalamin/folate biochemistry, methylfolate trap, clinical and haematological features, pernicious anaemia, diagnosis and treatment regimens (hydroxocobalamin $6 \times 1000 \mu\text{g}$ then 3-monthly; folate 5–15 mg).
- ▶ **CMDT 2026** — “Blood Disorders” (Vitamin B12 Deficiency; Folic Acid Deficiency): current diagnostic cut-offs (B12 <200/<100 pg/mL; RBC folate <150 ng/mL), MMA/homocysteine confirmation, parenteral and oral 1 mg replacement schedules, reticulocyte/hypokalaemia response.
- ▶ **Coverage note:** The assigned specialty text (DeVita’s *Cancer: Principles & Practice of Oncology*) covers haematological *malignancies*, not nutritional megaloblastic anaemia, and therefore was not a relevant source for this topic; grounding is from Harrison 22e and CMDT 2026, which cover it fully. The term *subacute combined degeneration* and the

standard 400 µg/5 mg NTD-prophylaxis doses are universally accepted internal medicine, consistent with Harrison's description of posterior/lateral-column demyelination and periconceptional folate.



Paroxysmal Nocturnal Hemoglobinuria: Etiology, Clinical Features, Evaluation and Management

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — Paroxysmal nocturnal hemoglobinuria (PNH) is an *acquired*, clonal hematopoietic stem-cell disorder characterised by **chronic complement-mediated intravascular hemolysis** with recurrent exacerbations, due to deficiency of glycosylphosphatidylinositol (GPI)-anchored complement-regulatory proteins on blood cells. The classic clinical triad is (1) **intravascular hemolysis**, (2) **a tendency to venous thrombosis**, and (3) **variable bone-marrow failure / pancytopenia** — a combination that makes PNH a unique entity. It is rare (prevalence ~5–10 per million), is *never inherited or congenital*, affects both sexes equally, and usually presents in young adults.

Etiology and Pathogenesis

- ▶ **Somatic mutation in the X-linked PIGA gene in a hematopoietic stem cell is the fundamental lesion. PIGA encodes an enzyme required for an early step in GPI biosynthesis*.*
- ▶ Loss of GPI means GPI-anchored surface proteins cannot be attached — most importantly the two complement regulators CD55 (decay-accelerating factor; blocks C3 convertase) and CD59 (membrane inhibitor of reactive lysis; blocks insertion of the C9 polymer / **membrane attack complex, MAC**).
- ▶ The marrow becomes a **mosaic** of mutant (GPI-negative, “PNH”) and normal (GPI-positive) cells; peripheral blood therefore always contains both populations, with PNH cells usually predominating.
- ▶ *PIGA* mutations occur in normal individuals too; clonal **expansion** requires a permissive marrow environment. PNH is closely linked to **aplastic anemia (AA)** — an organ-specific autoimmune attack (cytotoxic T cells) on stem cells, possibly directed at the GPI molecule itself, which spares (positively selects) the GPI-negative PNH clone. Thus PNH is a *clonal but non-malignant* disease arising from the combination of **failure of normal hematopoiesis + escape/expansion of the PNH clone**.
- ▶ **Hemolysis** is intravascular and complement-driven: chronic hemolysis is via the **alternative pathway**; the *classical* pathway (triggered by infection/inflammation) explains acute **exacerbations**. Free hemoglobin released into plasma **scavenges nitric oxide**, producing smooth-

muscle dystonia (abdominal pain, esophageal spasm, erectile dysfunction) and contributing to thrombosis.

- ▶ Rarely, PNH is caused by **biallelic mutations of the autosomal PIGT gene (20q) in the absence of a PIGA* mutation*; here GPI is made but cannot bind proteins, adding a chronic inflammatory picture.

Clinical Features

- ▶ **Hemoglobinuria** — the classic but inconstant presentation: passing “blood instead of urine,” typically the **first morning void** (nocturnal/early-morning acidosis from sleep hypoventilation lowers blood pH and facilitates complement activation — hence “*nocturnal*”). Urine is reddish-brown; hemoglobinuria fluctuates dramatically hour-to-hour and is often *not* noticed.
- ▶ **Anemia** — most patients present simply within the differential diagnosis of anemia (symptomatic or incidental); often associated fatigue.
- ▶ **Thrombosis** — the most immediately life-threatening and characteristic complication, typically **venous** and at **unusual sites**: intra-abdominal/mesenteric veins, **hepatic vein (Budd-Chiari syndrome** — hepatomegaly + ascites in absence of liver disease should raise suspicion of PNH), cerebral (sagittal sinus) veins, and dermal vessels (painful skin nodules).
- ▶ **Smooth-muscle dystonia** from NO depletion — recurrent severe **abdominal pain**, dysphagia/esophageal spasm, and **erectile dysfunction**.
- ▶ **Marrow failure features** — neutropenia and/or thrombocytopenia may be present from the outset (overlap with AA / MDS); patients may evolve from PNH → aplasia and vice-versa.
- ▶ **Iron deficiency** — from chronic urinary iron loss (hemoglobinuria/hemosiderinuria).
- ▶ **Natural history** — extends over decades; with supportive care only, median survival historically ~10–20 years, the commonest cause of death being **venous thrombosis** (then infection from neutropenia, hemorrhage from thrombocytopenia). Evolution to **acute myeloid leukemia is rare** (~1–2%); rare spontaneous remissions are documented.

Evaluation / Laboratory Diagnosis

- ▶ **Evidence of intravascular hemolysis**: normo- to macrocytic **anemia** (macrocytosis from reticulocytosis, up to ~20% / ~400,000/μL); **markedly elevated LDH** (often in thousands); **undetectable haptoglobin**; mildly–moderately raised **unconjugated bilirubin**; **hemoglobinuria** and **urine hemosiderin** (a useful marker of chronic intravascular hemolysis). Anemia may become **microcytic** if iron deficiency supervenes.
- ▶ **Direct antiglobulin (Coombs) test is characteristically NEGATIVE** — distinguishing PNH from autoimmune hemolytic anemia (it becomes positive only iatrogenically once C5 inhibitors are started).
- ▶ **Flow cytometry** — the **gold standard**: demonstrates a discrete population of CD59- and CD55-deficient cells on red cells *and* granulocytes/monocytes, giving a **bimodal distribution**. The

FLAER assay (fluorescein-labelled proaerolysin, which binds GPI directly) is more sensitive, especially on granulocytes/monocytes. Granulocyte clone size is more reliable than RBC clone size (the latter is lowered by ongoing hemolysis).

- **Diagnostic threshold:** a clinically meaningful diagnosis requires a *substantial* clone — roughly **≥5% of red cells and ≥20% of granulocytes** GPI-negative. Tiny clones (e.g. <2%) seen in aplastic anemia are *not* PNH per se.
- ▶ **Older tests:** the **acidified-serum (Ham) test** is reliable but now largely historical; the **sucrose hemolysis (sugar-water) test** is *unreliable*.
- ▶ **Bone marrow:** usually **cellular with erythroid hyperplasia** and mild dyserythropoietic features; may become hypocellular/aplastic at some stage; karyotype normal or clonal — performed to assess marrow failure and exclude MDS.
- ▶ **Screen for thrombophilia and complications** in those with thrombosis.

Management Options

Treatment is stratified by clone size, hemolysis severity, thrombosis, and degree of marrow failure. **Terminal/proximal complement inhibitors** have transformed prognosis; supportive care and transplantation retain key roles.

Agent	Target / class	Route & schedule	Key points
Eculizumab	Humanised anti-C5 mAb	IV every 14 days	First approved (2007); blocks MAC → abolishes intravascular hemolysis, reduces transfusion need & thrombosis; residual extravascular hemolysis (C3-opsonised RBCs cleared in spleen, Coombs becomes positive)
Ravulizumab	Anti-C5 (long-acting eculizumab derivative)	IV every 8 weeks	Fewer breakthrough hemolysis episodes; convenient dosing
Pegcetacoplan	C3 inhibitor	SC	Blocks <i>both</i> intra- and extravascular hemolysis → higher hemoglobin / fuller correction of anemia than C5 blockade
Iptacopan	Oral factor B inhibitor (alternative pathway)	Oral	Approved; proximal blockade

Agent	Target / class	Route & schedule	Key points
Danicipan	Oral factor D inhibitor	Oral	Add-on for inadequate response to C5 inhibitors

- ▶ **Mandatory before complement inhibitors: meningococcal vaccination** (serogroups ACWY and B) ± **penicillin prophylaxis**, because terminal-complement blockade markedly raises risk of *Neisseria meningitidis* infection.
- ▶ **Breakthrough hemolysis** can occur with incomplete blockade (more severe with proximal C3 blockade because of the large expanded PNH RBC mass) — abrupt cessation risks massive hemolysis.
- ▶ **Supportive care (essential where inhibitors are unaffordable):** leucodepleted red-cell transfusion; folic acid ≥ 3 mg/day (high marrow turnover); **iron supplementation** as needed (may transiently increase hemolysis); periodic monitoring for iron overload in transfused C5-inhibited patients.
- ▶ **Anticoagulation:** any patient with **venous thrombosis** or a thrombophilic risk factor needs **long-term anticoagulation**; **thrombolysis (tPA)** for refractory acute thrombosis.
- ▶ **Glucocorticoids:** *not* indicated for chronic hemolysis (no benefit + toxicity); a short course of prednisone may help an inflammatory exacerbation.
- ▶ **Allogeneic hematopoietic stem-cell transplantation (HSCT):** the only **curative** option; reserved for **severe PNH / PNH-AA syndrome**, especially young patients with an HLA-identical sibling (complement inhibitors do not correct marrow failure). **Immunosuppression** with **antithymocyte globulin + cyclosporine** is an alternative for the AA component.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Complement cascade on the PNH red cell** — label: *classical, lectin and alternative pathways* → C3 → C3 convertase → C5 → C5b-C9 = *membrane attack complex (MAC)*; show CD55 blocking the C3 convertase and CD59 blocking MAC on a normal RBC, and their **absence on the PNH RBC** → **intravascular hemolysis**. Mark drug sites: *eculizumab/ravulizumab at C5; pegcetacoplan at C3; iptacopan at factor B; danicipan at factor D*.
- ▶ **GPI-anchor schematic** — label: *PIGA mutation* → *no GPI anchor* → *loss of CD55 & CD59 (and other GPI-linked proteins) from cell surface*.

Clinical / Diagnostic significance

- ▶ Suspect PNH in any Coombs-negative intravascular hemolysis, hemolysis with pancytopenia, hemoglobinuria, unexplained venous thrombosis at unusual sites / Budd-Chiari, or aplastic anemia with hemolysis.

- ▶ Flow cytometry for CD55/CD59 (with FLAER) is the confirmatory test; markedly raised LDH with low haptoglobin and negative DAT is the screening signature.
- ▶ A PNH clone is found in ~50% of aplastic anemia patients at presentation — link the two diseases.
- ▶ Thrombosis drives mortality — early complement inhibition + anticoagulation are prognosis-changing.

High-yield exam pointers

- ▶ **Etiology = acquired somatic PIGA mutation (X-linked) → loss of GPI anchor → deficiency of CD55 + CD59 → complement-mediated intravascular hemolysis.**
- ▶ Triad: intravascular hemolysis + venous thrombosis + bone-marrow failure (pancytopenia).
- ▶ Coombs/DAT NEGATIVE intravascular hemolysis; LDH very high, haptoglobin absent, urine hemosiderin positive.
- ▶ Gold-standard diagnosis = flow cytometry (CD55/CD59 ± FLAER); clone ≥5% RBC / ≥20% granulocytes.
- ▶ Ham (acidified serum) test historically positive; sucrose lysis test unreliable.
- ▶ Hepatic vein thrombosis → Budd-Chiari; NO depletion → abdominal pain, dysphagia, erectile dysfunction.
- ▶ Eculizumab/ravulizumab (anti-C5), pegcetacoplan (C3), iptacopan (factor B), danicopan (factor D) — give meningococcal vaccine (ACWY + B) first.
- ▶ Folic acid ≥3 mg/day, iron, transfusion; allogeneic HSCT is the only cure (for severe PNH / PNH-AA).
- ▶ Thrombosis = leading cause of death; ~1–2% evolve to AML.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Hemolytic Anemias" (Paroxysmal Nocturnal Hemoglobinuria section, complement cascade and anticomplement therapy figures) and "Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia" (PNH–aplastic anemia relationship).
- ▶ CMDT 2026 — "Blood Disorders: Paroxysmal Nocturnal Hemoglobinuria" (FLAER assay, urine hemosiderin, meningococcal prophylaxis, current complement-inhibitor regimens).
- ▶ Coverage note: The assigned dedicated specialty text (*DeVita's Cancer: Principles & Practice of Oncology, 12e*) is an oncology/heme-malignancy reference and covers PNH only marginally (no dedicated section); the depth of this answer is therefore grounded in Harrison 22e + CMDT 2026, which between them carry the full etiology, evaluation and current management detail.



Disseminated intravascular coagulation

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — In 2001 the *International Society on Thrombosis and Haemostasis (ISTH)* defined DIC as “an acquired syndrome characterised by the **intravascular activation of coagulation with loss of localisation** arising from different causes that can originate from and cause damage to the microvasculature, which if sufficiently severe can produce **organ dysfunction**.” It is *never a primary disease* but always **secondary** to an underlying disorder. The central event is **uncontrolled, systemic generation of thrombin**, leading to widespread microvascular fibrin deposition (causing ischaemic organ failure) and simultaneous **consumption of platelets and clotting factors** with secondary hyperfibrinolysis (causing bleeding) — hence the older terms *consumptive coagulopathy* and *defibrination syndrome*.

Etiology — Common clinical triggers

DIC accompanies any condition that releases tissue factor into the circulation or causes diffuse endothelial injury.

Category	Representative causes
Sepsis / infection (commonest)	Gram-negative bacilli, <i>staphylococci</i> , <i>streptococci</i> , <i>pneumococci</i> , <i>meningococci</i> ; also viral, mycotic, parasitic, rickettsial
Trauma / tissue injury	Brain injury (gunshot), extensive burns, fat embolism, rhabdomyolysis
Obstetric	Abruptio placentae, amniotic fluid embolism, dead fetus (retained) syndrome, septic abortion; HELLP syndrome
Malignancy	Mucin-producing adenocarcinoma (prostate, pancreas); acute promyelocytic leukaemia (APL, AML-M3)
Vascular	Giant haemangioma (Kasabach-Merritt syndrome), large-vessel aneurysm (e.g. aorta)
Immunologic	Acute haemolytic transfusion reaction, transplant rejection, graft-versus-host disease, immunotherapy
Envenomation / drugs	Snake bite, insect venom; fibrinolytic agents, prothrombin complex concentrates, amphetamines
Liver / miscellaneous	Fulminant hepatic failure, fatty liver of pregnancy; shock, ARDS, massive transfusion

Pathophysiology

- ▶ **Initiation — uncontrolled thrombin generation:** Activation of inflammatory pathways markedly increases **tissue factor** expression, activates neutrophils/monocytes with **cytokine release**, forms **neutrophil extracellular traps (NETs)** and releases polyphosphates — collectively termed **thrombo-inflammation** — driving massive thrombin generation through the extrinsic pathway.
- ▶ **Amplification:** Simultaneous **disruption of physiological anticoagulants** (antithrombin, protein C/S, tissue factor pathway inhibitor) and **endothelial injury** (loss of native antithrombotic surface, prominent in sepsis and trauma) remove the normal brakes on coagulation.
- ▶ **Microvascular fibrin deposition:** Sustained fibrin formation in small and mid-size vessels compromises blood supply to **lung, kidney, liver and brain** → multi-organ ischaemia/failure (pulmonary microthrombosis contributes to ARDS).
- ▶ **Consumption → bleeding:** Continuous activation consumes platelets and coagulation factors faster than they are produced, producing systemic bleeding, aggravated in late stages by **secondary hyperfibrinolysis** (plasmin generation raising FDPs/D-dimer).
- ▶ **RBC fragmentation:** Fibrin strands across the microcirculation shear passing red cells → **schistocytes** and microangiopathic haemolysis.
- ▶ **SIRS / cytokine storm in the setting of infection drives this exuberant response and correlates with higher mortality. Purpura fulminans is the most severe form — extensive cutaneous thrombosis, classically in children after viral/bacterial infection or in neonates homozygous for protein C deficiency*.*

Clinical features

- ▶ **Bleeding (consumptive):** Petechiae, ecchymoses, oozing from venepuncture/catheter/incision sites; severe haemorrhage from the GI tract, lung, or CNS. Multiple simultaneous bleeding sites are characteristic.
- ▶ **Thrombosis (occlusive):** Microvascular occlusion → **organ failure** (oliguria/renal failure, hypoxia, hepatic dysfunction, delirium/coma); large-vessel thrombosis and cerebral embolism may occur. Malignancy-associated DIC may present chiefly as thrombosis (**Trousseau syndrome**, migratory thrombophlebitis).
- ▶ **Acute (decompensated) DIC:** Rapidly evolving, bleeding-dominant, with haemodynamic instability and **shock**; reported mortality 30 to >80%, largely driven by the underlying disease.
- ▶ **Chronic (compensated, low-grade) DIC:** Seen with giant haemangioma, metastatic carcinoma, or late-gestation fetal demise; compensated synthesis keeps PT/aPTT/fibrinogen normal or high with only mild thrombocytopenia and elevated D-dimer — *often thrombosis-predominant*.

Laboratory diagnosis & ISTH overt-DIC score

No single test is diagnostic; diagnosis rests on a **compatible clinical setting plus a panel of tests interpreted serially** (repeat every 6–8 h in the critically ill, as values change rapidly).

- ▶ **Platelet count** — low or progressively *falling* (a downward trend is more useful than a single value).
- ▶ **PT and aPTT** — prolonged (factor consumption).
- ▶ **Fibrinogen** — low or falling (an acute-phase reactant, so may be “normal” early — trend matters).
- ▶ **D-dimer / FDP** — elevated (the most sensitive marker of activation + secondary fibrinolysis).
- ▶ **Peripheral smear** — **schistocytes** (present in only ~10–20% of cases; their absence does not exclude DIC).

The ISTH overt-DIC scoring system (validated; *not for use in pregnancy* — a separate obstetric tool exists):

Parameter	Value	Points
Platelets	$>100 \times 10^9/L$	0
	$50-<100 \times 10^9/L$	1
	$<50 \times 10^9/L$	2
D-dimer / fibrin marker	Normal	0
	Moderate increase	2
	Severe increase	3
PT prolongation	<3 s	0
	$3-<6$ s	1
	>6 s	2
Fibrinogen	>1 g/L	0
	<1 g/L	1

- ▶ **Score ≥ 5 $\rightarrow$ overt DIC** (repeat labs *daily*). **Score <5 $\rightarrow$ suggests non-overt / low-grade DIC** (repeat every 1–2 days). A positive score should prompt a search for the underlying cause if not already evident.

Differential diagnosis

Condition	Discriminating features
Severe liver disease	Thrombocytopenia (hypersplenism), low factors, raised D-dimer — but parameters do not change rapidly on serial testing; FVIII normal/high (falls only if DIC superimposed); reduced FV reflects hepatocyte failure

Condition	Discriminating features
Thrombotic thrombocytopenic purpura (TTP)	Acute thrombocytopenia, schistocytes, organ failure, but PT/aPTT/fibrinogen near-normal; ADAMTS13 <10% with inhibitor is diagnostic
HIT	Thrombocytopenia + thrombosis after heparin; normal fibrinogen, positive anti-PF4 antibodies
Primary hyperfibrinolysis	Low fibrinogen, raised FDP but D-dimer relatively normal and platelets preserved

Treatment

- ▶ **Treat the underlying cause** — the single most important measure (antimicrobials for sepsis, delivery/uterine evacuation in obstetric DIC and HELLP, chemotherapy for malignancy). DIC will not resolve until the trigger is controlled; most overt cases need ICU support for shock physiology.
- ▶ **Blood-product/replacement support** — **only if active bleeding or high bleeding risk** (invasive procedure, post-chemotherapy); *do not transfuse merely to correct numbers*:
 - Platelets for counts <10,000–20,000/ μ L (or <50,000/ μ L with serious/intracranial bleeding or before procedures).
 - Cryoprecipitate / fibrinogen concentrate to keep fibrinogen >100–150 mg/dL.
 - FFP for bleeding with prolonged PT/aPTT; aim PT **no more than** ~3 s above ULN (target PT/aPTT <1.5 $\times$ normal).
 - Packed RBCs for symptomatic anaemia; give vitamin K.
- ▶ **Heparin (low-dose continuous infusion, 5–10 U/kg/h, no bolus)**: Indicated when **thrombosis predominates** — chronic/low-grade DIC with solid tumours, APL, Trousseau syndrome, and **purpura fulminans**. *Contraindicated/harmful in acute haemorrhagic DIC* and when platelets cannot be kept >20,000–50,000/ μ L, or with CNS/GI bleeding or placental abruption. It improves coagulation parameters but has **not shown a survival benefit** in severe DIC.
- ▶ **Anticoagulant concentrates** (antithrombin, recombinant thrombomodulin): little benefit overall, though post-hoc data in sepsis-confirmed DIC suggest possible advantage. *Activated protein C was withdrawn* after trial benefit was not reproduced.
- ▶ **Antifibrinolytics** (tranexamic acid, EACA): reserved for **primary-hyperfibrinolytic DIC with severe bleeding** (e.g. APL, giant haemangioma); risk of catastrophic thrombosis — often combined with heparin and used only with haematology input.
- ▶ **APL-associated DIC**: A haematological emergency — start **all-trans retinoic acid (ATRA)** at the *earliest suspicion* (do not wait for genetic confirmation) together with aggressive product support; modern induction is **ATRA + arsenic trioxide (ATO)**, which reduces early haemorrhagic death.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology flow diagram (Harrison Fig. 121-4):** Box-and-arrow cascade — *Trigger (sepsis/trauma/malignancy/obstetric)* → **Uncontrolled thrombin generation** → branch into (a) **Fibrin deposits in microcirculation** → *Ischaemic tissue damage + RBC damage/haemolysis (schistocytes)* → **Failure of multiple organs**; and (b) **Consumption of platelets and coagulation factors** → *Secondary fibrinolysis (↑FDP, ↑D-dimer)* → **Diffuse bleeding**. Add a side note: “Vessel patency vs occlusion = bleeding vs thrombosis balance.”
- ▶ **Coagulation cascade with test mapping (Fig. 121-1):** Intrinsic (XII→XI→IX→VIII, *aPTT*) and extrinsic (VIIa/tissue factor, *PT*) pathways converging on common pathway (X→Xa→prothrombin→**thrombin**→fibrinogen→fibrin, cross-linked by XIIIa, *TT*) — label PT, *aPTT*, *TT*, and “fibrin → FDP/D-dimer.”

Clinical / Diagnostic significance

- ▶ DIC is a **clinico-pathological diagnosis**: laboratory abnormalities must be interpreted *with* the clinical context and *serially* — an isolated abnormal value is non-specific.
- ▶ A **falling trend** in platelets and fibrinogen with a **rising D-dimer/PT** is more diagnostic than any single absolute value, especially in malignancy where baseline values may be normal.
- ▶ Recognising the **bleeding-vs-thrombosis phenotype** directs therapy: product replacement for the bleeding-dominant acute form, heparin for the thrombosis-dominant chronic/purpura fulminans form.
- ▶ The ISTH score gives an objective, reproducible threshold (≥ 5 = **overt DIC**) for diagnosis and serial monitoring — but is **not validated in pregnancy**.
- ▶ Distinguishing DIC from **liver disease** and **TTP** changes management entirely (TTP needs plasma exchange, not factor replacement); serial labs, FVIII level, and ADAMTS13 are the key discriminators.

High-yield exam pointers

- ▶ **ISTH 2001 definition** — acquired syndrome of intravascular activation of coagulation with loss of localisation. Always **secondary**; never primary.
- ▶ **Central mechanism** = **uncontrolled thrombin generation** via tissue factor + thrombo-inflammation (cytokines, NETs).
- ▶ **Commonest cause** = **sepsis** (esp. Gram-negative); other classics — **APL, abruptio placentae, amniotic fluid embolism, mucinous adenocarcinoma, snake bite, Kasabach-Merritt**.
- ▶ **Lab tetrad**: ↓platelets, ↑PT & *aPTT*, ↓fibrinogen, ↑D-dimer/FDP; **schistocytes in ~10–20%**.
- ▶ **ISTH overt-DIC score ≥ 5** = overt DIC (platelets, D-dimer, PT, fibrinogen).

- ▶ **Treat the underlying cause first**; transfuse only if bleeding/high risk — *don't treat numbers alone*.
- ▶ **Heparin** helps thrombotic/chronic DIC & purpura fulminans; **harmful in acute haemorrhagic DIC**.
- ▶ **APL** → start **ATRA** immediately on suspicion; **HELLP** → **deliver**; **Trousseau** → **LMWH/heparin** (warfarin ineffective).
- ▶ **DDx**: liver disease (parameters change slowly, FVIII normal/high) and **TTP** (ADAMTS13 <10% + inhibitor).
- ▶ Mortality of acute DIC **30 to >80%**, dictated by the underlying illness.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Coagulation Disorders” (Disseminated Intravascular Coagulation section, Tables 121-2 & 121-3, Fig. 121-4 pathophysiology).
- ▶ **CMDT 2026** — “Disorders of Hemostasis, Thrombosis & Antithrombotic Therapy” (DIC diagnosis, Table 16-6 management algorithm, HELLP/Trousseau).
- ▶ **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — Acute Promyelocytic Leukaemia (early ATRA initiation; ATRA + arsenic trioxide).



Multiple Myeloma — Spectrum of Clinical Presentation and the Laboratory Investigations Aiding Diagnosis

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — Multiple myeloma (MM) is a malignant proliferation of a single clone of bone-marrow **plasma cells** that secrete a monoclonal immunoglobulin (**M-protein / paraprotein**) and produce end-organ damage. The clinical picture arises from three mechanisms: (1) **expansion of the neoplastic clone** in marrow and bone, (2) **secreted cell products** (intact immunoglobulin, free light chains, osteoclast-activating cytokines), and (3) the **host response** to the tumour. It is a disease of older adults (median age ~69 years, uncommon under 40), commoner in men and roughly twice as frequent in people of African descent. The cardinal clinical tetrad is captured by the mnemonic **CRAB** — hyperCalcaemia, Renal failure, Anaemia, Bone lesions.

Spectrum of clinical presentation — the cardinal (CRAB) features

Feature	Frequency / mechanism	Clinical manifestation
Bone pain / lytic disease	~70% (most common symptom); osteoclast activation by RANKL,	Back / rib / hip pain, pathological fracture (femoral neck, vertebrae), vertebral collapse,

Feature	Frequency / mechanism	Clinical manifestation
	MIP-1 α , IL-1, IL-6, TNF with osteoblast suppression by DKK-1	spinal cord / root compression; “punched-out” osteolytic lesions, diffuse osteopenia
Hyper-Calcaemia	Mobilisation of calcium from lysed bone	Lethargy, weakness, confusion, constipation, polyuria, dehydration, nephrocalcinosis; a leading cause of acute renal failure
Renal failure	~25% at presentation, some pathology in >50%	Light-chain cast nephropathy (“myeloma kidney”), hypercalcaemia, hyperuricaemia, light-chain deposition disease, AL amyloid, NSAIDs/contrast; earliest sign = adult Fanconi syndrome (type 2 proximal RTA)
Anaemia	~80%; marrow replacement, cytokine suppression of erythropoiesis, low erythropoietin, mild haemolysis	Fatigue, pallor, breathlessness; normocytic normochromic (occasionally megaloblastic from folate/B12 deficiency)

Other / less common presentations (must also be elaborated)

- ▶ **Recurrent bacterial infection** — second commonest problem; presenting feature in ~25%, and >75% suffer a serious infection. Due to **hypogammaglobulinaemia (immunoparesis)**, poor antibody response to polysaccharide antigens, T-cell and complement defects. Typical: pneumonia (*S. pneumoniae*, *S. aureus*, *K. pneumoniae*) and pyelonephritis (*E. coli*, gram-negatives).
- ▶ **Hyperviscosity syndrome** — headache, fatigue, visual disturbance, retinopathy, mucosal bleeding, ataxia, somnolence, heart failure, coma. Occurs above ~4 cP; most frequent with **IgM, IgG3 and IgA** paraproteins (IgM in ~50% vs 2–4% for IgG/IgA).
- ▶ **Neurological** — cord/root compression and radicular pain from bony collapse; carpal tunnel and sensorimotor neuropathy from **amyloid** infiltration; hypercalcaemic encephalopathy; treatment-related (thalidomide, bortezomib) neuropathy; IgM-associated neuropathy often directed against **myelin-associated glycoprotein (MAG)**.
- ▶ **Bleeding / thrombosis** — M-protein interferes with platelets and clotting factors (I, II, V, VII, VIII); DVT with immunomodulatory drugs (thalidomide/lenalidomide/pomalidomide); cryoglobulins → Raynaud’s.
- ▶ **Medical emergencies at presentation** — cord compression, pathological fracture, hyperviscosity, hypercalcaemic crisis, sepsis, acute kidney injury.

- ▶ **Variants / related syndromes** — **solitary bone plasmacytoma** (single lytic lesion, no marrow involvement) and **extramedullary plasmacytoma** (nasopharynx/paranasal sinuses); **POEMS syndrome** (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes ± sclerotic bone lesions/Castleman's/raised VEGF); **plasma cell leukaemia** (circulating plasma cells >2000/ μ L); **nonsecretory** and **light-chain-only** myeloma. Notably, splenomegaly, lymphadenopathy and gut involvement are *rare*.

Laboratory investigations — detecting and characterising the M-protein

- ▶ **Serum protein electrophoresis (SPEP)** — sharp “*church-spire*” *M-spike*, usually in the γ (sometimes β_2/α_2) region; must be ≥ 5 g/L (0.5 g/dL) to be quantitated. M-protein level is an excellent **tumour-burden marker** for monitoring therapy.
- ▶ **Immunofixation electrophoresis (IFE) / immunoelectrophoresis** — confirms monoclonality and the heavy + light chain isotype; more sensitive than SPEP for low-level M-protein.
- ▶ **Serum free light-chain (FLC) assay (Freelite) and κ/λ ratio** — quantifies light chains; essential in **light-chain-only, nonsecretory and oligosecretory** myeloma; an **involved:uninvolved FLC ratio ≥ 100** is itself a myeloma-defining biomarker.
- ▶ **24-hour urine electrophoresis + IFE** — quantitates **Bence Jones protein** (free light chains). Urine dipstick is *unreliable* for light chains and the heat test is falsely negative in ~50%.
- ▶ **Quantitative immunoglobulins** — show suppression of uninvolved isotypes (immunoparesis).
M-protein distribution: IgG ~53%, IgA ~25%, IgD ~1%; ~20% secrete light chains only; <1% are truly non-secretory.

Laboratory investigations — marrow, end-organ and imaging workup

Purpose	Investigation	Expected finding
Clonal plasma cells	Bone-marrow aspirate and trephine biopsy with κ/λ immunostaining, flow cytometry / IHC	Plasmacytosis ($\geq 10\%$ for diagnosis); CD138+, monoclonal κ or λ ; binucleate/multinucleate forms
End-organ damage	CBC with film; ESR; serum calcium, creatinine/urea, uric acid; albumin	Anaemia, marked rouleaux , very high ESR; raised Ca^{2+} /creatinine; normal alkaline phosphatase despite bone disease
Biochemical clues	Electrolytes / protein	Decreased anion gap (cationic M-protein retains Cl^-); pseudohyponatraemia ; raised total protein with reversed A:G ratio

Purpose	Investigation	Expected finding
Skeletal imaging	Whole-body low-dose CT / skeletal survey, ¹⁸ F-FDG PET-CT, MRI spine & pelvis	Lytic “punched-out” lesions, osteopenia, focal marrow lesions; radionuclide bone scan is <i>unhelpful</i> (no osteoblastic reaction)
Prognosis / risk	Serum β 2-microglobulin + albumin, LDH; FISH / DNA sequencing	β 2M and LDH for staging; del(17p)/TP53, t(4;14), t(14;16), t(14;20), 1q gain/1p del = high-risk
Selected cases	Abdominal fat-pad aspirate; serum viscosity; MYD88/CXCR4 if IgM	Amyloid (Congo red, apple-green birefringence); confirm hyperviscosity

Diagnostic criteria — IMWG (CRAB + SLiM)

- Diagnosis requires **clonal bone-marrow plasma cells $\geq 10\%$ (or biopsy-proven plasmacytoma) PLUS ≥ 1 myeloma-defining event:**
- **C** — hyperCalcaemia: serum Ca > 2.75 mmol/L (> 11 mg/dL) or > 0.25 mmol/L (> 1 mg/dL) above ULN
- **R** — Renal: creatinine clearance < 40 mL/min or serum creatinine > 177 μ mol/L (> 2 mg/dL)
- **A** — Anaemia: Hb < 100 g/L or > 20 g/L below the lower limit of normal
- **B** — Bone: ≥ 1 osteolytic lesion on radiography, CT or PET-CT
- **SLiM biomarkers of malignancy** (added in 2014 to allow earlier treatment): **S** = clonal marrow plasma cells $\geq 60\%$; **Li** = involved:uninvolved serum FLC ratio ≥ 100 ; **M** = > 1 focal lesion ≥ 5 mm on MRI.
- **Distinguish from precursors:** MGUS (M-protein < 30 g/L, marrow plasma cells $< 10\%$, no CRAB/SLiM; $\sim 1\%$ /year progression) and **smoldering MM** (M-protein ≥ 30 g/L and/or 10–60% marrow plasma cells, no end-organ damage).

Staging and prognosis

ISS stage	Criteria	Median survival
I	β 2-microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL	~ 62 months
II	Neither I nor III	~ 44 months
III	β 2-microglobulin > 5.5 mg/L	~ 29 months

- **Revised ISS (R-ISS)** adds **high-risk cytogenetics** [t(4;14), t(14;16), del(17p)] and **serum LDH** to the ISS: R-ISS I = ISS I + normal LDH + no high-risk FISH; R-ISS III = ISS III + (high-risk

cytogenetics or raised LDH). β 2-microglobulin is the single most powerful prognostic factor; the older Durie–Salmon system is no longer used.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Labelled “spectrum-of-disease” spider/wheel centred on a myeloma plasma cell with spokes labelled: *Bone* (lytic lesions, fracture, cord compression), *Kidney* (cast nephropathy, Fanconi), *Blood* (anaemia, rouleaux, hyperviscosity), *Calcium* (hypercalcaemia), *Immune* (infection, immunoparesis), *Nerve* (amyloid neuropathy, MAG).
- ▶ SPEP tracing: x-axis = albumin $\rightarrow$ α 1 $\rightarrow$ α 2 $\rightarrow$ β $\rightarrow$ γ ; mark a tall narrow “M-spike / church-spire” in the γ region; contrast with a normal broad polyclonal γ hump. Label *albumin*, *γ -globulin region*, *M-component*.

Clinical / Diagnostic significance

- ▶ Suspect MM in any older patient with unexplained **back pain + anaemia + raised ESR/total protein**, lytic lesions, hypercalcaemia or acute renal failure — order SPEP/IFE, serum FLC and 24-h urine together.
- ▶ A **normal alkaline phosphatase with extensive lytic disease** and a **negative bone scan** are characteristic and help separate MM from metastatic carcinoma.
- ▶ The serum FLC assay rescues the diagnosis of **light-chain, oligo- and non-secretory** disease that SPEP misses; the κ/λ ratio also drives prognosis (MGUS $\rightarrow$ MM risk) and response monitoring.
- ▶ Light-chain cast nephropathy is potentially **reversible** — aggressive hydration, chemotherapy and (in selected oliguric cases) plasma exchange can recover renal function.
- ▶ Bone disease is managed with **bisphosphonates** (zoledronate/pamidronate) or **denosumab**, radiotherapy for cord compression/painful sites, and vertebroplasty/kyphoplasty.

High-yield exam pointers

- ▶ Bone pain is the commonest symptom (~70%); CRAB defines symptomatic disease.
- ▶ Anaemia ~80%, renal failure ~25%, hypercalcaemia and recurrent infection complete the classic picture.
- ▶ CRAB + SLiM = IMWG myeloma-defining events; $\geq 60\%$ plasma cells, FLC ratio ≥ 100 , >1 MRI lesion allow treatment before organ damage.
- ▶ Triad of tests: SPEP/IFE (serum) + 24-h urine IFE (Bence Jones) + serum free light chains.
- ▶ Decreased anion gap, pseudohyponatraemia, marked rouleaux, high ESR, normal ALP are signature lab clues.
- ▶ β 2-microglobulin + albumin = ISS; add cytogenetics + LDH for R-ISS.
- ▶ High-risk genetics: del(17p)/TP53, t(4;14), t(14;16), t(14;20), 1q gain — NOT t(11;14) or del(13).
- ▶ Radionuclide bone scan is useless; use skeletal survey/CT, MRI, or PET-CT.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Plasma Cell Disorders" (Multiple Myeloma: pathogenesis, clinical manifestations, IMWG diagnostic criteria Table, laboratory workup Table, ISS staging).
- ▶ DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e — "Plasma Cell Neoplasms" (Original ISS and **Revised ISS / mSMART** risk stratification).
- ▶ CMDT 2026 — "Plasma Cell Myeloma" (clinical findings, rouleaux/ESR, M-protein distribution, imaging and current management).



Enumerate the triggers, clinical presentation and management of acute chest syndrome in sickle cell disease

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — *Acute chest syndrome (ACS)* is an acute, pneumonia-like, vaso-occlusive complication of sickle cell disease (SCD) defined by a **new pulmonary infiltrate on chest radiograph involving at least one complete lung segment**, together with respiratory symptoms and/or fever. It is the **second most frequent acute sickle cell-related event** (after the acute painful episode), occurs in **>50% of patients** (often recurrently), and is a **leading cause of death and ICU admission** in adults with SCD. It results from the interplay of pulmonary vaso-occlusion, fat embolism, infection and hypoventilation, and ranges from a mild self-limiting illness (especially in children) to fulminant multilobar disease with ARDS, multiorgan failure and rapid death.

Pathophysiology in brief

- ▶ HbS ($\beta 6 \text{ Glu} \rightarrow \text{Val}$) polymerises when deoxygenated; the rate of polymerisation depends on roughly the **30th power of HbS concentration**, so small falls in oxygen saturation, pH or cell hydration markedly accelerate sickling.
- ▶ Sickled, rigid erythrocytes and *irreversibly sickled cells (ISCs)* occlude the **pulmonary microvasculature**, producing in-situ thrombosis, regional hypoxia and a self-amplifying cycle of further sickling.
- ▶ Intravascular **haemolysis scavenges nitric oxide**, activates endothelium and platelets, and is pro-inflammatory and vasoconstrictive — promoting lung injury and pulmonary vasculopathy.
- ▶ A final common pathway is **ventilation-perfusion mismatch and worsening hypoxaemia**, which begets more polymerisation: the cardinal vicious cycle of ACS.

Triggers / precipitating factors

ACS is frequently **multifactorial**, and a single cause is identified in fewer than half of episodes. The recognised triggers are:

Category	Specific triggers
Infection	Any infection — viral (common in children), bacterial and atypical organisms; pneumonia is a classic precipitant
Vascular / embolic	In-situ pulmonary microvascular thrombosis; pulmonary infarction; fat / bone-marrow embolism from infarcted (necrotic) marrow — the cause of the most severe, often fatal episodes
Hypoventilation	Postoperative hypoventilation; splinting from rib/sternal or thoracic-bone infarction pain; opioid-induced respiratory depression during treatment of an acute painful episode
Iatrogenic / fluid	Over-hydration (pulmonary oedema) and excessive opioids compound dyspnoea and hypoxia
Antecedent painful crisis	ACS follows within 72 h in ~25% (about one-quarter) of admissions for an acute painful episode
Other	Asthma/bronchospasm (very common in SCD); surgery and general anaesthesia; cold exposure, dehydration and hypoxia (shared sickling triggers)

Clinical presentation

- ▶ **Cardinal features (major diagnostic criteria):** chest pain, cough, fever, hypoxia, and a new pulmonary infiltrate on chest x-ray.
- ▶ **Respiratory:** tachypnoea, dyspnoea, wheeze, pleuritic chest pain; falling SpO₂; in severe disease, multilobar consolidation with profound hypoxaemia.
- ▶ **Systemic:** fever (often ≥ 38.5 °C), tachycardia, leucocytosis; frequently superimposed on an ongoing acute painful episode involving ribs, sternum or spine.
- ▶ **Spectrum:** *mild* (children, often viral) → *devastating* (adults — multiple lobes affected, severe hypoxia, multiorgan failure and death).
- ▶ **Course:** because the infiltrate may lag behind symptoms, an initially normal CXR does **not** exclude ACS; serial radiographs and pulse oximetry are essential.
- ▶ **Differential diagnosis:** must be distinguished from **infective pneumonia** (overlapping and often coexistent), pulmonary thromboembolism, fluid overload/pulmonary oedema, and from sepsis/multiorgan failure.

Predictors of severe disease

- ▶ Thrombocytopenia, leucocyte count $>20,000/\mu\text{L}$, and a rapidly developing/drastic fall in haemoglobin portend severe ACS with ARDS and multiorgan failure.

- ▶ The most catastrophic cases are typically due to **embolisation of necrotic bone marrow (fat embolism)** and may progress to death even with prompt, correct treatment.
- ▶ Multiorgan failure (CNS, liver, muscle, lung, kidney) can accompany severe ACS and is easily confused with — and may coexist with — sepsis.

Management

General principle: **severity-driven**, supportive and pre-emptive, with the threshold for transfusion and ICU care kept deliberately low.

Intervention	Practical detail
Monitoring & disposition	Hypoxic, febrile patients may be admitted directly to the ICU ; continuous pulse oximetry / monitored beds for the first 48–72 h of any pain admission help detect early ACS
Oxygen	Supplemental O ₂ for SpO ₂ <95% (or hypoxaemia); titrate to maintain saturation
Antibiotics	Almost always given , even though a causative organism is seldom cultured; cover typical and atypical respiratory pathogens
Analgesia	Adequate pain control to permit deep breathing — but avoid excessive opioids (respiratory depression worsens hypoxia)
Fluids	Careful hydration; avoid over-hydration (precipitates/worsens pulmonary oedema)
Incentive spirometry	Used during painful episodes to forestall pulmonary complications/atelectasis and ACS
Transfusion	Indicated for hypoxic, febrile patients with leucocytosis and more than a trivial infiltrate . Simple (top-up) transfusion suffices for less severe cases. Automated red-cell exchange transfusion is the preferred modality in severe ACS (and in stroke / multiorgan failure). If exchange will take hours to arrange in a severely ill patient, start a simple/top-up transfusion first
Transfusion safety	Extended red-cell antigen phenotyping where possible; antigen-match for Rh (C/c, E/e) and K in addition to ABO/RhD to reduce alloimmunisation
Supportive / ICU	Bronchodilators for bronchospasm/asthma; VTE prophylaxis; treat multiorgan failure with exchange transfusion and full ICU support

Preventive (disease-modifying) therapy that reduces ACS:

- ▶ **Hydroxyurea** — standard of care for HbSS and HbS- β^0 thalassaemia; raises HbF and **reduces pain and ACS by about half** and long-term mortality by ~49%. Adult dosing titrated to maximum tolerated dose by neutrophil/platelet counts (CMDT: 15–35 mg/kg/day); start infants at ~20 mg/kg from 9 months of age.
- ▶ **L-glutamine** — reduces painful episodes (~25%) and favourably modulates ACS.
- ▶ **Crizanlizumab** (anti-P-selectin) and **voxelotor** (increases Hb-O₂ affinity) modulate vaso-occlusion; **chronic transfusion** is used for recurrent severe ACS.
- ▶ **Curative options**: HLA-matched allogeneic stem-cell transplant (event-free survival >95% with matched related donor) and approved **ex-vivo gene therapies** (lovotibeglogene autotemcel — HbA^{T87Q}; exagamglogene autotemcel — CRISPR/Cas9 disruption of *BCL11A* to raise HbF).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Vicious cycle of ACS (flow diagram)**. Labels: *Trigger (infection / fat embolus / hypoventilation / pain) → Regional hypoxia & low pH → HbS polymerisation & sickling → Pulmonary microvascular vaso-occlusion + in-situ thrombosis → V/Q mismatch → Worsening hypoxaemia → (arrow looping back to HbS polymerisation); side-branch Intravascular haemolysis → NO depletion → endothelial activation/inflammation.*
- ▶ **Annotated chest radiograph schematic**. Labels: *new infiltrate involving ≥1 complete lung segment, multilobar consolidation, basal predominance, small pleural effusion* — captioned “ACS: new pulmonary infiltrate + respiratory symptom/fever/hypoxia.”

Clinical / Diagnostic significance

- ▶ **Definition (NHLBI/standard)**: a new radiodensity on CXR involving ≥1 complete lung segment, plus ≥1 of chest pain, fever ≥38.5 °C, tachypnoea/wheeze/cough, or hypoxia — operationalises the major criteria for the exam and the ward.
- ▶ **Investigations**: CBC (falling Hb, leucocytosis, platelet count), reticulocytes, ABG/pulse oximetry, chest radiograph (serial), blood and respiratory cultures, atypical-pathogen testing; consider CT-pulmonary angiography if thromboembolism is suspected.
- ▶ **Pearls**: an antecedent painful crisis is the commonest setting — anticipate ACS in the first 72 h; keep opioids and IV fluids restrained; transfuse early for hypoxia with infiltrate; **exchange (not simple) transfusion** for severe/multiorgan disease; antibiotics empirically despite negative cultures.
- ▶ ACS may leave a **chronic restrictive deficit with reduced DLCO** and contributes to pulmonary hypertension — both markers of poor long-term prognosis.

High-yield exam pointers

- ▶ ACS = new lung-segment infiltrate + (chest pain / fever / tachypnoea-cough-wheeze / hypoxia); second commonest acute SCD event, >50% lifetime incidence.

- ▶ Four classic trigger groups: **infection, fat/marrow embolism, in-situ pulmonary thrombosis, postoperative hypoventilation** — often multifactorial; cause unidentified in most.
- ▶ ~25% of acute pain admissions develop ACS within 72 h — monitor with pulse oximetry for 48–72 h.
- ▶ Severity predictors: **platelets ↓, WBC >20,000/μL, rapidly falling Hb** → ARDS/multiorgan failure; the worst cases are **bone-marrow fat embolism**.
- ▶ Treatment quartet: **oxygen (SpO₂ <95%), antibiotics, judicious analgesia/fluids, transfusion** — **exchange transfusion for severe disease**.
- ▶ **Avoid over-hydration and over-sedation with opioids** — both worsen hypoxia.
- ▶ **Incentive spirometry** prevents ACS during painful crises; **hydroxyurea halves ACS** as long-term prophylaxis.
- ▶ Transfuse with **Rh (C/c, E/e) and K antigen-matched** units to limit alloimmunisation.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Disorders of Hemoglobin” (sickle cell disease; complications — Acute Chest Syndrome; transfusion and disease-modifying therapy).
- ▶ **CMDT 2026** — “Blood Disorders” (Sickle Cell Anemia) for current management, drug regimens and the hemoglobin-distribution table.

Coverage note: The dedicated specialty text listed in the spec (DeVita's Cancer — haematological malignancies) contains only a single passing mention of ACS and is not the appropriate subspecialty source for this benign-haematology topic; depth was therefore drawn from Harrison 22e supplemented by CMDT 2026. The precise NHLBI consensus definition (“new radiodensity involving ≥1 complete lung segment plus a respiratory symptom/fever/hypoxia”) and the naming of atypical organisms (*Mycoplasma*, *Chlamydophila*) are universally accepted standard internal medicine stated for completeness beyond Harrison's exact “major diagnostic criteria” phrasing.



Flow cytometry: principle and application

Asked in: Paper I Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Flow cytometry is a laser-based technique that simultaneously measures multiple physical and antigenic characteristics of single cells as they flow, one at a time, in a fluid stream past a focused beam of light. Each cell is interrogated for its **size, internal complexity (granularity), and the panel of surface/intracytoplasmic molecules** bound by fluorochrome-labelled monoclonal antibodies — its *antigen footprint* or **immunophenotype**. Because it can characterise thousands of cells per second across several parameters at once (*multiparametric analysis*), it is indispensable in

haematology for diagnosing and sub-classifying leukaemias and lymphomas, detecting paroxysmal nocturnal haemoglobinuria (PNH), enumerating CD4 T-cells and CD34 stem cells, and tracking minimal residual disease (MRD). When the instrument also physically deflects and collects cells of interest it is called **fluorescence-activated cell sorting (FACS)**.

Principle and instrumentation

- ▶ **Pre-requisite — a single-cell suspension:** prepared from peripheral blood, bone marrow, body fluids (CSF, pleural/peritoneal), or *disaggregated solid tissue*; cells are stained with **fluorochrome-conjugated monoclonal antibodies** directed against the chosen antigens.
- ▶ Three integrated systems make up the cytometer:
 - **Fluidics** — *hydrodynamic focusing*: a fast outer sheath fluid constrains the sample core so cells file past the laser in **single line, one cell at a time**.
 - **Optics** — one or more **lasers** (e.g., 488 nm argon-blue) illuminate each cell; lenses, dichroic mirrors and band-pass filters separate the emitted light by wavelength onto detectors.
 - **Electronics** — **photodiodes/photomultiplier tubes (PMTs)** convert light pulses into digital voltage signals proportional to the parameter measured.
- ▶ **Two scatter (intrinsic) signals — require no antibody:**
 - **Forward scatter (FSC)** — light scattered in the direction of the beam; proportional to **cell size**.
 - **Side scatter (SSC)** — light scattered at $\sim 90^\circ$; proportional to **internal complexity/granularity** (e.g., high in granulocytes, low in lymphocytes).
- ▶ **Fluorescence (extrinsic) signals:** each bound fluorochrome absorbs laser light and re-emits at a longer wavelength; common dyes excited at 488 nm include **FITC (green)**, **PE (orange)**, **PerCP and PE-Cy5/APC tandems (red)** — allowing several antigens to be measured on one cell simultaneously.
- ▶ **Gating & display:** populations are electronically “gated” on dot-plots/histograms (classically **CD45 vs SSC** to resolve blasts, lymphocytes, monocytes and granulocytes), then analysed for their marker profile.
- ▶ **Cell sorting (FACS):** charged droplets containing target cells are deflected by electrostatic plates into collection tubes — used to purify CD34 stem cells or rare tumour cells (e.g., flow-sorting Hodgkin/Reed-Sternberg cells for sequencing).

Immunophenotyping — the antigen footprint

- ▶ The immunophenotype is *valuable diagnostically because it distinguishes specific tumour subtypes*, even though “stage of differentiation” itself does not predict natural history (Harrison).
- ▶ **Clonality** is the key malignant signature detectable by flow:

- **B-cell clonality** — *surface immunoglobulin light-chain restriction* (skewed kappa : lambda ratio) instead of the polyclonal mix of reactive lymphocytes.
 - **T-cell clonality** — aberrant antigen loss or an abnormal CD4:CD8 pattern (TCR clonality usually needs PCR).
- Antibodies may target **surface, cytoplasmic** (e.g., cytoplasmic CD3, CD79a, MPO) or **nuclear** antigens (e.g., TdT) after permeabilisation.

Lineage	Characteristic CD / marker profile
Haematopoietic stem/progenitor	CD34, CD117 (c-Kit), CD90 (Thy-1), CD133; TdT (lymphoblasts)
B-lymphoid	CD19, CD20, CD22, CD79a; surface Ig (kappa/lambda)
T-lymphoid	CD3, CD2, CD5, CD7, CD4, CD8
NK cell	CD16, CD56, CD57
Myeloid/monocytic	CD13, CD33, CD117, MPO; CD14, CD64 (monocytic)
Erythroid / megakaryocytic	CD71, glycophorin A; CD41, CD61
Plasma cell	CD138, CD38, CD56; cytoplasmic light-chain restriction
Common leucocyte / gating	CD45 (bright on lymphocytes, dim on blasts)

Applications in haematology and beyond

- **Acute leukaemia** — distinguishes AML (CD13, CD33, CD117, MPO+) from ALL, and B-ALL (CD19, CD10, TdT, cyto-CD79a) from T-ALL (cyto-CD3, CD7); identifies mixed-phenotype/biphenotypic acute leukaemia and acute promyelocytic leukaemia.
- **Chronic lymphocytic leukaemia (CLL)** — diagnostic immunophenotype is CD5+ CD19+ CD20(dim) CD23+ with light-chain restriction; a monoclonal B-cell count $\geq 5 \times 10^9/L$ defines CLL; flow confirms monoclonality in marrow/blood (DeVita).
- **Non-Hodgkin lymphoma sub-typing:**
 - *Follicular lymphoma* — CD19, CD20, CD10, BCL6 positive, CD5 and CD23 negative.
 - *Marginal-zone/MALT lymphoma* — CD19, CD20, CD22, CD79a positive; **negative for CD5, CD10, CD23 and cyclin D1**; light-chain restriction separates it from reactive infiltrates.
 - *Mantle cell* — CD5+, cyclin D1/t(11;14) (corroborated by FISH/IHC).
- **Hodgkin lymphoma** — flow-sorted Hodgkin/Reed-Sternberg cells express **bright CD30, CD15, CD40, CD95, CD64 but NOT CD20** (DeVita, Fig 66.4).
- **Paroxysmal nocturnal haemoglobinuria (PNH)** — flow is the **gold-standard** diagnostic test (replaces the old Ham/acidified-serum and sucrose lysis tests); see below.

- ▶ **Multiple myeloma / plasma-cell disorders** — peripheral-blood flow detects and quantifies circulating plasma cells; multiparametric flow estimates the **plasma-cell proliferative (S-phase) rate**; “absence of clonal plasma cells by 2- to 4-colour flow” is part of stringent CR; sensitive MRD assessment.
- ▶ **Minimal residual disease (MRD)** — multiparameter flow (alongside PCR/NGS) detects sub-microscopic residual leukaemia/lymphoma; uMRD status is independently prognostic in CLL and ALL.
- ▶ **CD4+ T-cell enumeration in HIV/AIDS** — flow cytometry is the standard method to count CD4 T-cells for staging (AIDS = CD4 <200/ μ L) and monitoring antiretroviral therapy.
- ▶ **CD34+ haematopoietic stem-cell enumeration** — quantifies the graft for autologous/allogeneic transplantation and apheresis adequacy.
- ▶ **DNA content / cell-cycle analysis** — DNA-binding dyes measure **ploidy (aneuploidy)** and **S-phase fraction** as prognostic markers in tumours.
- ▶ **Other uses** — lymphocyte subset quantitation in primary immunodeficiency (e.g., absent B and NK cells in GATA2 deficiency); **CSF flow cytometry** for lymphomatous/leukaemic meningitis; reticulocyte counting; fetomaternal haemorrhage (fetal Hb cells); platelet function/receptor disorders (CD41/CD61 in Glanzmann, CD42 in Bernard-Soulier); HLA-B27 typing; flow-based crossmatch in transplantation; increasing the sensitivity of antibody detection in autoimmune haemolytic anaemia to as few as 30–40 molecules per red cell.

PNH — the model “flow cytometry diagnosis”

- ▶ PNH arises from a somatic **PIGA** mutation → shortage of the **GPI anchor** → loss of GPI-linked complement-regulatory proteins **CD55 (DAF)** and **CD59 (MIRL)** from blood cells, causing complement-mediated intravascular haemolysis.
- ▶ Flow shows a **bimodal distribution**: a discrete population of cells that is **CD55 and CD59 negative** alongside normal cells.
- ▶ Run on **both granulocytes and red cells** (granulocytes avoid the confounding effect of haemolysis/transfusion on red cells); **FLAER** (fluorescein-labelled aerolysin, which binds GPI) is the preferred reagent for white cells.
- ▶ A diagnosis of PNH requires a *substantial* clone — roughly **≥5% of red cells and ≥20% of granulocytes** GPI-deficient (Harrison).
- ▶ Small PNH clones are detected by sensitive flow in **half or more of aplastic-anaemia patients** at presentation and signal an immune (immunosuppression-responsive) pathophysiology.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Schematic of a flow cytometer (label exactly)**: *Sample (single-cell suspension) → Sheath fluid → Flow cell / hydrodynamic focusing → Laser beam (488 nm) → Forward scatter*

detector (FSC = size) → Side scatter detector (SSC = granularity, 90°) → Dichroic mirrors/filters → Fluorescence PMTs (FITC / PE / APC) → Computer (dot-plot & histogram) → (FACS) charged-droplet deflection plates → collection tubes.

- ▶ A CD45-vs-SSC gating dot-plot labelling lymphocytes (CD45-bright, low SSC), monocytes, granulocytes (high SSC), and the blast gate (CD45-dim, low SSC); OR a PNH histogram showing the bimodal CD59-positive (normal) vs CD59-negative (PNH) red-cell populations.

Clinical / Diagnostic significance

- ▶ Provides **rapid, objective, quantitative** lineage assignment and clonality that, combined with morphology, cytochemistry, cytogenetics/FISH and molecular studies, completes the modern WHO classification of leukaemias and lymphomas.
- ▶ Works on **tiny / hypocellular samples** (CSF, fine-needle aspirates, “dry-tap” marrows) where histology may be insufficient.
- ▶ Enables **prognostication and MRD-guided therapy** (CLL, ALL, myeloma), **CD4-based HIV staging, stem-cell graft quantification**, and definitive, non-invasive diagnosis of PNH.
- ▶ Limitations: needs a viable single-cell suspension (poor for sclerotic/Hodgkin-rich tissue with few tumour cells), cannot show architecture (complementary to immunohistochemistry), is operator/panel-dependent, and degrades with delayed/old samples.

High-yield exam pointers

- ▶ FSC = cell size; SSC = granularity/internal complexity — the two antibody-independent parameters.
- ▶ **Hydrodynamic focusing** lines cells up singly; lasers + PMTs + fluorochromes (FITC/PE/APC) give multiparametric data.
- ▶ **CD45 vs SSC** is the standard gating plot; **light-chain (kappa:lambda) restriction** = B-cell clonality.
- ▶ PNH = flow is gold standard → **CD55 & CD59 negative**, bimodal, use **granulocytes + FLAER**; clone ≥5% RBC / ≥20% granulocytes.
- ▶ **CLL** = CD5+CD19+CD23+; **AML** = CD13/CD33/CD117/MPO; **B-ALL** = CD19/CD10/TdT.
- ▶ **Hodgkin/RS cells** = CD30+ CD15+ CD20– (flow-sorted).
- ▶ Flow enumerates **CD4 T-cells (HIV)** and **CD34 stem cells (transplant)**; tracks **MRD**.
- ▶ **FACS** = the sorting variant (charged-droplet deflection); also measures **DNA ploidy & S-phase**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Non-Hodgkin's Lymphoma” (immunophenotype/antigen footprint, single-cell suspension method, FL/MZL markers,

light-chain restriction); “Hemolytic Anemias” (PNH flow cytometry, CD55/CD59, bimodal clone, $\geq 5\%$ / $\geq 20\%$ thresholds, AIHA antibody sensitivity); “Bone Marrow Failure Syndromes including Aplastic Anemia and Myelodysplasia” (PNH-clone detection, GATA2); “Hematopoietic Stem Cells” (CD34/CD90/CD117/CD133); “Hematopoietic Cell Transplantation”; “HIV Disease/AIDS” (CD4 staging).

- ▶ **DeVita, Hellman, and Rosenberg’s Cancer: Principles & Practice of Oncology, 12e** — CLL immunophenotype (CD5/CD19/CD23) and MRD by flow; Hodgkin/Reed-Sternberg flow immunophenotype (CD30/CD15/CD40/CD95/CD64, not CD20); multiple-myeloma circulating plasma cells, S-phase and clonal-PC CR criteria; CSF flow cytometry in leptomeningeal disease; DNA/ploidy analysis.
- ▶ **CMDT 2026** — “Blood Disorders” (PNH: flow cytometry demonstrates deficiencies of CD55 and CD59).
- ▶ *Coverage note:* This is a laboratory-technique topic and Harrison/DeVita cover it **applied within disease chapters** rather than as a stand-alone “method” section. The detailed instrument physics (hydrodynamic focusing, FSC/SSC definitions, named fluorochromes FITC/PE/APC, PMTs, droplet-based FACS) and a few standard application specifics (FLAER reagent for PNH white cells; CD41/CD61 and CD42 in platelet disorders; CD4 counting “by flow cytometry”; reticulocyte/fetomaternal-haemorrhage assays) are **universally accepted standard laboratory/internal-medicine knowledge** included to satisfy the “principle” half of the question, as they are not described verbatim in the available corpus. All disease-specific marker panels, the PNH thresholds, and the clonality concepts are corpus-grounded as cited above.



Hereditary Spherocytosis

Asked in: Paper IV Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Hereditary spherocytosis (HS) is the commonest inherited haemolytic anaemia due to a **defect of the red-cell membrane–cytoskeleton complex**, in which mutations affecting the *vertical* anchoring proteins (ankyrin, band 3, spectrin, band 4.2) uncouple the lipid bilayer from the underlying cytoskeleton. The resulting loss of membrane surface area produces rigid, poorly deformable **spherocytes** that are selectively trapped and destroyed in the spleen (extravascular haemolysis). It was first described by *Minkowski and Chauffard* in the late 19th century, who recognised spherocytes in the peripheral blood and their abnormal susceptibility to lysis in hypotonic media. Estimated prevalence is 1:2000–1:5000 in populations of European ancestry, making it the most common HS of this group.

Molecular basis and genetics

- ▶ The red-cell cytoskeleton is built on the **spectrin tetramer** (head-to-head association of two α -spectrin/ β -spectrin heterodimers), linked to the overlying membrane through two multiprotein bridges: the **ankyrin complex** (ankyrin + band 3 [AE1] + band 4.2) and the **junctional complex** (band 4.1R + actin + adducin + dematin).
- ▶ The ankyrin complex provides mainly **vertical (radial)** connections; the junctional complex provides **horizontal (tangential)** connections. Pathogenic changes that weaken *vertical* links cause **spherocytosis**, whereas defects of *horizontal* links cause elliptocytosis; spectrin defects can cause either.
- ▶ **Band 3** (anion exchanger, ~1.2 million copies/cell) is the most abundant membrane protein; its surface exposure with ageing creates the antigenic signal for macrophage clearance — a process accelerated in HS.
- ▶ HS is **genetically heterogeneous** — a single phenotype arising from mutations in any one of several genes. Inheritance is most often **autosomal dominant** (heterozygous), but the most severe forms are **autosomal recessive** (homozygous). A negative family history may reflect either a **de novo mutation** or a recessive form.

Gene	Protein	Inheritance in HS	Approx. share / comment
ANK1 (8p11.2)	Ankyrin	Dominant	May account for the majority of HS
SLC4A1 (17q21)	Band 3 (AE1)	Dominant	~25% of HS
SPTB (14q23–q24)	β -spectrin	Dominant	Rare
SPTA1 (1q22–q23)	α -spectrin	Recessive	Rare; severe biallelic forms
EPB42 (15q15–q21)	Band 4.2	Recessive	~3% of HS

Pathophysiology

- ▶ A *vertical* anchoring defect leaves regions of the lipid bilayer unsupported by the cytoskeleton → the membrane **vesiculates and is shed** → progressive **loss of surface area relative to volume** → the biconcave disc becomes a **spherocyte**.
- ▶ Spherocytes have reduced **deformability**. As they traverse the narrow fenestrations of the **splenic** red pulp cords, the metabolically stressed, low-glucose, acidic environment promotes further membrane loss (“splenic conditioning”), and the cells are ultimately phagocytosed by splenic macrophages.
- ▶ The spleen therefore plays a **dual role**: it both *worsens* the membrane lesion (vesiculation on transit) and is the *major site of destruction*. This explains why splenectomy is therapeutically effective even though it does not correct the underlying defect.

- ▶ Chronic extravascular haemolysis → unconjugated hyperbilirubinaemia, raised LDH, reduced haptoglobin, reticulocytosis, and a tendency to **pigment (bilirubinate) gallstones** and **splenomegaly**.

Clinical presentation

- ▶ **Wide spectrum of severity**. Severe cases present in **infancy** with neonatal jaundice or transfusion-dependent anaemia; mild cases may present in young adults or even later, sometimes only when gallstones are detected.
- ▶ The classic triad is **anaemia, jaundice and splenomegaly**; the discovery of **gallstones in a young person** frequently triggers diagnostic work-up.
- ▶ Haemolysis is often **compensated** (no anaemia) but may *decompensate* with intercurrent stress — pregnancy, infection, folate deficiency or renal impairment reducing erythropoietin.
- ▶ **Crises**: (1) *Aplastic crisis* from **parvovirus B19** infection causing transient red-cell aplasia and a precipitous fall in haemoglobin; (2) *Haemolytic crisis* with intercurrent infection; (3) *Megaloblastic crisis* from folate depletion. Chronic skull marrow expansion can cause frontal bossing in severe congenital cases.

Diagnosis and investigations

- ▶ **Full blood count / film**: normocytic anaemia with **spherocytes** (small, densely staining cells lacking central pallor) on the smear; **reticulocytosis**.
- ▶ **Red-cell indices** are highly suggestive: **MCHC >34 g/dL** (cells are dehydrated/spheroidal) with raised **RDW >14%** and a normal or slightly low MCV — a powerful screening clue from a routine blood count.
- ▶ **Haemolysis markers**: raised unconjugated bilirubin and AST, raised urinary/faecal urobilinogen; LDH increased and haptoglobin reduced when an intravascular component is present.
- ▶ **Confirmatory tests** (when family history is negative or a recessive form is suspected):
 - **Osmotic fragility test** — classically *increased* fragility in hypotonic saline (the historical diagnostic test); sensitivity improves after 24-h incubation.
 - **Acid glycerol lysis test (AGLT)** — accelerated lysis.
 - **Eosin-5'-maleimide (EMA)-binding test** by flow cytometry — *reduced* fluorescence (band 3 / Rh-related membrane protein deficiency); a sensitive, widely used screen.
 - **SDS-PAGE** of membrane proteins — quantifies the specific deficient protein.
 - **Ektacytometry** (osmotic gradient / laser diffraction) — measures deformability and reliably **distinguishes spherocytosis from stomatocytosis**.
 - **Molecular genetic studies** for a definitive answer in ambiguous cases.
- ▶ A negative **direct antiglobulin (Coombs) test** is essential to separate HS from **autoimmune haemolytic anaemia**, which can also produce spherocytes.

Treatment

- ▶ No causal therapy exists; management is supportive and directed at the spleen and its complications.
- ▶ Splenectomy abolishes or markedly reduces haemolysis. Current recommendations: perform at age 4–6 years in severe cases, delay to puberty in moderate cases, and avoid in mild cases; partial (subtotal) splenectomy is an option that preserves some splenic immune function. Knowledge of outcomes in affected relatives helps guide the decision.
- ▶ Pre-splenectomy vaccination against encapsulated organisms — *Streptococcus pneumoniae* and *Neisseria meningitidis* (and *Haemophilus influenzae* type b) — is imperative; penicillin prophylaxis afterwards is recommended in children though its value in older patients is debated.
- ▶ Cholecystectomy (usually laparoscopic) should be done — often at the same sitting as splenectomy — only when gallstones are symptomatic/clinically indicated, not automatically.
- ▶ Supportive care: folic acid supplementation for the increased erythropoietic demand; blood transfusion during aplastic/haemolytic decompensation; in the <10% of most severe (transfusion-dependent) infants, erythropoietin may be transfusion-sparing, and recurrent transfusion mandates iron-overload surveillance and chelation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Red-cell membrane–cytoskeleton complex (schematic). Labels: lipid bilayer; band 3 (anion exchanger AE1); glycophorin A; ankyrin; protein band 4.2; α -spectrin and β -spectrin (tetramer); actin; band 4.1R; adducin; dematin; mark the ankyrin (vertical) complex vs the junctional (horizontal) complex — annotate “vertical-link defect $\rightarrow$ spherocytosis.”
- ▶ Peripheral blood smear / surface-area concept. Draw a normal biconcave disc beside a spherocyte (small, round, loss of central pallor); annotate “membrane vesiculation $\rightarrow$ $\downarrow$ surface-area-to-volume ratio $\rightarrow$ $\downarrow$ deformability $\rightarrow$ splenic trapping.” Optionally an osmotic fragility curve with the HS curve shifted left (lysis at higher NaCl concentration).

Clinical / Diagnostic significance

- ▶ Triad to recognise: haemolytic anaemia + splenomegaly + pigment gallstones in a young patient with autosomal-dominant family history.
- ▶ The MCHC >34 g/dL + spherocytes + reticulocytosis + negative DAT quartet is effectively diagnostic at the bedside; EMA-binding/osmotic fragility confirm it.
- ▶ Parvovirus B19 is the classic cause of aplastic crisis — anticipate it during any abrupt fall in haemoglobin.
- ▶ Splenectomy decisions balance haemolysis control against lifelong risk of overwhelming post-splenectomy infection (OPSI) and thrombosis — hence vaccination, prophylaxis and age thresholds.

- ▶ Distinguish from AIHA (DAT-positive), G6PD/pyruvate-kinase deficiency, and from dehydrated/overhydrated stomatocytosis (ektacytometry), in which splenectomy is *contraindicated* due to thrombo-embolic risk.

High-yield exam pointers

- ▶ HS = **vertical** membrane-protein defect (ankyrin/band 3/spectrin/4.2); elliptocytosis = horizontal (band 4.1/spectrin) defect.
- ▶ ANK1 (ankyrin) = commonest gene; band 3 (SLC4A1) ~25%; mostly **autosomal dominant**.
- ▶ Hallmark lab clue: **MCHC >34 g/dL**, **RDW >14%**, normal/low MCV, spherocytes, reticulocytosis.
- ▶ Best screening confirmatory tests today: **EMA-binding (flow cytometry)** and **osmotic fragility**; **ektacytometry** separates HS from stomatocytosis.
- ▶ **DAT (Coombs)** is **NEGATIVE** — separates HS from immune spherocytosis.
- ▶ **Splenectomy** at **4–6 yr (severe)** / puberty (moderate); avoid in mild — vaccinate against pneumococcus, meningococcus, Hib first.
- ▶ Haemolysis is **extravascular** → unconjugated bilirubin↑, LDH↑, haptoglobin↓, **pigment gallstones**, splenomegaly.
- ▶ Complications: **aplastic crisis (parvovirus B19)**, gallstones, folate-deficiency megaloblastic crisis; give **folic acid**.
- ▶ No curative therapy; **erythropoietin** may spare transfusions in severe infants; the most severe ~<10% are transfusion-dependent.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “**Hemolytic Anemias**” (red-cell membrane–cytoskeleton complex; Hereditary Spherocytosis section, Table of inherited membrane-cytoskeleton diseases, diagnostic tests and treatment). Primary source for this answer.
- ▶ **CMDT 2026** — “**Blood Disorders**” (haemolytic-anaemia classification and supportive context).
- ▶ *Coverage note:* The dedicated specialty text listed in the spec (**DeVita's Cancer**) covers haematologic *malignancies* and does **not** address hereditary spherocytosis, so it was not used. CMDT covers HS only briefly within its haemolysis classification; depth is therefore drawn from Harrison. Universally accepted standard points not stated verbatim in the corpus — *H. influenzae* type b vaccination, negative direct Coombs test, and folate/gallstone associations — are included as established internal-medicine teaching.



Hypoproliferative Anemias

Asked in: Paper IV Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — *Hypoproliferative (underproduction) anemias* are those in which anemia results from **inadequate red-cell production by the bone marrow** rather than from blood loss or accelerated destruction. They are characterised by an **inappropriately low reticulocyte response** for the degree of anemia (low absolute reticulocyte count; reticulocyte production index $<2-2.5$) with a marrow that fails to amplify erythropoiesis. They are the **largest group of anemias** — **at least 75% of all cases** — the commonest being iron deficiency and anemia of inflammation. The functional erythron requires three things: **renal erythropoietin (EPO)**, a **competent erythroid marrow**, and **adequate substrate (iron, folate, vitamin B12)**; a defect in any one produces a hypoproliferative anemia.

Pathophysiology — why production fails

- ▶ Erythropoiesis is driven by EPO, a glycoprotein made by renal peritubular interstitial cells; its synthesis is governed by **hypoxia-inducible factor (HIF)-1 α** . When haemoglobin falls below 100–120 g/L (10–12 g/dL), plasma EPO rises **logarithmically**.
- ▶ The pronormoblast undergoes **4–5 divisions** → **16–32 mature red cells**; with EPO stimulation, production can rise **4–5 fold in 1–2 weeks** — but *only if iron supply is adequate*.
- ▶ Hypoproliferation occurs when EPO is deficient, when the marrow cannot respond (aplasia, infiltration, dysplasia), or when substrate (chiefly iron) is unavailable or sequestered.
- ▶ The reticulocyte count is the **physiological pivot**: an elevated count signals haemolysis/haemorrhage (hyperproliferation), whereas a low/inappropriately normal count defines the hypoproliferative mechanisms.

Classification by mechanism (cause-based)

Mechanism	Representative causes
Nutritional / substrate deficiency	Iron, vitamin B12, folate, copper, vitamin C deficiency
Lack of erythropoietin	Chronic kidney disease, anemia of inflammation, anemia of aging; ACE-inhibitor effect
Anemia of inflammation (iron sequestration)	Infection, autoimmunity, malignancy, CHF, CKD — hepcidin-driven
Absence of red-cell precursors	Aplastic anemia (pancytopenia), pure red-cell aplasia (parvovirus B19)
Marrow replacement (myelophthisis)	Metastatic carcinoma, lymphoma/myeloma, granuloma (TB, histoplasmosis), myelofibrosis
Stem-cell / clonal defects	Myelodysplastic syndrome, acute/chronic leukemia

- ▶ A complementary morphological scheme (Wintrobe) groups anemia by **MCV**: *microcytic* (iron deficiency, thalassemia, sideroblastic, inflammation), *normocytic* (renal, aplastic, marrow invasion, endocrine), and *macrocytic* (B12/folate deficiency, MDS, alcohol/liver disease). Most hypoproliferative anemias are **normocytic-normochromic** or microcytic.

Iron-restricted hypoproliferation: deficiency vs inflammation

- ▶ **Iron metabolism** is governed by **hepcidin**, a 25-amino-acid hepatic peptide that degrades the iron exporter **ferroportin**, throttling iron release from enterocytes, macrophages and hepatocytes. Hepcidin is **suppressed** in iron deficiency (maximising absorption) and **raised by IL-6 (STAT3 pathway)** in inflammation.
- ▶ **Iron-deficiency anemia (IDA)**: absolute store depletion → low ferritin → iron-restricted erythropoiesis → **microcytic, hypochromic** cells with **high RDW**. Clues: pica, koilonychia, cheilosis, atrophic glossitis, and oesophageal webs (**Plummer-Vinson syndrome**). Severe IDA may cause **reactive thrombocytosis**.
- ▶ **Anemia of inflammation (chronic disease)**: the second commonest anemia worldwide; mild–moderate, **normocytic-normochromic** (microcytic if long-standing) with **low reticulocytes**. It is fundamentally a **disorder of iron distribution** — high hepcidin sequesters iron in macrophages (functional iron deficiency) with **reduced EPO production and blunted EPO response** (IL-1 β , TNF- α , IFN- γ).

Parameter	Iron deficiency	Anemia of inflammation	Thalassemia trait
Serum ferritin	Low ($\leq 15\text{--}30\text{ }\mu\text{g/L}$)	Normal–high (>100)	Normal–high
Serum iron	Low	Low	Normal–high
Transferrin saturation	Low ($<15\text{--}20\%$)	Low ($<20\%$)	Normal–high
MCV	Low ($<80\text{ fL}$)	Low–normal	Low
RDW	High	Normal	Low–normal
Soluble transferrin receptor (sTfR)	High	Low–normal	Normal–high
Hepcidin	Very low	Normal–high	Low–normal

(Normal serum iron 50–150 $\mu\text{g/dL}$; TIBC 300–360 $\mu\text{g/dL}$; transferrin saturation 25–50%; ferritin $<30\text{ }\mu\text{g/L}$ = depleted stores, sensitivity 92% / specificity 98%.)

Selected entities of marrow failure

- ▶ **Aplastic anemia**: bone-marrow failure from stem-cell injury/immune (T-cell) suppression → **pancytopenia with a hypocellular marrow** and no abnormal cells. Causes: idiopathic/autoimmune, drugs (chloramphenicol, sulfonamides, phenytoin, carbamazepine, gold), benzene/toluene, radiation, viral hepatitis, parvovirus/EBV/CMV, PNH, pregnancy;

inherited telomere/DNA-repair defects (**Fanconi anemia**, **dyskeratosis congenita**). **Severe aplastic anemia (Camitta criteria)**: marrow cellularity <20% **plus** ≥ 2 of — neutrophils <500/ μL , platelets <20,000/ μL , reticulocytes <1%.

- ▶ **Pure red-cell aplasia**: isolated erythroid precursor loss with severe reticulocytopenia; classic trigger **parvovirus B19** (also thymoma, autoimmune, drugs).
- ▶ **Anemia of CKD**: EPO deficiency once >50% renal function is lost; anemia is near-universal at $\text{GFR} < 30 \text{ mL/min/1.73 m}^2$, compounded by absolute and functional iron deficiency.
- ▶ **Anemia of aging**: roughly **one-third nutritional (iron)**, **one-third inflammation/CKD**, **one-third “unexplained”** (low EPO-for-Hb; associated with clonal hematopoiesis of indeterminate potential, CHIP).
- ▶ **Marrow infiltration / clonal disease**: carcinoma, lymphoma, myeloma, myelofibrosis or leukemia produce a **leukoerythroblastic (myelophthasic) smear** — nucleated RBCs, teardrop cells and immature myeloid forms — mandating marrow examination. **MDS** may present as an isolated macrocytic anemia or pancytopenia.

Diagnostic approach

- ▶ **Step 1 – CBC + reticulocyte count**: correct the percentage for anemia — *Corrected reticulocyte count = measured retic $\times$ (patient Hct / 45)*; a low/inappropriately normal value confirms hypoproliferation.
- ▶ **Step 2 – Blood smear**: microcytic-hypochromic (IDA), macro-ovalocytes + hypersegmented neutrophils (megaloblastic), teardrop/nRBC (myelophthasis), dimorphic with basophilic stippling (sideroblastic).
- ▶ **Step 3 – MCV-guided tests**: *low MCV* $\rightarrow$ ferritin/iron studies (IDA vs inflammation vs thalassemia, RDW helps); *normal MCV* $\rightarrow$ renal function, EPO level, SPEP/light chains; *high MCV* $\rightarrow$ B12/folate, then marrow for suspected MDS.
- ▶ **Step 4 – Bone marrow aspirate + biopsy** (biopsy first) for pancytopenia, very low reticulocytes (<0.1%), nRBC/teardrops, or suspected infiltration/aplasia/MDS; assess cellularity, **myeloid:erythroid ratio (normal $\approx 2.5:1$, range 2:1–5:1)** and iron stores (Perls stain — absent stainable iron is the gold standard for iron deficiency).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Physiological classification algorithm**: box “Anemia $\rightarrow$ CBC + reticulocyte count” branching to “High absolute reticulocyte count $\rightarrow$ haemolysis / haemorrhage” and “Low absolute reticulocyte count $\rightarrow$ HYPOPROLIFERATIVE $\rightarrow$ assess MCV”; under MCV draw three arms — *Low* $\rightarrow$ Ferritin (*low* = iron deficiency; *normal/high* = inflammation, thalassemia, sideroblastic), *Normal* $\rightarrow$ EPO level, BUN/creatinine, SPEP, marrow exam,

High → smear (hypersegmentation? Yes = B12/folate deficiency; No = MDS / drug effect).

Labels: CBC, reticulocyte count, MCV, ferritin, EPO, marrow exam.

- ▶ **Hepcidin–ferroportin axis:** liver hepcidin acting on ferroportin in **duodenal enterocyte, splenic macrophage, hepatocyte**; arrows “IL-6 → ↑hepcidin → ↓iron release (anemia of inflammation)” and “iron deficiency/erythroferrone → ↓hepcidin → ↑iron release.” Labels: *Hepcidin, Ferroportin, Transferrin, IL-6/STAT3, Erythroferrone.*

Clinical / Diagnostic significance

- ▶ The reticulocyte count is the single most useful triage test — it separates underproduction from increased destruction before any expensive workup.
- ▶ A low ferritin is **diagnostic of iron deficiency**, but ferritin is an acute-phase reactant; in inflammation use a higher cut-off (<100 µg/L) and transferrin saturation <20%.
- ▶ In **males and postmenopausal women**, IDA mandates GI evaluation (endoscopy) to exclude occult malignancy/bleeding.
- ▶ A **leukoerythroblastic smear or unexplained pancytopenia** is an absolute indication for bone-marrow biopsy.
- ▶ Distinguish **aplastic anemia (hypocellular marrow)** from **MDS and hypocellular leukemia** by morphology, blast percentage and cytogenetics.

Treatment (cause-directed)

- ▶ **Iron deficiency:** oral iron salts (iron sulfate, 65–100 mg elemental iron); **alternate-day single morning dose maximises absorption** (avoids the hepcidin peak of daily dosing) and is better tolerated; continue ≥3 months to refill stores. **IV iron** (ferric carboxymaltose, derisomaltose, ferumoxytol) for intolerance, malabsorption, severe anemia (Hb ≤8 g/dL), CKD, CHF, pregnancy 2nd–3rd trimester, or surgery within 6 weeks; watch for **hypophosphataemia** (FGF-23, with carboxymaltose).
- ▶ **Anemia of inflammation:** treat the underlying disorder; ESAs in CKD targeting Hb <11.5 g/dL, with IV iron to keep transferrin saturation 30–40% and ferritin 200–700 µg/L; HIF prolyl-hydroxylase inhibitors are an oral alternative.
- ▶ **Megaloblastic anemia:** replace B12/folate.
- ▶ **Aplastic anemia:** allogeneic HSCT for patients <40 yr with an HLA-matched donor; otherwise **immunosuppression** — equine ATG 40 mg/kg/day ×4 days + cyclosporine 6 mg/kg BID + eltrombopag 150 mg/day (response ~90%) with corticosteroid cover for serum sickness.
- ▶ **Transfusion** is reserved for haemodynamic instability or symptomatic anemia; use **restrictive thresholds** (7–8 g/dL) in stable patients. IDA itself should not be transfused unless decompensated.

High-yield exam pointers

- ▶ Hypoproliferative = low reticulocyte response; constitutes $\geq 75\%$ of all anemias.
- ▶ Reticulocyte production index $< 2\text{--}2.5$ = inadequate marrow response = hypoproliferative.
- ▶ Commonest two causes: iron deficiency and anemia of inflammation.
- ▶ Ferritin $< 30\text{ }\mu\text{g/L}$ = absolute iron deficiency; high hepcidin + hyperferritinaemia + hypoferremia = functional iron deficiency of inflammation.
- ▶ Plummer-Vinson = IDA + dysphagia + oesophageal web; koilonychia, pica, atrophic glossitis are IDA signs.
- ▶ Severe aplastic anemia (Camitta): cellularity $< 20\%$ + 2 of (ANC < 500 , platelets $< 20,000$, retics $< 1\%$).
- ▶ Parvovirus B19 $\rightarrow$ pure red-cell aplasia / transient aplastic crisis.
- ▶ CKD anemia = EPO deficiency, prominent once GFR $< 30\text{ mL/min}$.
- ▶ Leukoerythroblastic (myelophthistic) smear $\rightarrow$ suspect marrow infiltration $\rightarrow$ biopsy.
- ▶ Normal M:E ratio $\approx 2.5:1$; absent marrow stainable iron is the gold standard for iron deficiency.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "*Anemia and Polycythemia*" (physiological classification, reticulocyte interpretation, smear morphology, marrow indications) and "*Iron Deficiency and Other Acquired Anemias Due to Decreased Erythrocyte Production*" (iron metabolism, hepcidin, iron studies, anemia of inflammation, CKD and aging).
- ▶ CMDT 2026 — "*Blood Disorders*" (aplastic anemia causes, Camitta severity criteria, ATG/cyclosporine/eltrombopag regimen; iron-restricted anemia management).
- ▶ Coverage note: The dedicated specialty text assigned in the spec (DeVita's Cancer: Principles & Practice of Oncology) is oriented to haematological malignancies and contributes only peripherally here — to the *marrow-replacement / clonal stem-cell* causes (MDS, leukemia, lymphoma, myeloma). The spine of this benign-haematology topic is Harrison's two hematology chapters supplemented by CMDT 2026 for management; this is reflected in the citations above.



Light chain amyloidosis (AL)

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Amyloidosis is a group of protein-misfolding disorders defined by the extracellular deposition of insoluble, antiparallel β -pleated-sheet-rich protein fibrils that distort tissue architecture and impair organ function. AL (light-chain) amyloidosis is the form in which the

fibril precursor is a **monoclonal immunoglobulin light chain** produced by a clonal bone-marrow plasma-cell (or B-lymphoproliferative) disorder; it was formerly called *primary systemic amyloidosis*. It is the **most common systemic amyloidosis in North America** and is rapidly progressive and fatal if untreated. (The term *amyloid* was coined around 1854 by **Rudolf Virchow**, who thought the deposits resembled starch — Latin *amylum*.)

Classification & nomenclature context

- ▶ Amyloid diseases are named by the convention **A + X**, where **A** = amyloid and **X** = the fibril precursor protein; they are classed as **systemic vs localized** and **acquired vs inherited**.
- ▶ AL sits among the **systemic amyloidoses**; the major systemic types are contrasted below.

Type	Precursor protein	Clinical setting	Typical organ involvement
AL	Immunoglobulin light chain	Primary / myeloma-associated (plasma-cell dyscrasia)	Renal, heart, nerve, GI, soft tissue
AH	Immunoglobulin heavy chain	Rare variant of primary/myeloma-associated	Renal
AA	Serum amyloid A (SAA)	Secondary / reactive (chronic inflammation, infection, FMF)	Hepatic, renal
A β 2M	β 2-microglobulin	Long-term dialysis-associated	Synovium, bone, carpal tunnel
ATTR	Transthyretin (mutant / wild-type)	Familial / age-related	Cardiac, peripheral & autonomic nerve

- ▶ **Localized AL** can occur in skin, conjunctiva, urinary bladder and the tracheobronchial tree, produced by *local* clonal plasma cells.

Etiopathogenesis

- ▶ A **clonal plasma-cell expansion** secretes a **monoclonal light chain** whose primary sequence (and other genetic/epigenetic factors) predisposes it to **misfold** rather than fold normally; the misfolded protein forms oligomers → higher-order polymers → fibrils that deposit in tissues.
- ▶ The **amyloid hypothesis** holds that soluble **oligomeric intermediates are the most toxic species** (direct proteotoxicity, reactive oxygen species, stress signalling), while fibrillar deposits cause architectural disruption.
- ▶ Fibrils are composed of **full-length 23-kDa monoclonal light chains** plus fragments; **λ (lambda) subtypes predominate** (λ light chains are more amyloidogenic and more nephrotoxic than κ — *Ch 116*).

- ▶ Accessory molecules co-deposited with fibrils: **serum amyloid P component**, apolipoproteins E and A-IV, glycosaminoglycans, and metal ions.
- ▶ May coexist with **multiple myeloma**, **non-Hodgkin lymphoma**, or **Waldenström macroglobulinemia**. Estimated incidence 8–12 per 100,000; usually presents after age 40.

Clinical features (multisystem, pleiotropic)

Recognition of the *constellation* of syndromes — unexplained nephropathy, cardiomyopathy, neuropathy, enteropathy, arthropathy, macroglossia — is the key to early diagnosis.

Organ system	Frequency / features
Kidney	60–70%; proteinuria , often nephrotic-range → hypoalbuminemia, secondary hypercholesterolemia/triglyceridemia, edema/anasarca. Interstitial (vs glomerular) deposition → azotemia without proteinuria
Heart	70–80%; leading cause of death . ECG: low limb-lead voltage with pseudo-infarct pattern . Echo: concentrically thickened ventricles, diastolic dysfunction , abnormal global longitudinal strain , “sparkly” myocardium; poor atrial contractility (atrial thrombi/thromboembolism even in sinus rhythm). Cardiac MRI: increased wall thickness, delayed subendocardial gadolinium enhancement
Nervous system	Peripheral sensorimotor neuropathy and/or autonomic dysfunction — orthostatic hypotension, GI dysmotility (early satiety, diarrhea, constipation), dry eyes/mouth, impotence, neurogenic bladder
GI / liver / spleen	Hepatomegaly with cholestasis (raised alkaline phosphatase, preserved transaminases/synthetic function); splenic involvement with functional hyposplenism
Skin / soft tissue	Periorbital ecchymoses (“ raccoon-eye ” sign) and easy bruising (capillary amyloid ± acquired factor X deficiency); macroglossia (~10%); nail dystrophy, alopecia, amyloid arthropathy of wrists/shoulders

- ▶ **Macroglossia** and periorbital “**raccoon-eye**” ecchymoses are **pathognomonic** (each seen in a minority of patients).
- ▶ Endocrine deposition may cause **hypothyroidism**, **hypoadrenalism**, or **hypopituitarism**.

Diagnosis & investigations

Diagnosis requires (1) **histologic proof of amyloid**, (2) **accurate typing**, and (3) demonstration of an underlying **clonal plasma-cell disorder + a clonal light chain**.

- ▶ Tissue biopsy + Congo red stain → apple-green birefringence under polarized light; 10-nm fibrils on electron microscopy. Abdominal subcutaneous fat aspirate (16-gauge needle) is positive in >80% of systemic cases and avoids organ biopsy.
- ▶ **Typing** (essential — wrong type = wrong treatment): **laser-capture microdissection + tandem mass spectrometry is the diagnostic standard** (sensitivity 88%, specificity 96%); immunoelectron microscopy is more reliable than routine immunohistochemistry (commercial antibodies may mistype).
- ▶ **Plasma-cell / light-chain workup:**
 - SPEP/UPEP are poor screening tests in AL (an M-spike is often absent). >90% have monoclonal light chain/immunoglobulin detectable by serum/urine immunofixation (SIFE/UIFE) or by serum free light-chain (FLC) nephelometry.
 - Assess both the κ : λ FLC ratio AND the absolute FLC level — renal insufficiency reduces clearance and non-specifically raises both isotypes.
 - Bone marrow shows clonal plasma cells (typically 5–30% of nucleated cells in ~90%); demonstrate κ or λ restriction by flow cytometry, immunohistochemistry, or *in situ* hybridization.
- ▶ A monoclonal protein alone is **not** diagnostic (MGUS is common in the elderly) — but in biopsy-proven amyloid, AL must be **actively excluded/confirmed**.

Staging & prognosis

- ▶ **Mayo 2004 cardiac stage** — based on NT-proBNP and cardiac troponin (European modification identifies very-high-risk patients); most widely used.
- ▶ **Mayo 2012 stage** — adds dFLC (difference between involved and uninvolved circulating free light chains) as an independent survival predictor; dFLC <50 mg/L confers a better outcome regardless of cardiac stage.
- ▶ **Boston University stage** — incorporates BNP and troponin I.
- ▶ A validated **renal staging system** (24-h urine protein + eGFR) predicts progression to dialysis at 2 years.
- ▶ **High-risk patients** (~15–20%): advanced cardiac stage IIIb or severe heart failure (NYHA III–IV).

Treatment

Therapy targets the **clonal plasma cells** (myeloma-style regimens) to abolish the amyloidogenic light chain; **organ-function recovery lags 6–12 months** behind hematologic response.

- ▶ **High-dose IV melphalan + autologous stem-cell transplant (HDM/SCT)** — complete hematologic response in ~40%; durable remissions (sometimes >15 years). Only ~20–30% are eligible (cardiac stage, performance status limit candidacy).

- ▶ Transplant-ineligible (standard): FDA-approved CyBorD (cyclophosphamide + bortezomib + dexamethasone) plus daratumumab (anti-CD38).
- ▶ Bortezomib + melphalan-dexamethasone (MDex) can overcome the adverse genetics of gain of 1q21 and t(11;14).
- ▶ If bortezomib is contraindicated (pre-existing peripheral neuropathy): MDex or immunomodulatory drugs (lenalidomide, pomalidomide).
- ▶ Novel antifibril monoclonal antibodies are in trials, combined with anti-plasma-cell therapy.
- ▶ Localized AL: surgical excision or low-dose radiotherapy (~20 Gy); systemic chemotherapy is *not* appropriate.
- ▶ Supportive care:
 - *Nephrotic syndrome*: diuretics, support stockings, albumin infusion to aid diuresis; ACE inhibitors with caution (no proven renal benefit).
 - *Cardiac*: diuretics are mainstay; **digoxin, calcium-channel blockers and β -blockers are relatively contraindicated** (bind amyloid fibrils $\rightarrow$ heart block, worsening failure). Amiodarone for arrhythmia; **atrial ablation** for AF; **ventricular pacing** for conduction block; AICDs are less effective (thickened myocardium); consider **anticoagulation even without AF** (atrial thrombi).
 - *Autonomic*: **midodrine** (α -agonist) for orthostatic hypotension; motility/bulk agents for GI dysmotility; nutritional support.
- ▶ **Prognosis**: untreated median survival historically only ~1–2 years; markedly improved over four decades with modern therapy and earlier diagnosis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis flow diagram**: *Clonal plasma cells $\rightarrow$ monoclonal λ/κ light chain $\rightarrow$ misfolding $\rightarrow$ oligomers (toxic) $\rightarrow$ β -pleated-sheet fibrils $\rightarrow$ tissue deposition*. Labels: Clonal plasma cell, Free light chain, Misfolded monomer, Toxic oligomer, Amyloid fibril (β -sheet), Tissue deposit (heart/kidney/nerve), Serum amyloid P component.
- ▶ **Clinical signs sketch** (face/hand): label Macroglossia, Periorbital “raccoon-eye” ecchymoses, Nail dystrophy — alongside ECG strip showing low-voltage + pseudo-infarct pattern.

Clinical / Diagnostic significance

- ▶ Suspect AL in any patient with **unexplained nephrotic-range proteinuria**, “hypertrophic” cardiomyopathy with low ECG voltage, peripheral/autonomic neuropathy, hepatomegaly, or macroglossia — especially when **multiple** systems are involved.
- ▶ Fat-pad aspirate + Congo red + mass-spectrometry typing + serum FLC + bone marrow is the practical diagnostic quartet.

- ▶ Cardiac biomarkers (NT-proBNP, troponin) and dFLC drive staging, prognosis and monitoring — remember renal failure falsely elevates them.
- ▶ An acquired factor X deficiency explains the bleeding/bruising and must be checked before biopsy.

High-yield exam pointers

- ▶ AL = monoclonal light chain, formerly *primary systemic amyloidosis*; $\lambda > \kappa$, fibril = 23-kDa light chain.
- ▶ Congo red → apple-green birefringence; abdominal fat-pad aspirate positive in >80%.
- ▶ Kidney 60–70%, Heart 70–80% (commonest cause of death).
- ▶ Macroglossia and periorbital “raccoon-eye” ecchymoses = pathognomonic signs.
- ▶ ECG low voltage + pseudo-infarct; echo with concentric thickening + abnormal global longitudinal strain.
- ▶ Mass spectrometry typing is the gold standard (88%/96%); SPEP/UPEP unreliable — use FLC + SIFE/UIFE.
- ▶ Staging: Mayo 2004/2012 (NT-proBNP, troponin, dFLC); dFLC <50 mg/L = better outcome.
- ▶ Treatment: HDM/SCT (eligible ~20–30%) or CyBorD + daratumumab; β -blockers, CCBs, digoxin relatively contraindicated in cardiac amyloid.

SOURCE & COVERAGE

Harrison’s Principles of Internal Medicine, 22e — Ch 117 “Amyloidosis” (Berk & Sanchorawala); cross-reference Ch 116 “Plasma Cell Disorders” (light-chain physiology, λ amyloidogenicity, free light-chain ratio). Coverage note: the topic is fully supported by the provided chapters; specific Mayo/BU staging cut-off values (exact NT-proBNP/troponin thresholds, Roman-numeral substages) are referenced by name in Harrison but the numeric thresholds are not tabulated in the provided text, so only the named systems and the dFLC <50 mg/L threshold are stated here.



Management of Multiple Myeloma

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Multiple myeloma (MM) is a malignant proliferation of a single clone of plasma cells derived from the late B-lymphocyte lineage, characterised by clonal bone-marrow plasmacytosis, a serum and/or urine monoclonal (M) protein, and myeloma-defining end-organ damage (CRAB — hyperCalcaemia, Renal insufficiency, Anaemia, Bone lesions). It is incurable but highly treatable: with modern triplet/quadruplet induction, autologous transplantation and continuous maintenance, median overall survival now exceeds 8 years. Management is risk-adapted and rests on

three pillars — accurate diagnosis/staging, sequential anti-myeloma therapy, and vigorous supportive care.

Diagnosis, staging and risk stratification (the basis for treatment)

- **Diagnosis (IMWG):** clonal bone-marrow plasma cells $\geq 10\%$ (or biopsy-proven plasmacytoma) plus ≥ 1 myeloma-defining event — either CRAB features or a SLiM biomarker of malignancy: clonal marrow plasma cells $\geq 60\%$, involved:uninvolved serum **free light chain (FLC) ratio** ≥ 100 , or **>1 focal lesion on MRI** (each ≥ 5 mm).
- **CRAB thresholds:** Calcium >11 mg/dL (or >1 mg/dL above normal); creatinine >2 mg/dL or creatinine clearance <40 mL/min; haemoglobin <10 g/dL (or >2 g/dL below normal); ≥ 1 osteolytic lesion on skeletal survey, CT or PET-CT.
- **Distinguish from precursors:** MGUS (M-protein <30 g/L, marrow PCs $<10\%$, no MDE) and *smoldering MM* (M-protein ≥ 30 g/L and/or marrow PCs 10–60%, no MDE) — these are **observed, not treated** (except high-risk SMM, see below).
- **Workup:** SPEP + immunofixation, serum FLC and quantitative immunoglobulins, 24-h urine for Bence Jones protein; marrow aspirate/biopsy with κ/λ clonality (CD138⁺); FISH/DNA-sequencing; $\beta 2$ -microglobulin, albumin, LDH; whole-body low-dose CT / PET-CT or MRI (radionuclide bone scan is **not** useful — lesions are purely lytic).

System	Parameters	Strata
ISS	$\beta 2$ -microglobulin + albumin	I: $\beta 2M <3.5$ + alb ≥ 3.5 (median ~62 mo); II: intermediate (~44 mo); III: $\beta 2M >5.5$ (~29 mo)
R-ISS	ISS + high-risk cytogenetics + LDH	I: ISS-I, normal LDH, no high-risk FISH; III: ISS-III with high-risk FISH or high LDH; II: rest
High-risk FISH	—	t(4;14), t(14;16), t(14;20), del(17p)/TP53, gain/amp 1q, del 1p
Standard-risk FISH	—	t(11;14), t(6;14), hyperdiploidy; del(13q) & t(11;14) are NOT high-risk

- **mSMART/Mayo:** “double-hit” = any 2 high-risk lesions, “triple-hit” = ≥ 3 — confer the worst prognosis (median OS ~3 yr vs >7 –10 yr for standard risk).

Goals and overall framework of therapy

- Two parallel aims: (1) **systemic anti-myeloma therapy** to achieve the deepest possible response, and (2) **supportive care** for complications and treatment toxicity.

- ▶ Therapy is sequenced as **induction** → **high-dose therapy/ASCT (consolidation)** → **maintenance** → **therapy of relapse**, partitioned by **transplant eligibility** (age, performance status, comorbidity).
- ▶ The three backbone drug classes for newly diagnosed MM are **immunomodulatory drugs (IMiDs)**, **proteasome inhibitors (PIs)** and **anti-CD38 monoclonal antibodies**, almost always combined with **dexamethasone**.

Class	Representative agents (dose)	Key toxicity
IMiD	Lenalidomide (5–25 mg PO × 21/28 d); thalidomide; pomalidomide (2–4 mg)	VTE, cytopenias, neuropathy (thalidomide), teratogenicity
Proteasome inhibitor	Bortezomib (1.3 mg/m ² SC d1,4,8,11); carfilzomib (20–56 mg/m ²); ixazomib (4 mg PO, oral)	Bortezomib → peripheral neuropathy, HZV reactivation; carfilzomib → cardiac/pulmonary
Anti-CD38 mAb	Daratumumab (16 mg/kg IV or SC); isatuximab (10 mg/kg)	Infusion reactions, infection
Other antibody/ADC	Elotuzumab (anti-SLAMF7); belantamab mafodotin (anti-BCMA ADC)	Belantamab → keratopathy (ocular)
Alkylator / steroid	Melphalan (high-dose conditioning); cyclophosphamide; dexamethasone 40 mg/wk	Marrow toxicity, secondary MDS/leukaemia

Front-line therapy

- ▶ **Smoldering MM**: generally observed; **high-risk SMM** — early **lenalidomide ± dexamethasone** delays progression to active disease and may prolong survival.
- ▶ **Transplant-ELIGIBLE (newly diagnosed)**:
 - **Induction**: a PI + IMiD + dexamethasone triplet — **VRd** (bortezomib–lenalidomide–dexamethasone) or **KRd** (carfilzomib-based) achieves ~100% overall and >50% complete response (CR); alternatives VTd, VCd. **Adding daratumumab/isatuximab as a quadruplet** (e.g. **Dara-VRd**) gives deeper responses and is now becoming standard of care. Give **4–6 cycles** to achieve maximal cytoreduction.
 - **Stem-cell collection**: harvest **within ~6 months** as prolonged lenalidomide impairs stem-cell yield.
 - **High-dose therapy + autologous SCT (ASCT)**: conditioning with **high-dose melphalan**; adds 25–40% further CRs and prolongs PFS/OS. **Tandem ASCT** benefits only patients failing

to reach $\geq$ VGPR after the first. Delayed (relapse) transplant is an acceptable alternative as upfront ASCT showed no OS difference vs delayed in a randomised trial.

- **Maintenance: lenalidomide** (continuous) prolongs PFS and OS — small increased risk of second primary malignancy is outweighed by benefit. **Add bortezomib or ixazomib (a PI)** for high-risk cytogenetics; **daratumumab** maintenance is also beneficial.
- ▶ **Transplant-INELIGIBLE (age >70, significant cardiopulmonary disease, comorbidity):** the same triplets with frailty-adjusted dosing — **DRd** (daratumumab–lenalidomide–dexamethasone, ORR ~93%) or **RVD-lite** (ORR ~86%); fit older patients may receive quadruplets. Older melphalan-prednisone (MP)-based regimens (MPT, VMP) are now largely superseded but retain a role where novel agents are unavailable.

Relapsed / refractory disease and immunotherapy

- ▶ Treatment of relapse uses **alternate combinations** incorporating agents not previously used or to which the patient is not refractory.
- ▶ **Salvage agents:** carfilzomib and pomalidomide (active even in lenalidomide/bortezomib-refractory disease); all-oral **IRd** (ixazomib-Rd); anti-CD38 **daratumumab/isatuximab** combinations; **elotuzumab** + Rd; **belantamab mafodotin** (BCMA ADC — needs ophthalmologic monitoring); **selinexor** (first-in-class XPO1/exportin nuclear-export inhibitor); **panobinostat** (HDAC inhibitor) + bortezomib-dexamethasone; melflufen.
- ▶ **BCMA-directed cellular therapy (CAR-T):** **idecabtagene vicleucel (Ide-cel)** — after ≥ 2 prior lines (IMiD + PI + anti-CD38); **ciltacabtagene autoleucel (Cilta-cel)** — after ≥ 1 prior line and lenalidomide-refractory; response rates ~81–98% with high CR rates.
- ▶ **Bispecific T-cell engagers** (after ≥ 4 prior lines): **teclistamab** and **elranatamab** (anti-BCMA $\times$ CD3); **talquetamab** (anti-GPRC5D $\times$ CD3); ORR ~60–70%.
- ▶ **Class toxicities of immunotherapy:** cytokine-release syndrome, neurotoxicity (ICANS), and prolonged hypogammaglobulinaemia/infection — may need IVIG support.

Supportive and adjunctive care (often as important as anti-tumour therapy)

- ▶ **Bone disease:** monthly **bisphosphonate** — zoledronate 4 mg or pamidronate 90 mg (12–24 months) — reduces skeletal events; **denosumab 120 mg SC monthly** is the alternative (preferred in renal impairment). Watch for **osteonecrosis of the jaw**. **Vertebroplasty/kyphoplasty** for painful vertebral collapse; **local radiotherapy** (~40 Gy) for focal painful lesions and solitary plasmacytomas.
- ▶ **Renal protection:** hydration, avoid NSAIDs/iodinated contrast/nephrotoxins; treat hypercalcaemia and hyperuricaemia; rapid M-protein reduction with **bortezomib-based therapy** can recover renal function; **plasma exchange** considered for cast nephropathy/light-chain-induced AKI.

- ▶ **Hypercalcaemia:** hydration + natriuresis, bisphosphonates, glucocorticoids ($\pm$ calcitonin).
- ▶ **Hyperviscosity:** plasmapheresis.
- ▶ **Infection prophylaxis:** pneumococcal (conjugate) and influenza vaccination; **herpes-zoster prophylaxis** with bortezomib or anti-CD38 therapy; **IVIG** for recurrent serious infection or post CAR-T/bispecific hypogammaglobulinaemia.
- ▶ **VTE prophylaxis** with IMiDs: **aspirin** (low risk) or **LMWH/warfarin/DOAC** (high risk).
- ▶ **Anaemia:** erythropoietin with haematinics.

Response assessment (IMWG)

- ▶ Hierarchy of depth: **MRD-negative** > **stringent CR (sCR)** > **CR** > **VGPR** > **PR** > **minor response** > **stable** > **progressive disease**.
- ▶ **CR** = negative serum/urine immunofixation, no soft-tissue plasmacytoma, marrow plasma cells <5%; **sCR** adds normal FLC ratio and absence of clonal plasma cells; **VGPR** = M-protein detectable by immunofixation but not electrophoresis, or $\geq 90\%$ serum reduction.
- ▶ **MRD** by next-generation flow/sequencing at 10^{-5} **sensitivity** is the deepest endpoint and predicts longer PFS and OS.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Risk-adapted treatment algorithm of MM** — boxes/arrows: *Newly diagnosed MM* $\rightarrow$ assess MDE $\rightarrow$ (Smoldering $\rightarrow$ observe / high-risk SMM $\rightarrow$ Len $\pm$ Dex) and (Symptomatic $\rightarrow$ split by Transplant-eligible vs ineligible) $\rightarrow$ **Induction (triplet/quadruplet)** $\rightarrow$ eligible arm: **HDT + autologous SCT** $\rightarrow$ **consolidation** $\rightarrow$ both arms: **Maintenance (lenalidomide $\pm$ PI)** $\rightarrow$ **Relapse** $\rightarrow$ **alternate regimens** $\rightarrow$ **CAR-T / bispecifics**. Label drug classes IMiD/PI/anti-CD38.
- ▶ **Pathophysiology / CRAB wheel** — central *clonal plasma cell* with spokes labelled: **RANKL $\uparrow$ /OPG $\downarrow$** $\rightarrow$ osteoclast activation $\rightarrow$ lytic bone lesions & hyperCalcaemia; **light chains** $\rightarrow$ cast nephropathy/Renal failure; **marrow infiltration** $\rightarrow$ Anaemia; **immunoparesis** $\rightarrow$ infection; **M-protein** $\rightarrow$ hyperviscosity/amyloid.

Clinical / Diagnostic significance

- ▶ The **serum M-component** is the **best tumour marker** for monitoring; serum/urine FLC fall faster ($t_{1/2} \sim 6$ h) than intact Ig ($t_{1/2} \sim 3$ wk) and track tumour kill earlier.
- ▶ Recognise **myeloma emergencies**: spinal cord compression, pathological fracture, hypercalcaemia, hyperviscosity, sepsis and AKI — each alters immediate management priorities.
- ▶ Cytogenetics (FISH/sequencing) drive both **prognosis (R-ISS)** and **treatment intensity** (add a PI to maintenance in high-risk disease).

- ▶ Achieving and sustaining **MRD negativity** is the emerging therapeutic goal and a powerful surrogate for survival.

High-yield exam pointers

- ▶ **Diagnosis** = $\geq 10\%$ clonal marrow PCs + M-protein + ≥ 1 MDE (CRAB or SLiM biomarker).
- ▶ **SLiM**: Sixty% PCs, Light-chain ratio ≥ 100 , MRI > 1 focal lesion.
- ▶ **R-ISS** = ISS ($\beta 2M$ + albumin) + **high-risk cytogenetics** + LDH.
- ▶ **High-risk FISH**: $t(4;14)$, $t(14;16)$, $t(14;20)$, $del(17p)$, 1q gain — *$t(11;14)$ and $del(13q)$ are standard-risk.*
- ▶ **Backbone classes**: IMiD + PI + anti-CD38 + dexamethasone; quadruplet (Dara-VRd) is the modern standard induction.
- ▶ **ASCT conditioning** = **high-dose melphalan**; lenalidomide is standard **maintenance**.
- ▶ **BCMA targets**: CAR-T (Ide-cel, Cilta-cel) and bispecifics (teclistamab, elranatamab); talquetamab targets GPRC5D.
- ▶ **Bone disease**: monthly zoledronate/pamidronate or denosumab; beware osteonecrosis of jaw.
- ▶ IMiD $\rightarrow$ **mandatory VTE prophylaxis**; bortezomib $\rightarrow$ **HZV prophylaxis** + **give SC/weekly** to cut neuropathy.
- ▶ Median OS now > 8 years; **MRD negativity (10^{-5})** = deepest response.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Plasma Cell Disorders" (diagnostic criteria, ISS/R-ISS components, drug classes/doses, treatment algorithm, supportive care).
- ▶ DeVita, Hellman & Rosenberg's *Cancer: Principles & Practice of Oncology*, 12e — "Plasma Cell Neoplasms" (Revised ISS table, Mayo/mSMART double-hit/triple-hit risk stratification, IMWG response & MRD criteria).
- ▶ CMDT 2026 — "Plasma Cell Myeloma" (current induction/maintenance approach, ASCT, salvage and immunotherapy, supportive management).



Microangiopathic Haemolytic Anaemia (MAHA)

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Microangiopathic haemolytic anaemia (MAHA) is a form of acquired, predominantly **intravascular haemolysis** caused by **mechanical fragmentation of red cells** as they are sheared in a microvasculature distorted by platelet/fibrin microthrombi, abnormal endothelium or turbulent flow. It is defined by the combination of **thrombocytopenia** and **fragmented RBCs (schistocytes)** on the peripheral smear with laboratory evidence of haemolysis (raised LDH and

unconjugated bilirubin, low/absent haptoglobin) and microvascular thrombosis. The thrombotic microangiopathies — **thrombotic thrombocytopenic purpura (TTP)** and **haemolytic-uraemic syndrome (HUS)** — are the prototype causes; disseminated intravascular coagulation (DIC), malignant hypertension, pregnancy syndromes, prosthetic-valve haemolysis, drugs and vasculitis also produce a microangiopathic picture.

Pathophysiology — why red cells fragment

- ▶ Red cells normally survive ~120 days and are remarkably deformable, squeezing through capillaries narrower than themselves thousands of times. MAHA occurs when they **succumb to shear stress** in an abnormal microcirculation, producing intravascular haemolysis and haemoglobinuria.
- ▶ **Mechanical trauma** to the cell membrane generates **schistocytes** (helmet cells, fragmented RBCs) and microspherocytes; the freed haemoglobin saturates haptoglobin and spills into urine (haemoglobinuria ± haemosiderinuria).
- ▶ In the thrombotic microangiopathies, **platelet-rich microthrombi** deposited in arterioles/capillaries create the fibrin/platelet strands against which circulating RBCs are lacerated, simultaneously **consuming platelets** (hence thrombocytopenia).
- ▶ **TTP mechanism:** the plasma metalloprotease **ADAMTS13** normally cleaves the ultra-large von Willebrand factor (VWF) multimers secreted by endothelium into smaller multimers. Deficiency of, or **antibodies to, ADAMTS13** allow ultra-large VWF multimers to persist, driving pathological platelet adhesion and aggregation and widespread microvascular thrombosis. **ADAMTS13 activity <10% is diagnostic of TTP.** (ADAMTS13 deficiency alone is insufficient — congenital deficiency causes disease only episodically, e.g., a first pregnancy — so a trigger is required.)
- ▶ **HUS mechanism:** endothelial injury — by **Shiga toxin** (*E. coli* O157:H7) in typical/diarrhoea-associated HUS, or by **uncontrolled complement alternative-pathway activation** in atypical HUS (aHUS) — initiates the microangiopathy, with the kidney bearing the brunt.
- ▶ **Common pathophysiologic theme:** increased red-cell turnover. Chronic intravascular haemolysis causes urinary iron loss (and may need iron replacement), whereas recurrent haemolysis raises folate demand and bilirubin (pigment gallstones).

Classification / Causes of MAHA

- ▶ In Harrison's classification of haemolytic anaemias, MAHA falls under **acquired, extracorporeal** causes — “**Mechanical destruction (microangiopathic)**” — alongside toxic agents, drugs, infection and autoimmune mechanisms (the lone inherited extracorporeal exception being familial/atypical HUS).

Category	Representative causes
Primary thrombotic microangiopathies	TTP (ADAMTS13 deficiency/inhibitor); HUS (Shiga toxin); atypical HUS (complement dysregulation)
Pregnancy-associated	HELLP syndrome, pre-eclampsia/eclampsia; pregnancy may unmask TTP
Drug-induced	Antibody-mediated: ticlopidine (possibly clopidogrel). Direct endothelial toxicity: cyclosporine, tacrolimus, gemcitabine, mitomycin C
Infection	Shiga-toxin <i>E. coli</i> O157:H7; systemic sepsis (often with DIC); HIV
Consumptive coagulopathy	Disseminated intravascular coagulation (DIC)
Mechanical / cardiac	Prosthetic (especially leaky/paraprosthetic-regurgitant) heart valves; cardiac haemangioma
Transplant / systemic	Haematopoietic stem-cell (bone-marrow) transplantation; vasculitis; (malignant hypertension, disseminated malignancy — standard textbook additions)

Peripheral smear and laboratory diagnosis

- ▶ **Peripheral blood smear is the cornerstone:** schistocytes/fragmented RBCs + thrombocytopenia define MAHA (Fig. 120-1D). Polychromasia, macrocytosis and occasional nucleated RBCs reflect the brisk reticulocyte response.
- ▶ **Haemolysis markers** (largely intravascular pattern):

Parameter	Finding in MAHA
Haemoglobin	Reduced (may fall acutely)
Reticulocytes / MCV	Increased
Peripheral smear	Schistocytes , helmet cells, low platelets
Bilirubin	Increased, mostly unconjugated
LDH	Markedly increased (up to ~10× normal with intravascular haemolysis)
Haptoglobin	Reduced to absent
Urine	Haemoglobinuria ± haemosiderinuria
Direct antiglobulin (Coombs) test	Negative (mechanical, not immune — key distinguishing point)

Parameter	Finding in MAHA
Platelet count	Low (consumption)

- **Distinguishing MAHA mechanism by coagulation profile:** in DIC, although thrombocytopenia and microangiopathy occur, a **coagulopathy predominates** — consumption of clotting factors and fibrinogen prolongs the PT and often the aPTT. By contrast, PT and aPTT are **characteristically normal in TTP and HUS**. This single distinction is high-yield.
- A complete diagnostic panel in suspected TTP/MAHA: CBC with platelet count and smear, ADAMTS13 activity ($\pm$ inhibitor assay), LDH, bilirubin, haptoglobin, PT/aPTT/fibrinogen, direct antiglobulin test and renal function.

Differentiating TTP vs HUS vs DIC

Feature	TTP	HUS (typical)	DIC
Core defect	ADAMTS13 deficiency / inhibitor $\rightarrow$ ultra-large VWF	Shiga-toxin (E. coli O157:H7) endothelial injury	Systemic coagulation activation
Classic age/setting	Adults; women > men; HIV, pregnancy	Children; preceded by (often bloody) diarrhoea	Sepsis, malignancy, obstetric catastrophe
Predominant organ	CNS (neurologic findings)	Kidney (acute renal failure)	Multi-organ
Renal failure	Variable	Prominent	Variable
PT / aPTT	Normal	Normal	Prolonged
Fibrinogen	Normal	Normal	Low (consumed)
ADAMTS13	<10% (diagnostic)	Generally normal	Normal
First-line therapy	Therapeutic plasma exchange	Supportive ($\pm$ dialysis)	Treat cause; replace factors

- The classic TTP “pentad” (first described by *Eli Moschcowitz, 1924*): **microangiopathic haemolytic anaemia, thrombocytopenia, renal failure, neurologic findings and fever**. The full pentad is now seen less often because of earlier diagnosis — do not wait for all five before treating.

Specific syndromes and management

- TTP — a medical emergency. Inherited TTP is *Upshaw-Schulman syndrome*; idiopathic TTP (more common in women, and in HIV/pregnancy) is autoantibody-mediated against ADAMTS13.

- **Therapeutic plasma exchange (TPE)** is the mainstay — it transformed mortality from 85–100% down to 10–30%. Continue TPE until the platelet count normalises and signs of haemolysis resolve for at least **2 days**.
- **Glucocorticoids** are a reasonable adjunct to TPE. **Rituximab** added to initial therapy reduces relapse. **Caplacizumab** (anti-VWF nanobody) reduces mortality and care burden in patients with ADAMTS13 <10% or high clinical probability. ISTH guidance: start caplacizumab and rituximab in those with diagnostic ADAMTS13 (usually <10%), and rituximab additionally where an inhibitor is demonstrated.
- **Relapse** is significant: 25–45% within 30 days of remission and 12–40% late relapses, more frequent with severe ADAMTS13 deficiency. Treat suspected relapse **before** confirmatory assays return.
- ▶ **HUS**. Triad of acute renal failure, MAHA and thrombocytopenia, typically following haemorrhagic diarrhoea in children (*E. coli* O157:H7). Treatment is **primarily supportive**; ~40% of diarrhoea-associated cases need dialysis but overall mortality is <5%. Non-diarrhoeal HUS carries higher mortality (~26%). Plasma infusion/exchange has **not** been shown to alter the course of HUS/aHUS, **except** where anti-factor-H antibodies are present.
- ▶ **Atypical HUS (aHUS)**. Due to dysregulation of the **complement alternative pathway** — anti-factor-H autoantibodies in some, but mostly germline mutations in **CFH, CFI, CD46 (MCP), C3, CFB, THBD (thrombomodulin)** — inherited (autosomal dominant) with incomplete penetrance, needing a trigger (usually infection). Shiga-toxin HUS is regarded as a *phenocopy* of aHUS. The anti-C5 inhibitor **eculizumab** markedly ameliorates the microangiopathy, improving platelet counts and renal function and largely abrogating the need for plasma exchange; aHUS remains a **diagnosis of exclusion**.
- ▶ **Drug-induced MAHA**: withdrawing or reducing the endothelial-toxic agent usually settles the microangiopathy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Peripheral blood smear in MAHA (label exactly)**: *Schistocytes (fragmented RBC) / helmet cells, microspherocyte, polychromatic macrocyte (reticulocyte), nucleated RBC, markedly reduced platelets*. Caption: “Schistocytes + thrombocytopenia = MAHA.”
- ▶ **Diagram 2 — Pathogenesis of TTP (Fig. 120-4 style; label exactly)**: *Endothelial cell, ultra-large VWF multimers, ADAMTS13 (cleaving protease), normal multimers (protease present) vs ultra-large multimers (no protease → TTP), platelet aggregation / microthrombus, sheared/fragmented red cell*.

Clinical / Diagnostic significance

- ▶ The triad **schistocytes + thrombocytopenia + negative Coombs** in a patient with haemolysis (high LDH, low haptoglobin, unconjugated hyperbilirubinaemia) mandates urgent evaluation for a thrombotic microangiopathy.
- ▶ **PT/aPTT** rapidly separate TTP/HUS (normal) from DIC (prolonged, low fibrinogen) — order them early.
- ▶ **ADAMTS13 <10%** confirms TTP and predicts relapse risk; send the sample **before** starting plasma exchange but **do not delay TPE** awaiting the result.
- ▶ Recognise **secondary settings**: malignant hypertension, HELLP/pre-eclampsia, prosthetic-valve dysfunction, sepsis-DIC and drugs — management is of the cause, not blind plasma exchange.
- ▶ Eculizumab has reframed aHUS therapy; correctly distinguishing aHUS from TTP and Shiga-toxin HUS changes treatment entirely (complement blockade vs TPE vs supportive care).

High-yield exam pointers

- ▶ **MAHA = mechanical, intravascular haemolysis** → schistocytes + thrombocytopenia + raised LDH + low haptoglobin + **negative direct Coombs**.
- ▶ **TTP pentad (Moschcowitz, 1924)**: MAHA, thrombocytopenia, renal failure, neurologic signs, fever — treat before the pentad is complete.
- ▶ **ADAMTS13 <10% is diagnostic of TTP**; inherited form = **Upshaw-Schulman syndrome**.
- ▶ **TTP: TPE is life-saving** (mortality 85–100% → 10–30%); adjuncts rituximab, caplacizumab, steroids.
- ▶ **HUS**: children, bloody diarrhoea, **E. coli O157:H7**, kidney-predominant; treatment mainly supportive, mortality <5%.
- ▶ **aHUS**: complement alternative-pathway mutations (CFH, CFI, CD46, C3, CFB, THBD) → **eculizumab**.
- ▶ **DIC vs TTP/HUS**: PT/aPTT **prolonged in DIC, normal in TTP/HUS**; fibrinogen low in DIC.
- ▶ Drug culprits: **ticlopidine** (immune); **gemcitabine, mitomycin C, cyclosporine, tacrolimus** (endothelial toxicity).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — Ch 120 "Disorders of Platelets and Vessel Wall" (TTP/HUS/aHUS, MAHA definition, ADAMTS13–VWF pathogenesis, treatment) and Ch 105 "Hemolytic Anemias" (classification, mechanical/microangiopathic destruction, intravascular-haemolysis laboratory features, familial/atypical HUS complement genes). Coverage note: A few standard exam additions not explicitly named as MAHA causes in the provided chapters — HELLP/pre-eclampsia, malignant hypertension, disseminated malignancy and the universally taught point that the **direct Coombs test is negative** in MAHA — are included

as accepted textbook internal medicine; all eponyms, drug names, gene names and numerical values are grounded in the two chapters above.



Myelodysplastic Syndromes

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — The myelodysplastic syndromes (MDS) are a heterogeneous group of acquired clonal haematopoietic stem-cell neoplasms defined by two hallmarks: (1) peripheral cytopenias due to ineffective, dysplastic haematopoiesis (a bone-marrow failure phenotype), and (2) a variable but substantial risk of progression to acute myeloid leukaemia (AML). The marrow is typically normo- or hypercellular (hypocellular in ~20%) yet produces too few mature cells, and the disease is characterised by morphological dysplasia plus recurrent cytogenetic and somatic-mutational abnormalities. MDS is fundamentally a disease of the elderly arising from age-related genomic instability.

Epidemiology and Aetiology

- **Disease of older adults:** mean age at onset >70 years, slight male predominance; incidence 35 to >100 per million in the general population and 120 to >500 per million in older adults (~30,000–40,000 new US cases/year). Overall 5-year survival is poor (~30%).
- **Rare in children/young adults** — when MDS occurs before age 40 it is frequently constitutional/germline, mandating predisposition gene screening.

Aetiological category	Key features
Primary (de novo)	Most cases; no identifiable exposure or antecedent haematologic disease
Therapy-related (t-MDS)	Alkylating agents (busulfan, melphalan, chlorambucil, nitrosourea, procarbazine) — 5–7 yr latency, complex karyotype/–5/–7; topoisomerase-II inhibitors — ~2 yr latency, 11q23 (MLL) lesions. Age-independent, very poor prognosis
Environmental	Ionising radiation (atomic-bomb survivors), benzene, tobacco smoking, pesticides
Germline predisposition	GATA2 deficiency (MonoMAC), familial RUNX1 (familial platelet disorder), DDX41, SAMD9/SAMD9L (MIRAGE/ataxia-pancytopenia), ETV6, ANKRD26; inherited marrow-failure syndromes — Fanconi anaemia, telomere biology disorders (dyskeratosis congenita), Shwachman-Diamond

Aetiological category	Key features
Evolution	Acquired aplastic anaemia and other marrow-failure states may transform to MDS

Pathophysiology and Molecular Genetics

- ▶ MDS is a **clonal stem-cell disorder** with disordered proliferation, impaired differentiation and aberrant maturation, producing **ineffective haematopoiesis** — cytopenias despite a cellular marrow (intramedullary apoptosis).
- ▶ **Cytogenetic abnormalities** in ~50% of patients; non-random and aneuploidy (loss/gain) predominates over translocations — **del(5q)**, **-7/del(7q)**, **del(20q)**, **trisomy 8**; type and number of lesions strongly predict leukaemic transformation and survival.
- ▶ **Somatic mutations** are detectable in **80–90%** across ~100 recurrently mutated myeloid genes, grouped by function:

Functional class	Genes (frequency)	Prognostic note
Spliceosome (commonest)	SF3B1 (20–25%; up to 80% of ring-sideroblast cases), SRSF2 (~20–30% MDS, ~55% CMML), U2AF1, ZRSR2	SF3B1 favourable; SRSF2/U2AF1 adverse
DNA methylation / epigenetic	TET2 (~30%), DNMT3A (R882), IDH1/IDH2 (→ 2-hydroxyglutarate oncometabolite)	EZH2/ASXL1 adverse
Chromatin / transcription factors	ASXL1 (20–25%), EZH2 (~10%), RUNX1, ETV6	EZH2, RUNX1, ASXL1 adverse
Tumour suppressor	TP53 (17p13.1)	Biallelic/"multi-hit" = complex karyotype, very poor
Signal transduction	FLT3, NRAS, KRAS, CBL	Drive secondary-AML transformation
Cohesin	STAG2	Adverse

- ▶ **Genotype–phenotype links:** *SF3B1* → ring sideroblasts; *del(5q)* → heterozygous ribosomal-protein loss mimicking red-cell aplasia. Distinguish **clonal haematopoiesis of indeterminate potential (CHIP)** (mutation without cytopenia/dysplasia, ~10% of those ≥70 yr) and **CCUS** (clonal cytopenia of undetermined significance) from frank MDS.

Clinical Features and Laboratory Diagnosis

- ▶ **Anaemia** dominates the early course (fatigue, dyspnoea, pallor); ~50% are asymptomatic, diagnosed incidentally on a blood count. Bleeding (thrombocytopenia *and* platelet dysfunction; ~50% have a bleeding event) and **infection** (neutropenia + impaired neutrophil function; ~40%

of deaths, mostly pneumonia) occur. **Splenomegaly** in ~20%. Fever/weight loss favour a myeloproliferative process.

- ▶ **Autoimmune/inflammatory associations** (e.g. *Sweet's syndrome*); MDS with inflammation should prompt consideration of **VEXAS syndrome** (somatic *UBA1* mutation; cytoplasmic vacuoles in myeloid/erythroid precursors).
- ▶ **Peripheral blood**: macrocytic anaemia with **macro-ovalocytes**, reticulocytopenia; **pseudo-Pelger-Huët** neutrophils (hypogranular, hyposegmented, Döhle bodies); large hypogranular platelets; circulating blasts mirror marrow blast count.
- ▶ **Bone marrow** (hyper- or normocellular; hypocellular in ~20%): **dyserythroidopoiesis** (nuclear budding/multinuclearity, megaloblastoid change, **ring sideroblasts** on Prussian-blue), **dysgranulopoiesis** (hypogranular/hyposegmented), **dysmegakaryopoiesis** (**micromegakaryocytes**, dwarf megakaryocytes with unilobed nuclei) — megakaryocyte changes are the most reliable. Blast percentage is enumerated manually and by flow cytometry; cytogenetics/FISH and an NGS myeloid panel are integral.
- ▶ **Diagnostic criteria**: persistent unexplained cytopenia(s) **plus** dysplasia in ≥10% of cells in ≥1 myeloid lineage, **or** an MDS-defining cytogenetic lesion, **or** **5–19% blasts**. Ring-sideroblast threshold is ≥15% (or ≥5% if *SF3B1* mutated). Exclude **B12/folate/copper deficiency**, HIV/parvovirus B19, alcohol, drugs and copper depletion.

Classification

- ▶ **FAB (1983)** — five subtypes: refractory anaemia (RA), RA with ring sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-t), and chronic myelomonocytic leukaemia (CMML). WHO later moved RAEB-t into AML and reclassified CMML as an **MDS/MPN-overlap (myeloproliferative)** neoplasm (monocytosis >1000/μL).
- ▶ Two current schemes — **WHO 5th edition (2022)** and the **International Consensus Classification (ICC 2022)** — both integrate morphology, cytopenias, blast %, cytogenetics and molecular data; **≥20% marrow/blood blasts separates AML from MDS** (ICC adds an MDS/AML category at 10–19% blasts, emphasising the continuum).

WHO 2022 category	Blasts / defining feature
MDS with isolated del(5q)	<5% BM, <2% PB; del(5q) alone or +1 other (not -7/7q)
MDS with <i>SF3B1</i> mutation	<5% BM, <2% PB; ≥15% ring sideroblasts may substitute
MDS with biallelic TP53 inactivation	<20% blasts; usually complex karyotype
MDS with low blasts	<5% BM, <2% PB
MDS, hypoplastic	≤25% cellularity

WHO 2022 category	Blasts / defining feature
MDS with increased blasts-1 (IB1)	5–9% BM or 2–4% PB
MDS with increased blasts-2 (IB2)	10–19% BM or 5–19% PB, or Auer rods
MDS with fibrosis	5–19% BM; 2–19% PB

Prognosis — IPSS-R / IPSS-M

- ▶ The IPSS (1997) was refined to the Revised IPSS (IPSS-R, 2012) using: marrow blast %, five cytogenetic risk subgroups (very good → very poor), and depth of each cytopenia (Hb <80 / 80–<100 / ≥100 g/L; platelets <50 / 50–100 / ≥100 ×10⁹/L; ANC <800 vs ≥800/μL).
- ▶ Five IPSS-R risk categories with median overall survival:

IPSS-R category	Median OS
Very low	8.8 years
Low	5.3 years
Intermediate	3.0 years
High	1.6 years
Very high	0.8 years

- ▶ The molecular IPSS-M (2022) adds ~2 dozen genes (notably multi-hit *TP53*) and re-stratifies ~45% of patients (mostly upstaged) — now the emerging standard. For management, patients are dichotomised into **lower-risk** (very-low/low/intermediate) vs **higher-risk** (high/very-high) disease.
- ▶ **Favourable:** isolated del(5q), *SF3B1*/ring-sideroblast disease. **Adverse:** complex karyotype, chromosome-7 lesions, *TP53*. Most patients die of **cytopenia complications** (infection, bleeding) or comorbidity rather than overt leukaemia.

Risk-adapted Treatment

Setting	Therapy
All patients (supportive)	RBC transfusion (+ iron chelation — deferasirox/deferrioxamine/deferiprone — when ferritin >2500 ng/mL or ≥20 units); platelet transfusion if <10 ×10 ⁹ /L; aggressive infection management
Lower-risk, anaemia	ESA (epoetin/darbepoetin) if serum EPO ≤500 U/L (~50% response) ± G-CSF; luspatercept (TGF-β/SMAD2-3 ligand trap) after ESA failure, esp. <i>SF3B1</i> /RS — RBC-independence ~38%; imetelstat (telomerase inhibitor) for transfusion-dependent low/int-1 with EPO >500

Setting	Therapy
Lower-risk, del(5q)	Lenalidomide 10 mg/day — 55–80% erythroid response + cytogenetic remission; watch myelosuppression and VTE (aspirin prophylaxis)
Lower-risk, hypoplastic/young	Immunosuppression — ATG ± cyclosporine; responders <60 yr, absent 5q–, HLA-DR15; TPO mimetics (eltrombopag/romiplostim) for thrombocytopenia
Higher-risk	Hypomethylating agents — azacitidine 75 mg/m ² ×7 days q28 (AZA-001: median OS 24.5 months); decitabine; oral decitabine-cedazuridine; ± venetoclax; ivosidenib (IDH1)
Curative	Allogeneic HSCT — only curative option (cure ~30–60% by risk); reduced-intensity conditioning extends eligibility to older/fit patients; aim marrow blasts <5% pre-transplant

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Dysplasia montage (peripheral smear + marrow)** — label: *pseudo-Pelger-Huët neutrophil (hypogranular, bilobed), ring sideroblast (perinuclear iron granules, Prussian blue), micromegakaryocyte / unilobed “dwarf” megakaryocyte, macro-ovalocyte, dyserythropoiesis with nuclear budding, myeloblast with Auer rod.*
- ▶ **Risk-adapted treatment algorithm (flowchart)** — MDS diagnosis → IPSS-R/IPSS-M risk → **Lower-risk:** ESA / luspatercept / lenalidomide (del5q) / IST / imetelstat → **Higher-risk:** hypomethylating agent (azacitidine) → **allogeneic HSCT** if fit.

Clinical / Diagnostic significance

- ▶ A bone-marrow aspirate **plus trephine biopsy with iron stain, cytogenetics/FISH and an NGS myeloid panel** is mandatory; megakaryocyte dysplasia and *SF3B1/TP53* status drive both classification and therapy.
- ▶ Always **exclude reversible mimics** — B12/folate/copper deficiency, HIV, alcohol, drugs — before labelling MDS; transient dysplasia is common in these.
- ▶ **Hypoplastic MDS vs aplastic anaemia:** clonal cytogenetic/molecular lesions and dysplasia favour MDS; some (del13q/del20q, *DNMT3A/ASXL1*) overlap and respond to immunosuppression.
- ▶ *TP53* multi-hit and complex karyotype predict transplant relapse; pre-HSCT cyto-reduction to <5% blasts improves outcome.

High-yield exam pointers

- ▶ MDS = **acquired clonal stem-cell neoplasm** → ineffective haematopoiesis (cytopenias with cellular marrow) + AML risk; mean age >70.

- ▶ $\geq 20\%$ blasts = AML; MDS blast range 5–19%; IB1 = 5–9%, IB2 = 10–19% (or Auer rods).
- ▶ **Commonest mutation** = SF3B1 (spliceosome) → ring sideroblasts, **good prognosis**; TP53 / complex karyotype / -7 = worst.
- ▶ **Pseudo-Pelger-Huët** neutrophils, **ring sideroblasts**, **micromegakaryocytes** — classic dysplastic triad.
- ▶ **del(5q) syndrome**: macrocytic anaemia, normal/high platelets, hypolobated megakaryocytes → **lenalidomide**; 5-yr survival $>90\%$.
- ▶ IPSS-R (blasts, cytogenetics, cytopenias) → 5 groups, median OS 8.8 to 0.8 yr; IPSS-M adds molecular data.
- ▶ Lower-risk → ESA/luspatercept/lenalidomide/IST; higher-risk → **azacitidine**; **allogeneic HSCT is the only cure**.
- ▶ Suspect **germline predisposition** (GATA2, RUNX1, DDX41) if MDS at <40 years or strong family history; consider **VEXAS** (UBA1) when MDS coexists with systemic inflammation.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia” (WHO 2022 & ICC classification tables, IPSS-R, treatment).
- ▶ **DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — “Myelodysplastic Syndromes” (molecular pathogenesis by functional gene class, germline predisposition, IPSS-R/IPSS-M risk stratification, risk-adapted therapy and trial data).
- ▶ **CMDT 2026** — “Myelodysplastic Neoplasms” (diagnostic essentials, current drug regimens and doses, prognosis).



Neuroendocrine Tumors

Asked in: Paper III May 2022 · Paper IV Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Neuroendocrine tumors (NETs) are neoplasms arising from cells of the diffuse neuroendocrine system that retain the ability to synthesize and ectopically secrete peptides, growth factors and bioactive amines, giving rise to characteristic clinical syndromes. Gastrointestinal NETs are broadly grouped by site of origin as **extrapancreatic** NETs (historically called *carcinoid tumors*) or **pancreatic** NETs. They classically pursue a more indolent course than most other malignancies, though behavior ranges from benign to highly aggressive. Diagnosed incidence has risen markedly (≈ 6.4 -fold in U.S. SEER data, 1973–2012), partly reflecting improved diagnosis and classification.

Classification

NETs are categorized along three axes — anatomic site, functional status, and histologic differentiation/grade. Histologic grade (mitotic count and Ki-67 index) is the single most important determinant of behavior and treatment.

Axis		Categories		
Anatomic		Pancreatic NETs; extrapancreatic GI (“carcinoid”) — stomach, small intestine (terminal ileum), appendix, rectum; bronchial/thymic		
Functional		<i>Functional</i> (hormone-secretion symptoms) vs <i>non-functional</i> ($\approx 80\%$ of pancreatic NETs; silent or anatomic symptoms)		
Histologic (WHO/Table 89-1)		See grading table below		
Tumor	Differentiation	Grade	Mitoses /10 HPF	Ki-67
NET	Well-differentiated	Low (G1)	<2	<3%
NET	Well-differentiated	Intermediate (G2)	2–20	3–20%
NET	Well-differentiated	High (G3)	>20	>20%
Neuroendocrine carcinoma	Poorly differentiated	High (G3)	>20	>20%

- **Histology:** monotonous sheets of small round cells with uniform nuclei; immunostaining positive for **chromogranin A** and **synaptophysin**; ultrastructural electron-dense neurosecretory granules.
- **Molecular:** sporadic pancreatic NETs — *MEN1* mutated in 44%, *DAXX/ATRX* in 43%, mTOR-pathway genes in 15%. Small-intestinal NETs — recurrent *CDKN1B* (p27^{Kip1}) mutation in 8% and loss of chromosome 18.
- **Inherited syndromes (minority):** MEN 1 (*menin*, 11q13 — commonest), von Hippel–Lindau (*VHL*, 3p25), neurofibromatosis type 1 (*NF1*, von Recklinghausen), tuberous sclerosis (*TSC1* hamartin / *TSC2* tuberin).

Functional pancreatic NET syndromes

Tumor	Syndrome / features	Key marker	Symptom control
Insulinoma (commonest)	Fasting hypoglycemia — confusion, coma, weight gain	↑Fasting insulin + proinsulin + C-peptide	Diazoxide, everolimus (SSA with caution)
Glucagonoma	<i>Necrolytic migratory erythema</i> , glucose	Glucagon >1000 pg/mL	Somatostatin analogue (SSA)

Tumor	Syndrome / features	Key marker	Symptom control
	intolerance, weight loss; hypercoagulable ($\approx 33\%$)		
Gastrinoma	Zollinger-Ellison syndrome — peptic ulcers, GERD, diarrhea	Fasting hypergastrinemia	PPIs, SSA
VIPoma	Verner-Morrison / WDHA / pancreatic cholera — watery diarrhea, hypokalemia, achlorhydria	$\uparrow$ VIP (28-aa peptide)	SSA + fluid/electrolyte replacement
Somatostatinoma	Diabetes, cholelithiasis, diarrhea, steatorrhea	$\uparrow$ Plasma somatostatin	Surgery (SSA value questionable)
ACTHoma	Ectopic Cushing's — hyperglycemia, hypokalemia	$\uparrow$ ACTH/cortisol	Ketoconazole, metyrapone, $\pm$ adrenalectomy

- **Gastrinomas** mostly arise in the **gastrinoma triangle** (bounded by duodenum, pancreas and confluence of cystic and common bile ducts); 50–90% of sporadic ZES gastrinomas are duodenal; up to 25% of ZES patients have MEN 1.
- **Insulinomas** are usually <2 cm and best localized by **endoscopic ultrasound (EUS)**; enucleation is the primary surgical option. SSAs may worsen hypoglycemia by suppressing counter-regulatory hormones.

Extrapancreatic (“carcinoid”) NETs and the carcinoid syndrome

- **Gastric NETs:** *type 1* (chronic atrophic gastritis/pernicious anemia, high gastrin, multifocal, benign — commonest); *type 2* (gastrinoma/ZES); *type 3* (sporadic, normal gastrin, aggressive).
- **Small-intestinal NETs:** terminal ileum, submucosal, often multifocal; serotonin-driven **mesenteric fibrosis/desmoplasia** $\rightarrow$ intermittent obstruction and the classic “**spoke-and-wheel**” calcified mesenteric mass on CT.
- **Appendiceal NETs:** <2 cm $\rightarrow$ appendectomy alone (very low metastatic risk); 2–3 cm $\approx$ 20–30% metastatic risk; >3 cm $\rightarrow$ right hemicolectomy.
- **Rectal NETs:** <1 cm well-differentiated $\rightarrow$ endoscopic removal; 1–2 cm metastasize in up to one-third; >2 cm metastasize in >70%.
- **Carcinoid syndrome** — driven mainly by **serotonin (5-HT)** (synthesized from tryptophan by **tryptophan hydroxylase**; metabolite **5-HIAA** measurable in 24-h urine), plus histamine and tachykinins (substance P). Usually emerges only after **hepatic metastases** allow vasoactive substances into the systemic circulation. Features: sudden **flushing** (face/neck), secretory

diarrhea, wheezing/bronchospasm, and tryptophan diversion may cause niacin deficiency (pellagra). Most common with appendiceal/small-intestinal primaries.

- **Carcinoid heart disease** (≈two-thirds of carcinoid-syndrome patients): plaque-like fibrous endocardial thickening of the **right heart** mediated by serotonin acting on **5-HT_{2B} receptors**; **tricuspid regurgitation** is near-universal (also tricuspid stenosis, pulmonary regurgitation/stenosis). Left-sided disease in <10% (associated with patent foramen ovale).
- **Carcinoid crisis**: life-threatening release of vasoactive substances (profound hypotension or hypertension) precipitated by tumor manipulation at surgery, embolization, or anesthesia induction — prevented/treated with **somatostatin analogues**.

NETs in MEN syndromes (Ch 400)

Syndrome	Gene (locus)	Key NET-associated tumors
MEN 1 (<i>Wermer</i>)	<i>MEN1</i> / <i>menin</i> (11q13)	Parathyroid adenoma (90%); enteropancreatic NETs 30–70% (gastrinoma >50%, insulinoma 10–30%, non-functioning/PPoma); anterior pituitary (prolactinoma)
MEN 2A (<i>Siipple</i>)	<i>RET</i> (10q11.2), codon 634	Medullary thyroid carcinoma (MTC) 90%, pheochromocytoma >50%, parathyroid 10–25%
MEN 2B / MEN 3	<i>RET</i> codon 918 (Met→Thr)	MTC, pheochromocytoma, mucosal neuromas, marfanoid habitus, megacolon (<i>no</i> hyperparathyroidism)
FMTc (MTC only)	<i>RET</i> codon 618	MTC alone
MEN 4	<i>CDKN1B</i> (p27 ^{Kip1} , 12p13)	Parathyroid + pituitary adenoma
MEN 5	<i>MAX</i> (14q23.3)	Pheochromocytoma, pituitary, parathyroid

- **Menin** is a 610-amino-acid tumor-suppressor protein; tumorigenesis follows the Knudson **two-hit hypothesis**.
- In MEN 1, pancreatic NETs are typically **multiple**, of earlier onset, and often indolent; gastrinoma/foregut carcinoid is a leading cause of death — favoring conservative/selective surgery.
- In MEN 2, *RET*-mutation carriers are offered **prophylactic total thyroidectomy** (between age <1 and 5 years per codon risk); pheochromocytoma must be excluded before any surgery. Metastatic MTC: TKIs **vandetanib**, **cabozantinib**, **selpercatinib**.

Diagnosis and investigations

- ▶ **Functional/biochemical:** hormone-specific assays (insulin/C-peptide, gastrin, glucagon, VIP), **urinary 5-HIAA** for carcinoid syndrome; **chromogranin A** as a general (but neither sensitive nor specific) marker — falsely raised by PPIs and renal impairment.
- ▶ **Imaging:** CT/MRI for anatomy; **somatostatin-receptor imaging** since >90% of NETs express SSTRs — **Gallium-68 (⁶⁸Ga) DOTATATE PET** (also DOTATOC, ⁶⁴Cu-dotatate) is highly sensitive. **FDG-PET** is typically negative in low-grade but positive in high-grade tumors.
- ▶ **Localization:** EUS for small pancreatic/duodenal tumors; receptor-positivity on DOTATATE PET predicts SSA and PRRT responsiveness.

Management

- ▶ **Localized disease:** surgical resection is the mainstay; appendiceal/rectal small tumors may be cured endoscopically or by limited resection. Adjuvant therapy is **not** recommended after resection of well-differentiated NETs.
- ▶ **Hormone-symptom control: somatostatin analogues** — octreotide, lanreotide (14-aa somatostatin analogues binding **SSTR subtypes 2 and 5**); **telotristat ethyl** (tryptophan hydroxylase inhibitor) for refractory carcinoid diarrhea; prophylactic cholecystectomy if long-term SSA planned (gallstone risk).
- ▶ **Anti-tumor systemic therapy (Table 89-3):**
 - **SSAs** also slow growth — *PROMID* (octreotide LAR, midgut), *CLARINET* (lanreotide; 2-yr PFS 65% vs 33%).
 - **Peptide receptor radioligand therapy (PRRT)** — ¹⁷⁷Lu-DOTATATE (NETTER-1: PFS at 20 months 65.2% vs 10.8%); requires positive SSTR imaging; renal toxicity mitigated by amino-acid co-infusion.
 - **mTOR inhibitor everolimus** 10 mg/day (RADIANT-3 pancreatic 11 vs 4.6 months; RADIANT-4 GI/lung) — stomatitis, rash, pneumonitis.
 - **TKIs** — sunitinib 37.5 mg/day (pancreatic NET 11.4 vs 5.5 months), cabozantinib (CABINET), surufatinib, pazopanib — hypertension, proteinuria.
 - **Chemotherapy** — **temozolomide + capecitabine** is the preferred regimen for advanced pancreatic NET (has replaced streptozocin).
- ▶ **Hepatic-directed therapy** (liver-predominant disease): resection, radiofrequency/cryoablation, hepatic-artery embolization (bland/chemo/radio-embolization), selective transplantation.
- ▶ **High-grade neuroendocrine carcinoma:** treated on a small-cell paradigm with **platinum** (cisplatin/carboplatin) + **etoposide**; response best when Ki-67 ≥55%; immune checkpoint blockade (ipilimumab + nivolumab) shows activity in poorly differentiated tumors.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Serotonin pathway in carcinoid (Fig. 89-6):** label *Tryptophan* → (*tryptophan hydroxylase*) → *5-Hydroxytryptophan (5-HTP)* → (*aromatic L-amino acid decarboxylase*) → *Serotonin (5-HT)* → stored in secretory granules → secretion → (*monoamine oxidase, aldehyde dehydrogenase*) → *5-HIAA* → *urine*; mark **telotristat ethyl** inhibiting tryptophan hydroxylase.
- ▶ **Carcinoid heart disease (Fig. 89-8):** right heart with fibrous endocardial plaque, retracted tricuspid valve leaflets, **tricuspid regurgitation**; label right atrium, right ventricle, pulmonary valve, and “serotonin / 5-HT2B mediated”.

Clinical / Diagnostic significance

- ▶ Suspect NET in unexplained flushing + secretory diarrhea, refractory peptic ulcers (ZES), fasting hypoglycemia, or necrolytic migratory erythema.
- ▶ A diagnosis of gastrinoma or multiple/young-onset pancreatic NETs mandates screening for **MEN 1** (calcium, PTH, gut hormones, pituitary MRI).
- ▶ ⁶⁸Ga-DOTATATE PET both stages disease and selects patients for SSA/PRRT; chromogranin A is used for monitoring, not screening.
- ▶ Grade (Ki-67) dictates therapy: well-differentiated → SSA/PRRT/targeted agents; high-grade carcinoma → platinum–etoposide.

High-yield exam pointers

- ▶ Commonest functional pancreatic NET = **insulinoma**; commonest *overall* pancreatic NET = **non-functioning**.
- ▶ **Whipple’s triad** + ↑insulin/proinsulin/C-peptide = insulinoma; normal C-peptide with hypoglycemia suggests exogenous insulin.
- ▶ **Gastrinoma triangle:** cystic + common bile duct confluence, 2nd–3rd part duodenum, pancreatic neck/body.
- ▶ **WDHA = Verner-Morrison = pancreatic cholera (VIPoma)**.
- ▶ Carcinoid syndrome needs **hepatic metastases**; diagnostic test = **24-h urinary 5-HIAA**.
- ▶ Carcinoid heart disease = **right-sided, tricuspid regurgitation**, via 5-HT2B receptors.
- ▶ ¹⁷⁷Lu-DOTATATE PRRT for progressive SSTR-positive NETs (NETTER-1/2).
- ▶ **MEN 2 = RET:** codon 634 (2A), 918 (2B), 618 (FMTC); prophylactic thyroidectomy in carriers.
- ▶ **Temozolomide + capecitabine** = preferred chemo for pancreatic NET.

SOURCE & COVERAGE

Harrison’s Principles of Internal Medicine, 22e — Ch 89 “Gastrointestinal Neuroendocrine Tumors” (Kulke) and Ch 400 “Multiple Endocrine Neoplasia Syndromes” (Thakker). Coverage

note: both asks (“Neuroendocrine tumors”) are fully supported; *spec.gap* = *false*. Bronchial/thymic and lung NETs are covered only briefly in the provided GI/MEN chapters (detailed pulmonary NET pathology lies outside these two chapters). MEN 2 management specifics (vandetanib/cabozantinib/selpercatinib, prophylactic thyroidectomy timing) are from Ch 400 and are standard internal medicine.



Neurological Manifestations of Paraneoplastic Syndrome

Asked in: Paper IV Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect **any level of the neuraxis** — brain, brainstem, cerebellum, spinal cord, dorsal root ganglia, peripheral nerve, neuromuscular junction or muscle — and are caused by **remote immune effects of a tumour, not by metastasis, direct infiltration, infection, metabolic derangement or treatment toxicity**. Most are autoimmune, triggered by neuronal proteins ectopically expressed by the tumour. Clinically disabling PNDs occur in 0.5–1% of all cancer patients, but in 2–3% of small-cell lung cancer (SCLC) and neuroblastoma and 30–50% of thymoma. Crucially, in ~60% of patients the neurologic syndrome precedes the cancer diagnosis, develops subacutely producing severe deficits, and prompt tumour control improves outcome — making early recognition vital.

Pathogenesis and antibody-based risk classification

- ▶ PNDs arise when tumour cells aberrantly express neuronal antigens; antigen is processed by antigen-presenting cells → CD4+ helper T-cell activation → B-cell differentiation and autoantibody production, with CD8+ cytotoxic T cells for intracellular targets.
- ▶ **Two immunopathological groups** with prognostic and therapeutic relevance:
 - **Antibodies to intracellular antigens** (e.g., Hu, Yo, Ri, CRMP5, Ma2, amphiphysin): antibody is a *marker*; injury is **cytotoxic T-cell mediated** → extensive neuronal loss → **strong cancer association, poor response to immunotherapy**.
 - **Antibodies to neuronal cell-surface/synaptic antigens** (e.g., NMDAR, LGI1, GABA-B, AMPAR, Caspr2): antibody is **directly pathogenic** (receptor cross-linking/internalisation, functional block) → **more often respond to immunotherapy**, may occur without cancer and in children/young adults.
- ▶ Modern (Graus 2021) terminology abandons “onconeural antibody” for **probability of underlying cancer**: high-risk >70%, intermediate 30–70%, low <30%.

Risk / antibody	Classic neurologic phenotype	Commonest tumour
Anti-Hu (ANNA-1)	Encephalomyelitis, sensory neuronopathy	SCLC
Anti-Yo (PCA-1)	Rapidly progressive cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA-2)	Cerebellar degeneration, opsoclonus, brainstem encephalitis	Breast, gynaecologic, SCLC
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis, uveitis, neuropathy	SCLC, thymoma
Anti-Ma2	Limbic, hypothalamic, brainstem encephalitis	Testicular germ cell
Anti-Tr (DNER)	Cerebellar degeneration	Hodgkin lymphoma
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, SCLC
Anti-SOX1	LEMS ($\pm$ cerebellar)	SCLC
Anti-KLHL11	Brainstem encephalitis, ataxia, sensorineural deafness	Seminoma/germ-cell
Anti-NMDAR (<i>intermediate</i>)	Anti-NMDAR encephalitis	Ovarian teratoma
Anti-AMPA / GABA-B (<i>intermediate</i>)	Limbic encephalitis ($\pm$ seizures)	SCLC, thymoma, breast
Anti-Caspr2 (<i>intermediate</i>)	Morvan syndrome, neuromyotonia	Thymoma
Anti-VGCC (P/Q) (<i>intermediate</i>)	LEMS, cerebellar degeneration	SCLC
Anti-LGII (<i>low</i>)	Limbic encephalitis, hyponatraemia, faciobrachial dystonic seizures	Rarely thymoma
Anti-GAD65 (<i>low</i>)	Stiff-person, cerebellar ataxia, epilepsy	Usually none

CNS and dorsal-root-ganglion syndromes (high-risk “classic” phenotypes)

- Paraneoplastic encephalomyelitis — multifocal inflammation; combinations of cortical encephalitis (*epilepsia partialis continua*), limbic, brainstem, cerebellar, myelitic and autonomic involvement. Usually SCLC with **Hu antibodies**; death may result from cardiac arrhythmia, postural hypotension or central hypoventilation.

- ▶ **Limbic encephalitis** — subacute confusion, agitation, anxiety/depression, **profound short-term (anterograde) memory loss** and temporal-lobe seizures; MRI shows **unilateral/bilateral medial temporal-lobe T2/FLAIR hyperintensity**. Antibodies: Hu, Ma2, AMPAR, GABA-B, LGI1, Caspr2.
- ▶ **Paraneoplastic cerebellar degeneration (rapidly progressive cerebellar syndrome)** — prodrome of dizziness, oscillopsia, nausea → dysarthria, gait and limb ataxia, **downbeating nystagmus**; due to extensive **Purkinje-cell loss**; MRI normal early, **cerebellar atrophy** later. Tumours: SCLC, breast/ovary (anti-Yo), Hodgkin (anti-Tr/DNER).
- ▶ **Opsoclonus-myoclonus syndrome** — chaotic, involuntary multidirectional saccades + myoclonus + ataxia from **disinhibition of the cerebellar fastigial nucleus**; **neuroblastoma in children (≥50%)**, lung/breast (± anti-Ri) in adults; in children with hypotonia, irritability and “dancing eyes–dancing feet”.
- ▶ **Paraneoplastic sensory neuronopathy (dorsal root ganglionopathy)** — immune attack on **dorsal root ganglia**; asymmetric/symmetric sensory loss in all modalities (including face/trunk), painful dysesthesias, sensory ataxia, areflexia; **absent/reduced SNAPs with preserved motor conduction**; Hu antibodies, SCLC.
- ▶ **Paraneoplastic stiff-person syndrome / PERM** — progressive axial and limb rigidity with painful stimulus-triggered spasms, continuous motor-unit activity on EMG; **amphiphysin antibodies** = paraneoplastic (breast, SCLC), whereas GAD65 is usually non-paraneoplastic.
- ▶ Myelopathy (longitudinally extensive), paraneoplastic visual syndromes (cancer-associated retinopathy with anti-recoverin in SCLC; melanoma-associated retinopathy), and autonomic neuropathy (anti-ganglionic α3-AChR) also occur.

Neuromuscular junction, nerve and muscle syndromes

- ▶ **Lambert-Eaton myasthenic syndrome (LEMS)** — antibodies to **presynaptic P/Q-type voltage-gated calcium channels** reduce ACh release. Triad of **proximal lower-limb weakness, hyporeflexia/areflexia and autonomic features** (dry mouth, constipation, impotence); strength and reflexes transiently **improve after brief exercise (post-tetanic facilitation)**. >50% have SCLC. Electrodiagnosis: **low resting CMAP amplitude, decrement on low-rate (2–3 Hz) repetitive nerve stimulation, and >100% increment after high-rate stimulation or brief exercise**.
- ▶ **Peripheral nerve hyperexcitability (neuromyotonia / Isaacs syndrome)** — cramps, myokymia/fasciculations, pseudomyotonia; Caspr2 antibodies; thymoma/SCLC. **Morvan syndrome** adds encephalopathy, insomnia (*agrypnia excitata*) and dysautonomia (Caspr2, thymoma in ~50%).
- ▶ **Dermatomyositis** (and, weakly, polymyositis) and **immune-mediated necrotizing myopathy** (anti-HMGCR or seronegative carry higher cancer risk); subacute sensorimotor neuropathies and POEMS/paraproteinaemic neuropathies; paraneoplastic **myasthenia gravis** with thymoma.

Autoimmune encephalitides with neuronal surface antibodies

- ▶ **Anti-NMDAR encephalitis** — young women/children: viral-like prodrome → psychiatric symptoms, reduced speech, memory loss, **orofacial/limb dyskinesias**, seizures, decreased consciousness, **autonomic instability and central hypoventilation**. ~46% of females ≥12 yr have an **ovarian teratoma**; ~85–90% improve substantially; relapses 12–24%. Diagnosis: CSF antibodies to the **GluN1 subunit** of NMDAR.
- ▶ **Anti-LGI1 encephalitis** — older men: limbic encephalitis with **hyponatraemia** and pathognomonic **faciobrachial dystonic seizures** (brief unilateral arm/face contractions preceding amnestic syndrome).
- ▶ **Anti-GABA-B** (prominent early seizures, SCLC), **anti-AMPA** (relapsing limbic encephalitis), **anti-GABA-A** (refractory seizures/status), **anti-mGluR5** (Ophelia syndrome with Hodgkin lymphoma) and **anti-IgLON5** (NREM/REM parasomnia, stridor, tauopathy).

Diagnostic approach

- ▶ **Exclude mimics first**: metastasis/leptomeningeal disease (contrast MRI brain + spine, CSF cytology), infection, metabolic and treatment-related causes.
- ▶ CSF typically shows mild–moderate lymphocytic pleocytosis (<200 cells), raised protein and oligoclonal bands. **Test paired serum and CSF antibodies** (CSF essential and more specific for NMDAR).
- ▶ Only ~60–70% of CNS PNDs and <20% of PNS-PNS have a detectable antibody — **a negative panel does not exclude PND**.
- ▶ **Tumour hunt**: CT chest/abdomen + whole-body FDG-PET; testicular/pelvic ultrasound and MRI for germ-cell tumours/teratoma; **mammography for anti-Yo/Ri**. If initial screen negative in a high-risk phenotype/antibody, **repeat every 4–6 months for ≥2 years**.
- ▶ **PNS-Care Score** (Graus 2021): grades phenotype (high 3 / intermediate 2), antibody (high 3 / intermediate 2) and cancer findings (present/consistent 4) → **Definite ≥8, Probable 6–7, Possible 4–5**.
- ▶ **DELTA-P score** predicts SCLC in LEMS: Dysarthria/dysphagia/bulbar weakness, Erectile dysfunction, Loss of weight ≥5%, Tobacco, Age ≥50 yr, Performance status (Karnofsky <70) — each 1 point; score 0–1 virtually excludes SCLC, ≥3 implies >80% risk.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Neuraxis “site map” of PNDs**: a sagittal CNS + peripheral nerve/muscle outline with labels — *Limbic encephalitis (medial temporal lobe), Brainstem encephalitis, Cerebellar degeneration (Purkinje cells), Opsoclonus-myoclonus (fastigial nucleus), Myelitis, Dorsal root ganglion → sensory neuronopathy, Neuromuscular junction → LEMS, Muscle → dermatomyositis.*

- ▶ **NMJ in LEMS:** presynaptic terminal with P/Q-type VGCC blocked by antibody, reduced ACh-vesicle release into the cleft, postsynaptic nicotinic AChR. Labels: *autoantibody, P/Q VGCC, Ca^{2+} influx ↓, ACh vesicles, post-tetanic facilitation.*

Clinical / Diagnostic significance

- ▶ A subacute, otherwise unexplained neurologic syndrome in a smoker or older adult should trigger **antibody testing and a tumour search** — the PND often unmasks an occult, frequently still-curable cancer.
- ▶ **Antibody specificity guides the cancer search:** anti-Yo → breast/ovary, anti-Ma2 → testis, anti-Tr → Hodgkin, anti-NMDAR → ovarian teratoma, anti-Hu/VGCC/SOX1 → SCLC.
- ▶ **Management** = treat the tumour + immunotherapy. **First line:** IV methylprednisolone 1 g/day × 3–5 days, IVIG (≈2 g/kg over 5 days) and/or plasma exchange. **Second line:** rituximab 375 mg/m² weekly × 4, cyclophosphamide, azathioprine/mycophenolate; refractory NMDAR encephalitis — tocilizumab or bortezomib. **Symptomatic:** diazepam/baclofen for stiff-person; amifampridine (3,4-diaminopyridine) and pyridostigmine for LEMS.
- ▶ Surface-antibody syndromes respond well; intracellular-antibody (Hu, Yo) syndromes often stabilise at best — **early treatment before irreversible neuronal loss is key.**
- ▶ Immune-checkpoint inhibitors can precipitate neurologic immune-related adverse events clinically identical to PNDs.

High-yield exam pointers

- ▶ 60% of PNDs present before the cancer is found; SCLC is the commonest associated tumour.
- ▶ Intracellular antigen = T-cell mediated, marker antibody, poor response; surface antigen = directly pathogenic, treatment-responsive.
- ▶ Anti-Hu = encephalomyelitis + sensory neuronopathy + SCLC; Anti-Yo = pure cerebellar degeneration + breast/ovary.
- ▶ LEMS = proximal weakness + areflexia + autonomic features, facilitation on exercise, incremental RNS at high rate, P/Q VGCC antibodies, SCLC.
- ▶ Anti-NMDAR encephalitis = young woman, psychiatric → dyskinesia → seizures → dysautonomia, ovarian teratoma, CSF GluN1 antibody, good recovery.
- ▶ Anti-LGI1 = limbic encephalitis + hyponatraemia + faciobrachial dystonic seizures.
- ▶ Opsoclonus-myoclonus = “dancing eyes” + neuroblastoma (child); stiff-person = amphiphysin/GAD65, EMG continuous motor-unit activity.
- ▶ Diagnostic tools: paired serum/CSF antibodies, MRI, whole-body PET-CT, PNS-Care score, DELTA-P score; rescreen for cancer every 4–6 months for ≥2 years.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis” (Dalmau & Graus): pathogenesis, high/intermediate/low-risk antibody tables, individual syndromes, MRI/CSF, treatment.
- ▶ **DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — “Paraneoplastic Syndromes”: Graus 2021 revised criteria, PNS Euronetwork epidemiology, high/intermediate-risk antibody table, **PNS-Care Score**, **DELTA-P score**, and immunotherapy regimens/doses.
- ▶ **CMDT 2026** — “Cancer” / Lung cancer: frequency of paraneoplastic syndromes and LEMS in clinical practice.



Non-Hodgkin's Lymphoma

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of malignancies of mature B, T, and **natural-killer (NK)** lymphocytes, distinguished from Hodgkin's lymphoma by the *absence of Reed-Sternberg cells* and by their biologically and clinically diverse behaviour. About **85–90%** are of B-cell origin and **10–15%** are T/NK-cell. They span a spectrum from **indolent** (slow-growing, treatable but usually incurable) to **aggressive/highly aggressive** (rapidly fatal if untreated, but potentially curable). NHL is the seventh most common cause of cancer death; incidence rises with age and has been increasing by ~1.5–2% per year, with a 5-year survival of ~74%.

Etiology, risk factors & infectious associations

- ▶ **Immunodeficiency** is the strongest predisposer — HIV, post-transplant immunosuppression (~100-fold increased risk, greatest in first post-transplant year), and inherited defects (*ataxia-telangiectasia*, *Wiskott-Aldrich*, *X-linked lymphoproliferative*, *Chédiak-Higashi*, *common variable immunodeficiency*). Most immunodeficiency-associated NHLs are EBV-driven DLBCLs.
- ▶ **Autoimmune disease** — Sjögren's syndrome and Hashimoto's thyroiditis (MALT lymphoma), rheumatoid arthritis, SLE, celiac sprue (enteropathy-associated T-cell lymphoma).
- ▶ **Chemical/iatrogenic** — phenoxy herbicides/dioxin, phenytoin, anti-TNF agents, prior chemo-/radiotherapy.
- ▶ **Infectious agents** (chronic antigenic stimulation or direct transformation):

Agent	Associated lymphoma
EBV	Burkitt's, post-transplant LPD, primary CNS DLBCL, extranodal NK/T-cell (nasal)

Agent	Associated lymphoma
HTLV-1	Adult T-cell leukemia/lymphoma (ATLL)
HIV	Aggressive DLBCL, Burkitt's
Hepatitis C	Lymphoplasmacytic lymphoma, splenic marginal-zone lymphoma
H. pylori	Gastric MALT lymphoma (regresses with eradication)
HHV-8	Primary effusion lymphoma, multicentric Castleman's disease
<i>Borrelia</i> / <i>C. psittaci</i> / <i>C. jejuni</i>	Cutaneous / ocular adnexal / small-bowel (IPSID) MALT

Classification (WHO-HAEM5, 2022) & cytogenetics

- ▶ Lymphoid neoplasms are grouped as **mature B-cell** vs **mature T/NK-cell**, each containing indolent and aggressive entities.
- ▶ **B-cell**: follicular lymphoma (FL), DLBCL, Burkitt's, mantle-cell (MCL), marginal-zone (splenic/MALT/nodal), lymphoplasmacytic, primary mediastinal large B-cell, high-grade B-cell with *MYC* + *BCL2* rearrangements.
- ▶ **T/NK-cell**: peripheral T-cell lymphoma (PTCL)-NOS, angioimmunoblastic (AITL), anaplastic large-cell (ALCL, ALK±), mycosis fungoides/Sézary, ATLL, extranodal NK/T-cell nasal type.
- ▶ ~90% of lymphomas arise from B cells after immunoglobulin gene recombination/somatic hypermutation; the error-prone nature of these processes underlies recurrent translocations:

Translocation	Gene(s)	Lymphoma
t(8;14)(q24;q32)	<i>MYC</i> / <i>IgH</i>	Burkitt's (also t(2;8), t(8;22))
t(14;18)(q32;q21)	<i>BCL2</i> / <i>IgH</i>	Follicular, DLBCL
t(11;14)(q13;q32)	<i>CCND1</i> (<i>cyclin D1</i>) / <i>IgH</i>	Mantle-cell
t(11;18)(q21;q21)	<i>API2</i> / <i>MALT1</i>	MALT (commonest, up to 50%)
t(2;5)(p23;q35)	<i>NPM1</i> / <i>ALK</i>	Anaplastic large-cell
t(3;14) / 3q27	<i>BCL6</i> / <i>IgH</i>	DLBCL, FL

- ▶ Gene-expression profiling splits DLBCL into **germinal-centre B-cell (GCB)** type (better prognosis) and **activated B-cell (ABC)** type (worse); the **Hans algorithm** (CD10, BCL6, MUM1 by IHC) approximates this.

Clinical features & staging

- ▶ Commonest presentation is **painless lymphadenopathy** (peripheral, central/retroperitoneal, or both); ~85% of indolent NHLs are disseminated at diagnosis with frequent marrow involvement.
- ▶ “**B**” symptoms — fever, drenching night sweats, weight loss >10% of body weight over the preceding 6 months.
- ▶ Extranodal disease is common (GI tract, skin, Waldeyer’s ring, marrow, CNS, testis); pace of progression distinguishes aggressive from indolent disease.
- ▶ **Diagnosis requires excisional/core tissue biopsy** with histology, immunophenotype (flow cytometry/IHC) and cytogenetics/FISH — *fine-needle aspiration alone is inadequate*.
- ▶ **Staging** — **Ann Arbor system** (adapted for NHL), now applied as the modern **Lugano classification** using whole-body 18F-FDG PET/CT:

Stage	Extent
I	Single nodal region (I) or single extranodal site (IE)
II	≥2 nodal regions, same side of diaphragm (± contiguous extranodal IIE)
III	Nodal regions on both sides of diaphragm (± spleen, IIIS)
IV	Diffuse/disseminated extranodal involvement (marrow, liver, etc.)

Suffix **A** = no B symptoms, **B** = B symptoms present; **E** = extranodal extension; **bulky** = mediastinal mass >1/3 chest diameter or any mass >10 cm. Bone-marrow biopsy is not required when PET/CT is performed. Because NHL disseminates non-contiguously, **histology + clinical risk score predict outcome better than anatomic stage**.

Prognostic indices

- ▶ **International Prognostic Index (IPI)** for aggressive NHL — 1 point each for: Age ≥60, raised LDH, ECOG Performance status ≥2, Ann Arbor stage III/IV, >1 extranodal site (mnemonic *APLES*). Risk groups: low (0–1), low-intermediate (2), high-intermediate (3), high (4–5) → 5-yr OS ~73%, 51%, 43%, 26% respectively. The **R-IPI** (rituximab era) gives 4-yr survival of 94/80/53%.
- ▶ **FLIPI** (follicular) — age >60, stage III/IV, >4 **nodal sites**, raised LDH, haemoglobin <12 g/dL.
- ▶ **MIPI** (mantle-cell) — age, performance status, LDH, WBC count, **Ki-67** index.
- ▶ Raised serum LDH and **β2-microglobulin** are independent adverse markers.

Major subtypes — features & treatment

- ▶ **Diffuse large B-cell lymphoma (DLBCL)**: commonest NHL (~1/3 of cases), aggressive but curable. Standard first-line **R-CHOP** (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) × 6 cycles cures ~65–70%; **Pola-R-CHP** (polatuzumab vedotin replacing vincristine)

benefits IPI ≥ 2 disease (POLARIX). “**Double-hit**” lymphoma (*MYC* + *BCL2* rearranged, a high-grade B-cell lymphoma) carries a poor prognosis and is often treated with DA-EPOCH-R.

Relapsed/refractory disease $\rightarrow$ salvage chemo + **autologous stem-cell transplant**, or **CD19 CAR-T cells** (axi-cel, liso-cel, tisa-cel; ZUMA-7, TRANSFORM) which are now preferred for primary-refractory/early-relapsing disease.

- ▶ **Burkitt’s lymphoma**: one of the fastest-growing human tumours (**doubling time** <24 h); *MYC* t(8;14) in >95%. Biopsy shows monomorphic medium B cells, ~100% proliferation and a classic “**starry-sky**” appearance from **tingible-body macrophages**; CD10+, BCL6+, BCL2-negative. Three forms — **endemic** (African, jaw/EBV+), **sporadic** (abdominal), **immunodeficiency-associated**. Needs *urgent* intensive cyclophosphamide-based therapy (**modified Magrath/CODOX-M-IVAC** or DA-EPOCH-R) with **mandatory CNS prophylaxis**; cure 80–90%. High tumour burden mandates **tumour-lysis-syndrome** prophylaxis.
- ▶ **Follicular lymphoma (FL)**: commonest indolent NHL; t(14;18)/*BCL2* in >85%; CD10+, BCL6+, CD5/CD23-negative. Graded I–III by centroblast count. Asymptomatic patients are **observed** (“**watch and wait**”); symptomatic/bulky disease $\rightarrow$ **bendamustine-rituximab (BR)**, R-CHOP or R-CVP, $\pm$ maintenance rituximab; obinutuzumab and rituximab-lenalidomide are alternatives. Median survival 15–20 years; **histologic transformation to DLBCL** ~3% per year.
- ▶ **Marginal-zone lymphoma (MZL)**: splenic (HCV-associated, villous lymphocytes), **MALT** (often localised stage I/II — *H. pylori* eradication or radiotherapy can be curative), and nodal types.
- ▶ **Lymphoplasmacytic lymphoma / Waldenström’s macroglobulinaemia**: IgM paraprotein, MYD88 L265P mutation in >90%; hyperviscosity $\rightarrow$ **plasmapheresis**; therapy with BR or **BTK inhibitors** (ibrutinib).
- ▶ **Mantle-cell lymphoma (MCL)**: t(11;14)/*cyclin D1*, CD5+, CD23-negative; intermediate-grade, not curable conventionally. Cytarabine-containing induction $\pm$ autologous transplant; **BTK inhibitors** (ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib) and CD19 CAR-T at relapse.
- ▶ **T-cell NHLs** (generally poorer prognosis): **mycosis fungoides/Sézary** (cutaneous, indolent); **PTCL-NOS** and **AITL** (CHOP/CHOEP); **ALCL** — CD30+, *ALK*+ favourable (8-yr OS 82%) vs *ALK*-negative; **brentuximab vedotin** + **CHP** for CD30+ disease (ECHELON-2). **ATLL** (HTLV-1, “flower cells”, hypercalcaemia); **extranodal NK/T-cell nasal type** (EBV+, **SMILE** regimen + radiotherapy).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathway of normal B-cell differentiation and related lymphomas** (Harrison Fig. 113-2): label *lymphoid stem cell* $\rightarrow$ *pre-B* (*TdT*+, *CD19*+) $\rightarrow$ *early/intermediate B cell* $\rightarrow$ *germinal-centre/follicular-centre B cell* $\rightarrow$ *mantle-zone B cell* $\rightarrow$ *mature/secretory B cell* $\rightarrow$ *plasma cell*; map pre-B ALL, mantle-cell lymphoma (CD5+), CLL/SLL, follicular lymphoma,

Burkitt's, lymphoplasmacytic/Waldenström's, multiple myeloma; annotate markers CD10, CD19, CD20, CD22, CD5, CD23, surface Ig, HLA-DR.

- ▶ “Starry-sky” Burkitt histology — label *monomorphic medium-sized blue B cells* and pale-staining *tinkable-body (reactive) macrophages*.

Clinical / Diagnostic significance

- ▶ Excisional biopsy with immunophenotyping is mandatory — subtype dictates whether to observe, give curative chemo, or treat as an emergency.
- ▶ Baseline work-up: CBC, LDH, β 2-microglobulin, LFTs, uric acid, calcium, serum protein electrophoresis, HIV and hepatitis B/C serology (HBV reactivation risk with rituximab — give antiviral prophylaxis), PET/CT, marrow biopsy where indicated, and lumbar puncture/CNS imaging in Burkitt's, lymphoblastic, testicular/paranasal/epidural/breast/renal/adrenal DLBCL.
- ▶ Oncologic emergencies: tumour-lysis syndrome (hydration + allopurinol or rasburicase), SVC obstruction, malignant spinal-cord compression, hypercalcaemia (ATLL), hyperviscosity (Waldenström's).
- ▶ Rituximab (anti-CD20) transformed B-cell NHL outcomes; CAR-T cell therapy and bispecific antibodies (epcoritamab, glofitamab, mosunetuzumab) are major recent advances for relapsed disease.

High-yield exam pointers

- ▶ NHL = mature B/T/NK malignancy, no Reed-Sternberg cells; ~85% B-cell.
- ▶ t(14;18)/BCL2 → follicular; t(8;14)/MYC → Burkitt; t(11;14)/cyclin D1 → mantle-cell; t(11;18)/API2-MALT1 → MALT; t(2;5)/ALK → ALCL.
- ▶ IPI = age ≥ 60 , LDH $\uparrow$, PS ≥ 2 , stage III/IV, >1 extranodal site.
- ▶ DLBCL is commonest; R-CHOP is standard, curative in ~65–70%.
- ▶ Burkitt's — “starry sky”, doubling <24 h, needs urgent therapy + CNS prophylaxis + TLS precautions.
- ▶ FL — indolent, watch-and-wait, transforms to DLBCL ~3%/yr.
- ▶ Gastric MALT regresses with *H. pylori* eradication; splenic MZL with HCV treatment.
- ▶ B symptoms = fever, night sweats, weight loss $>10\%$ over 6 months.
- ▶ Diagnosis needs excisional/core biopsy — never FNA alone; staging by PET/CT (Lugano).

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — “Non-Hodgkin's Lymphoma” (Jacobson & Longo): WHO-HAEM5 classification, infectious associations, cytogenetics, Ann Arbor staging, IPI/FLIPI/MIPI, subtype features and regimens.

- ▶ DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e — Lugano staging classification, bulky-disease definition, tumour-lysis syndrome management.
- ▶ CMDT 2026 — “Non-Hodgkin Lymphomas” (Blood Disorders): current management algorithms (R-CHOP, BR, CAR-T, bispecific antibodies), prognosis, when to refer/admit.



Oncogenes, Mechanism and Associated Tumors

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — **Oncogenes** are mutated or aberrantly activated genes that promote unregulated cell growth and are one of the two major classes of cancer *driver genes* (the other being tumour-suppressor genes). Their normal, tightly regulated cellular counterparts are called **proto-oncogenes**, which encode proteins acting at critical steps of growth-factor signal-transduction pathways (receptors, kinases, G-proteins, transcription factors). A single genetic event affecting **one allele** (gain-of-function, *dominant*) is sufficient to convert a proto-oncogene into an oncogene — in contrast to tumour-suppressors, where **both alleles** must be inactivated. First discovered in the late 1970s through the study of tumour-causing retroviruses, oncogenes are now the central targets of molecular (precision) cancer therapy.

Proto-oncogene vs oncogene — the core concept

- ▶ **Historical basis:** Peyton Rous (early 1900s) showed a chicken sarcoma was transmissible by a cell-free extract — the *Rous sarcoma virus (RSV)* — whose transforming gene was later identified as **v-SRC**. The normal cellular homologues of such viral genes are the **proto-oncogenes**, captured and mutated by retroviruses.
- ▶ A proto-oncogene becomes an oncogene by mutations that **relieve normal control and increase the activity** of the gene product.
- ▶ Oncogene activation is **monoallelic and dominant** — *one genetic event* activates it; activation requires *precise* gain-of-function changes at specific residues (**mutational hotspots**), unlike the diverse loss-of-function mutations seen in tumour-suppressors.
- ▶ Proto-oncogenes have crucial physiological roles in **cell proliferation, differentiation and cell death**; inappropriate pathway activation leads to tumorigenesis.
- ▶ Malignant transformation is **multistep**: most common adult solid cancers require roughly **three driver-gene mutations** (some childhood tumours only two), accumulating over years/decades.

Functional classes of oncogene products

Oncogene products act at successive levels of the growth-signalling cascade (growth factor → receptor → cytoplasmic transducer → nuclear effector):

Functional class	Representative oncogene(s)	Example tumour association
Receptor / signal-transduction (RTK)	EGFR, ERBB2/HER2, FLT3, KIT, RET, ALK, ROS1, MET, NTRK	Lung (EGFR/ALK/ROS1), breast (HER2), AML (FLT3)
Non-receptor (cytoplasmic) tyrosine kinase	ABL, SRC	CML (BCR-ABL)
Small GTPase (G-protein)	KRAS, NRAS	Pancreas/colon/lung (KRAS), melanoma (NRAS)
Serine/threonine kinase	BRAF, AKT1	Melanoma, thyroid, colorectal (BRAF)
Lipid kinase	PIK3CA	Multiple cancers
Transcription factor	MYC, MYCN, MYCL1, PML-RAR α	Burkitt's/breast (MYC), neuroblastoma (MYCN), APL (PML-RAR α)
Cell-cycle regulator	CCND1 (cyclin D1), CDK4	Mantle-cell lymphoma, oesophageal/head-and-neck
Apoptosis regulator	BCL2 (anti-apoptotic)	Follicular lymphoma
Inhibitor of p53	MDM2, MDM4	Sarcoma, glioma (MDM2); breast (MDM4)
Chromatin modifier	IDH1	Glioma

Mechanisms of oncogene activation

There are **three principal mechanisms** by which a proto-oncogene is activated in human cancer (Harrison Ch 76):

1. Point mutation (single-nucleotide substitution)

- ▶ The commonest mechanism; produces a constitutively active protein.
- ▶ *Prototype* — RAS: activating KRAS mutations occur in **>95% of pancreatic cancers** and **~40% of colon cancers** (less commonly in leukaemia, lung, thyroid).
- ▶ Mutations are restricted to **hotspot codons 12, 13 and 61**, locking RAS in the active GTP-bound state (RAS is a GTPase, *not* a kinase — active when bound to GTP, inactive when bound to GDP).
- ▶ Other examples: BRAF V600E (melanoma, thyroid, colorectal), EGFR (lung), PIK3CA, IDH1 (glioma).

2. Gene (DNA) amplification → over-expression

- ▶ An increase in DNA copy number raises the dose of a normal gene product.
- ▶ Cytogenetically seen as **homogeneously staining regions (HSRs)** when intrachromosomal, or **double minutes (dmins)** when extrachromosomal.
- ▶ Amplicons may co-amplify several genes (e.g., **MDM2, GLI1, CDK4, TSPAN31** at 12q13–15 in sarcomas).
- ▶ Amplification often predicts **poor prognosis** — e.g., **ERBB2/HER2** in aggressive breast cancer and **MYCN (NMYC)** in neuroblastoma.

3. Chromosomal rearrangement (translocation) Two consequences:

- ▶ (a) **Creation of a novel chimeric fusion gene** with deregulated enzymatic activity — *prototype* the **Philadelphia chromosome**, the first reproducible chromosome abnormality in human malignancy. A reciprocal **t(9;22)(q34;q11)** juxtaposes **ABL** (chr 9, a tyrosine kinase) with **BCR** (chr 22), generating the **BCR-ABL** fusion protein, a constitutively active tyrosine kinase driving growth-factor-independent proliferation in CML.
- ▶ (b) **Juxtaposition next to a strong promoter/enhancer** causing over-expression of a structurally normal protein — typically by translocation into **antigen-receptor loci (IgH or TCR)**; e.g., **BCL2-IgH** (follicular lymphoma, over-expressed anti-apoptotic protein), **CCND1/BCL1-IgH** (mantle-cell lymphoma, cyclin D1), and **MYC-IgH t(8;14)** in Burkitt's lymphoma.
- ▶ Recurrent fusions also occur in **solid tumours**, e.g., **TPRSS2-ERG** in >one-third of prostate cancers.

Representative oncogenes and their associated tumours

Oncogene	Function	Mode of activation	Associated tumour
KRAS	GTPase	Point mutation (codons 12/13/61)	Pancreatic, colorectal, lung
NRAS	GTPase	Point mutation	Melanoma
BRAF	Ser/Thr kinase	Point mutation (V600E)	Melanoma, thyroid, colorectal
EGFR	RTK signal transduction	Point mutation	Lung adenocarcinoma
ERBB2/HER2	RTK	Amplification	Breast (aggressive)
FLT3	Signal transduction	Point mutation	AML
PIK3CA	PI3-kinase	Point mutation	Multiple cancers
MYC	Transcription factor	Amplification / translocation	Burkitt's, prostate, breast, liver
MYCN	Transcription factor	Amplification	Neuroblastoma

Oncogene	Function	Mode of activation	Associated tumour
CCND1 (cyclin D1)	Cell-cycle progression	Amplification / t(11;14)	Mantle-cell lymphoma, oesophageal
BCL2	Anti-apoptotic	Translocation t(14;18)	Follicular lymphoma
ABL (BCR-ABL)	Tyrosine kinase	Translocation t(9;22)	CML
MDM2	p53 inhibitor	Amplification	Sarcoma, glioma
IDH1	Chromatin modification	Point mutation	Glioma

Recurrent oncogenic translocations (high-yield)

Fusion / gene	Translocation	Malignancy
BCR-ABL	t(9;22)(q34;q11)	Chronic myeloid leukaemia
PML-RAR α	t(15;17)	Acute promyelocytic leukaemia (M3 AML)
BCL1 (CCND1)-IgH	t(11;14)(q13;q32)	Mantle-cell lymphoma
BCL2-IgH	t(14;18)(q32;q21)	Follicular lymphoma
MYC-IgH	t(8;14)	Burkitt's lymphoma
EWSR1-FLI1	t(11;22)(q24;q12)	Ewing's sarcoma
PAX3-FOXO1	t(2;13)(q35;q14)	Rhabdomyosarcoma
PAX8-PPARG	t(2;3)(q13;p25)	Thyroid carcinoma
TMPRSS2-ERG	rearrangement Chr21q22	Prostate cancer

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Mechanisms of oncogene activation:** A central proto-oncogene with three radiating arrows labelled (1) **Point mutation** (RAS, hotspot codons 12/13/61 → constitutive GTP-bound activation), (2) **Amplification** (multiple gene copies → over-expression; label HSR and **double minutes**; e.g., HER2, MYCN), (3) **Translocation** (label **fusion protein** e.g. BCR-ABL, and **promoter/enhancer juxtaposition** e.g. IgH-MYC).
- **Diagram 2 — Philadelphia chromosome (CML):** Two chromosomes labelled Chr 9 (ABL, 9q34) and Chr 22 (BCR, 22q11) with crossing arrows showing reciprocal translocation → derivative Ph chromosome carrying the BCR-ABL chimeric gene → BCR-ABL fusion protein (active tyrosine kinase).

Clinical / Diagnostic significance

- ▶ **Targeted (precision) therapy:** Because tumours frequently depend on a single activated pathway — **oncogene addiction** — they are exquisitely vulnerable to inhibitors of that pathway. **Imatinib** (and dasatinib, nilotinib, ponatinib, bosutinib) blocks ATP-binding in the **BCR-ABL** kinase in CML — the *paradigm* of molecularly targeted therapy (>80% 10-year survival).
- ▶ **Drug–target–tumour examples:** **ATRA** for PML-RAR α APL; **osimertinib** for EGFR-mutant lung cancer; **BRAF inhibitors** ($\pm$ MEK inhibitor) for V600E melanoma; **crizotinib/alectinib** for ALK+, **larotrectinib/entrectinib** for NTRK-fusion cancers; **sotorasib/adagrasib** for KRAS-G12C lung cancer; **trastuzumab/pertuzumab** for HER2+ breast/gastric cancer; **JAK inhibitors** for JAK2-driven myeloproliferative disease.
- ▶ **Diagnostic / prognostic biomarkers:** Detection of oncogenic mutations, amplifications and fusions (tissue and circulating tumour DNA) guides therapy, monitors response and detects resistance; **HER2/MYCN amplification** flags poor prognosis.
- ▶ **Acquired resistance:** point mutation in the target kinase (e.g., **BCR-ABL T315I** — threonine $\rightarrow$ isoleucine at codon 315) prevents imatinib binding; bypass-pathway activation also occurs.
- ▶ **Synthetic lethality:** an allied strategy — e.g., **PARP inhibitors** in homologous-recombination-deficient (BRCA-mutant) cancers.

High-yield exam pointers

- ▶ Proto-oncogene $\rightarrow$ oncogene = **gain-of-function, dominant, one allele**; tumour-suppressor = **loss-of-function, recessive, both alleles** (Knudson two-hit).
- ▶ **Three mechanisms of activation: point mutation, amplification, translocation** — be ready to give one tumour example for each.
- ▶ **RAS** is a GTPase, **not a kinase** — active when GTP-bound; mutations cluster at **codons 12, 13, 61**; KRAS in >95% pancreatic and ~40% colon cancers.
- ▶ **HSRs and double minutes** = cytogenetic signatures of **gene amplification**; **HER2** (breast) and **MYCN** (neuroblastoma) are the classic amplified oncogenes.
- ▶ **Philadelphia chromosome t(9;22) $\rightarrow$ BCR-ABL $\rightarrow$ CML $\rightarrow$ imatinib**; the molecular-therapy prototype.
- ▶ Memorise the translocation set: **t(15;17) APL**, **t(14;18) follicular**, **t(11;14) mantle-cell**, **t(8;14) Burkitt's**, **t(11;22) Ewing's**.
- ▶ **Oncogene addiction** explains the dramatic responses to targeted agents; **T315I** explains imatinib resistance.
- ▶ **v-SRC** (Rous sarcoma virus) = first oncogene concept; **Vogelstein “three-strikes”** = multistep colorectal carcinogenesis (APC $\rightarrow$ KRAS $\rightarrow$ SMAD4/TP53).

SOURCE & COVERAGE

Harrison 22e — Ch 76 “Cancer Genetics” (mechanisms of oncogene activation, Tables 76-1 oncogenes and 76-2 translocations, BCR-ABL) and Ch 77 “Cancer Cell Biology” (signal-transduction classes, RAS biology, oncogene addiction, targeted agents Table 77-2). *Coverage note:* The specific MYC-IgH t(8;14) translocation of Burkitt’s lymphoma and the **Knudson two-hit / Vogelstein three-strikes** eponyms are standard, universally accepted internal medicine (and appear elsewhere in Harrison 22e, e.g. Ch 113) but are not detailed verbatim within the two provided chapters; all other specifics (gene names, codons, percentages, translocation notations, drug–target pairs) are taken directly from Ch 76 and Ch 77.



Paraneoplastic Syndromes Associated with Bronchogenic Carcinoma

Asked in: Paper III Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Paraneoplastic syndromes are disorders that accompany a malignancy but are **not** caused by the local mass effect, invasion, or distant metastasis of the tumour; rather they result from tumour-elaborated peptide hormones, cytokines and growth factors, or from tumour-triggered autoimmunity. Bronchogenic (lung) carcinoma — especially the neuroendocrine **small-cell lung cancer (SCLC)** and carcinoids — is the single most prolific solid-tumour cause of these syndromes. They are clinically important because they may be the **presenting feature**, may herald **recurrence**, can mimic metastatic (incurable) disease, and frequently regress when the primary tumour is treated.

Classification (by organ system) and histological associations

System	Syndrome	Mediator / mechanism	Commonest lung histology
Endocrine	SIADH (hyponatraemia)	Ectopic vasopressin (± ANP)	SCLC
Endocrine	Hypercalcaemia of malignancy	PTHrP (humoral); rarely 1,25-(OH) ₂ D, ectopic PTH	Squamous cell
Endocrine	Ectopic ACTH (Cushing’s)	POMC → ACTH; rarely CRH	SCLC, bronchial carcinoid
Neurological	Lambert-Eaton myasthenic syndrome (LEMS)	Anti-P/Q-type VGCC, anti-SOX1	SCLC
Neurological	Encephalomyelitis, sensory neuronopathy, limbic/brainstem	Anti-Hu, anti-CRMP5, anti-AMPA, anti-GABA-B, anti-recoverin	SCLC

System	Syndrome	Mediator / mechanism	Commonest lung histology
	encephalitis, cerebellar degeneration, opsoclonus, CAR (retinopathy)		
Haematologic	Granulocytosis, thrombocytosis, eosinophilia, anaemia	G-CSF/GM-CSF, IL-6, IL-5	NSCLC > SCLC
Vascular	Migratory thrombophlebitis (Trousseau), marantic endocarditis, DIC, VTE	Tumour procoagulants	Adenocarcinoma
Skeletal/cutaneous	Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA) , dermatomyositis, acanthosis nigricans	Unknown / autoimmune	Adenocarcinoma (HPOA)

- ▶ *Rule of thumb*: SCLC drives the endocrine (SIADH, ectopic ACTH) and neurological (LEMS, encephalomyelitis) syndromes; **squamous cell** drives hypercalcaemia (PTHrP); **adenocarcinoma** drives HPOA/clubbing and is the most thrombogenic.

Endocrine / metabolic syndromes

- ▶ **SIADH (ectopic vasopressin)** — occurs in *at least half* of SCLC patients (clinically apparent in ~11%). Hyponatraemia with **low serum osmolality**, **inappropriately concentrated urine (urine osmolality not maximally dilute)**, **urine Na⁺ normal/high**, and clinical euvolaemia; exclude renal/adrenal/thyroid causes. Symptoms (lethargy, confusion, seizures) reflect *rate* and *severity* of fall in Na⁺. **Treatment**: fluid restriction (first line); **demeclocycline** 150–300 mg PO 3–4×/day; V2-receptor antagonists **tolvaptan** 15 mg PO OD or **conivaptan**; hypertonic (3%) saline + furosemide for Na⁺ <115 meq/L or seizures. Correct **slowly (0.5–1 meq/L/h)** to avoid central pontine myelinolysis. SIADH usually resolves within 1–4 weeks of effective chemotherapy.
- ▶ **Humoral hypercalcaemia of malignancy (HHM)** — seen in ~10–25% of lung cancers, most often **advanced squamous cell carcinoma**. Mediated chiefly by PTHrP (structurally related to PTH, acts on the PTH receptor → hypercalcaemia, hypophosphataemia, hypercalciuria). Features favouring HHM over primary hyperparathyroidism: known malignancy, recent/abrupt onset, very high Ca²⁺, **metabolic alkalosis**, and a **suppressed PTH** with **elevated PTHrP** (raised in ~80% of hypercalcaemic cancer patients). Symptoms: polyuria, dehydration, constipation, confusion; ECG shows **short QT**. **Treatment**: IV saline rehydration (200–500 mL/h), IV **bisphosphonates**

(zoledronate 4 mg, pamidronate 60–90 mg), **denosumab** if refractory, calcitonin, glucocorticoids (lymphoma/myeloma), loop diuretics only after rehydration.

- **Ectopic ACTH (Cushing's syndrome)** — accounts for 10–20% of all Cushing's; SCLC is the commonest cause, followed by **bronchial and thymic carcinoids**. Due to aberrant POMC expression. Because exposure is brief and cachexia coexists, the classic centripetal phenotype is often *absent*; instead patients show **hypokalaemic metabolic alkalosis, hypertension, oedema, hyperglycaemia, hyperpigmentation** (high MSH) and steroid psychosis. **Diagnosis:** urine free cortisol $>2-4\times$ normal, plasma ACTH usually >100 pg/mL, **failure to suppress on high-dose (8 mg) dexamethasone in ~90%** (bronchial carcinoid is a notable exception that may suppress); inferior petrosal sinus sampling (central:peripheral ACTH $\geq 3:1$ favours pituitary source) localises ambiguous cases. **Treatment:** steroidogenesis inhibitors — ketoconazole, metyrapone, mitotane, etomidate; mifepristone; treat the tumour; bilateral adrenalectomy in extreme refractory cases.

Neurological paraneoplastic syndromes

- **Lambert-Eaton myasthenic syndrome (LEMS)** — the classic neuromuscular-junction paraneoplastic syndrome of SCLC; antibodies against **presynaptic P/Q-type voltage-gated calcium channels (VGCC)** (and **anti-SOX1**, a high-risk SCLC marker) reduce quantal acetylcholine release. *Triad:* **proximal lower-limb weakness, autonomic dysfunction** (dry mouth, impotence), and **hyporeflexia/areflexia**. Distinguishing point from myasthenia gravis: **strength and reflexes augment after brief sustained/repeated effort** (post-exercise facilitation); on repetitive nerve stimulation there is an **incremental response at high frequency** (vs decrement in MG). Treat the SCLC (chemotherapy is the initial treatment of choice); symptomatic relief with **3,4-diaminopyridine (amifampridine)** and pyridostigmine; immunotherapy (IVIg, steroids) for refractory cases.
- **CNS / antibody-mediated syndromes** ($\approx$ SCLC, antibodies often precede cancer diagnosis):

Antibody	Syndrome
Anti-Hu (ANNA-1)	Encephalomyelitis, subacute sensory neuronopathy (dorsal-root ganglionopathy)
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis/uveitis, peripheral neuropathy
Anti-AMPA / anti-GABA-B	Limbic encephalitis (GABA-B $\rightarrow$ early prominent seizures)
Anti-VGCC / P/Q, anti-Yo	Subacute cerebellar degeneration
Anti-recoverin	Cancer-associated retinopathy (CAR) — photosensitivity, night blindness, ring scotomata, attenuated ERG

- ▶ Other reported syndromes: opsoclonus-myoclonus, brainstem encephalitis, polymyositis/dermatomyositis and stiff-person syndrome (anti-amphiphysin). Neurological syndromes occur in ~1% of lung cancers but are dramatic; antibodies against **intracellular** antigens (Hu, CRMP5, Yo) carry a high tumour probability but respond *poorly* to immunotherapy.

Haematologic, vascular and skeletal/cutaneous syndromes

- ▶ **Haematologic** (usually asymptomatic, parallel tumour course): **granulocytosis** (G-CSF/GM-CSF/IL-6; ~40% of lung cancers), **thrombocytosis** (IL-6; ~17–40%, poorer prognosis), **eosinophilia** (IL-5), anaemia, and leukoerythroblastosis with marrow invasion.
- ▶ **Hypercoagulability / vascular** — the most consequential haematologic effect. **Migratory/recurrent superficial thrombophlebitis with visceral carcinoma = Trousseau's syndrome** (classically pancreatic, also lung); also deep vein thrombosis, pulmonary embolism, **non-bacterial thrombotic (marantic) endocarditis** with arterial emboli, and DIC. Lung scores 1 point on the **Khorana VTE risk score**. Treat with LMWH or a DOAC (e.g., apixaban) — generally preferred over warfarin in cancer-associated VTE.
- ▶ **Skeletal / cutaneous** — **digital clubbing** (~30%, usually NSCLC) and **hypertrophic pulmonary osteoarthropathy (HPOA)** (1–10%, classically adenocarcinoma): symmetrical periostosis of long bones with painful arthropathy and a positive bone scan. Cutaneous: **dermatomyositis** (heliotrope rash, Gottron's papules — strong cancer association), acanthosis nigricans, erythema gyratum repens. Renal ($\leq 1\%$): membranous nephropathy / nephrotic syndrome.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Schematic of a bronchogenic carcinoma with labelled paraneoplastic “satellites”** radiating by system: *Endocrine* — SIADH (vasopressin), Hypercalcaemia (PTHrP), Ectopic ACTH (POMC); *Neurological* — LEMS (anti-P/Q VGCC), Encephalomyelitis (anti-Hu), Cerebellar degeneration; *Haematologic/Vascular* — Trousseau's thrombophlebitis, marantic endocarditis; *Skeletal* — Clubbing + HPOA. Label each satellite with **mediator + commonest histology**.
- ▶ **LEMS neuromuscular junction diagram** — label: *presynaptic terminal*, *P/Q-type voltage-gated Ca^{2+} channel*, *anti-VGCC antibody blocking Ca^{2+} entry*, *reduced acetylcholine vesicle release*, *post-synaptic AChR*, and an inset RNS tracing showing **incremental response at high-frequency stimulation**.

Clinical / Diagnostic significance

- ▶ A paraneoplastic syndrome may be the **first clue** to an occult bronchogenic carcinoma — e.g., unexplained hyponatraemia, hypercalcaemia, hypokalaemic alkalosis, or new proximal weakness in a smoker should trigger imaging (CT chest, PET-CT) and onconeural antibody panels.

- ▶ Distinguishing paraneoplastic effects from true metastasis is **prognostically critical** — paraneoplastic syndromes **do not preclude curative-intent treatment**, whereas mislabelling them as metastatic disease wrongly relegates the patient to palliation.
- ▶ **Management hierarchy**: treat the underlying tumour (often produces the most durable response) **plus** syndrome-specific therapy (vaptans for SIADH, bisphosphonates for hypercalcaemia, steroidogenesis inhibitors for ectopic ACTH, 3,4-DAP for LEMS, anticoagulation for VTE).
- ▶ Antibody profiling both **localises the likely primary** (SCLC for anti-Hu/VGCC/SOX1) and **prognosticates** (intracellular-antigen antibodies = poor neurological recovery).

High-yield exam pointers

- ▶ SCLC = the **paraneoplastic powerhouse** of the lung: SIADH, ectopic ACTH, LEMS, anti-Hu encephalomyelitis.
- ▶ Squamous cell → hypercalcaemia (PTHrP); adenocarcinoma → HPOA/clubbing and the most thrombogenic histology.
- ▶ SIADH: euvolaemic hyponatraemia, low serum osmolality, inappropriately concentrated urine, urine $\text{Na}^+ > 20\text{--}40$; correct Na^+ at **0.5–1 meq/L/h** to prevent osmotic demyelination.
- ▶ HHM: suppressed PTH + **elevated PTHrP**, hypophosphataemia, metabolic alkalosis, short QT; treat with saline + bisphosphonate.
- ▶ Ectopic ACTH: hypokalaemic metabolic alkalosis + hyperpigmentation; **fails high-dose dexamethasone suppression**; ACTH > 100 pg/mL.
- ▶ LEMS vs MG: LEMS = proximal weakness, areflexia, autonomic features, **post-exercise facilitation**, **incremental** RNS response, anti-P/Q VGCC; MG = fatigable ocular/bulbar weakness, **decremental** response, anti-AChR.
- ▶ Trousseau's syndrome = migratory thrombophlebitis with visceral (lung/pancreatic) cancer; consider occult malignancy in recurrent/migratory/unusual-site thrombosis.
- ▶ Dermatomyositis (heliotrope rash + Gottron's papules) carries a strong association with internal malignancy including lung.
- ▶ Onconeural antibodies **precede the cancer diagnosis in ~60%** of paraneoplastic neurological disorders.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Paraneoplastic Syndromes: Endocrinologic/Hematologic”; “Neoplasms of the Lung”; “Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis”; “Myasthenia Gravis and Other Diseases of the Neuromuscular Junction” (LEMS).

- ▶ DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 12e — lung cancer paraneoplastic syndromes (HHM 10–25%, SIADH ~11% SCLC, HPOA, leukocytosis/thrombocytosis, VTE data).
- ▶ CMDT 2026 — current management framing (SIADH, hypercalcaemia, cancer-associated VTE).
- ▶ *Coverage note:* The “P/Q-type” VGCC subtype and the high-frequency **incremental** RNS response in LEMS are universally accepted standard neuromuscular medicine; Harrison states the antibody as anti-voltage-gated calcium channel / P/Q calcium channel and contrasts it with the decremental MG response.



Paraneoplastic syndromes

Asked in: Paper IV Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Paraneoplastic syndromes are disorders that accompany benign or malignant tumours but are **not** caused by the local mass effect, invasion, or distant metastasis of the tumour. They arise from substances elaborated by the tumour (peptide hormones, cytokines, growth factors) or from tumour-triggered immune responses (onconeural antibodies). Neuroendocrine tumours — particularly **small-cell lung carcinoma (SCLC)** and carcinoids — are the commonest culprits. They are important because they are more frequent than appreciated, may be the **presenting feature** of an occult malignancy, can cause major morbidity independent of tumour burden, and characteristically wax and wane with the activity of the underlying cancer.

Pathogenesis / Mechanisms

- ▶ **Ectopic hormone production** — *Eutopic* = hormone from its normal tissue (e.g., ACTH from pituitary corticotropes); *ectopic* = hormone from an atypical source (e.g., ACTH from SCLC). Mechanisms include cellular **dedifferentiation** (re-expression of fetal genes such as hCG, PTHrP, α-fetoprotein), epigenetic derepression, and rarely gene rearrangement bringing a hormone gene under an atypical promoter.
- ▶ **Loss of normal feedback regulation and aberrant peptide processing** — e.g., ectopic ACTH arises from unregulated proopiomelanocortin (POMC) expression and is released largely as inactive precursor fragments.
- ▶ **Immune-mediated (neurologic syndromes)** — neuronal proteins ectopically expressed by the tumour break immune tolerance, generating **onconeural antibodies** and cytotoxic T-cell responses that cross-react with the nervous system.
- ▶ **General criteria confirming an ectopic hormone syndrome** — (1) hormone excess from an atypical source; (2) demonstration of tumour hormone production (immunostaining, mRNA,

in-vitro secretion); (3) arteriovenous hormone gradient across the tumour; (4) fall in hormone levels after tumour debulking.

Endocrine paraneoplastic syndromes

Treatment of the **underlying tumour** is the mainstay; specific measures relieve symptoms but rarely alter survival.

Syndrome	Ectopic mediator	Typical tumours	Key points
Humoral hypercalcaemia of malignancy (HHM)	PTHrP; rarely 1,25-(OH) ₂ D (lymphoma), PTH	Squamous (lung, head & neck, skin), breast, GU, oesophagus; myeloma, lymphoma	Commonest endocrine PNS; ~20–30% of cancers; PTHrP raised in ~80%; PTH suppressed , hypophosphataemia, metabolic alkalosis
SIADH (ectopic ADH/vasopressin)	Arginine vasopressin	SCLC (≥50%), carcinoid, head & neck, GU	Euvolaemic hyponatraemia; low serum osmolality with inappropriately concentrated urine
Ectopic Cushing's syndrome	ACTH (POMC); rarely CRH	SCLC (commonest), bronchial/thymic carcinoid, islet cell, pheochromocytoma, medullary thyroid Ca	10–20% of Cushing's; hypokalaemia, metabolic alkalosis, oedema, hyperpigmentation; ACTH usually >100 pg/mL, fails high-dose dexamethasone suppression
Non-islet-cell tumour hypoglycaemia	IGF-II precursor (big IGF-II)	Large mesenchymal tumours, sarcoma, hepatic, adrenal	Fasting hypoglycaemia with suppressed insulin; IGF-II : IGF-I ratio >10:1
hCG-related (gynaecomastia, precocious puberty)	hCG	Testicular germ cell, choriocarcinoma, lung, hepatic, islet	Leydig-cell stimulation → oestrogen excess
Oncogenic (tumour-induced) osteomalacia	FGF23 (phosphatonin)	Haemangiopericytoma, fibroma, giant-cell tumour	Renal phosphate wasting, hypophosphataemia, low 1,25-(OH) ₂ D; normal Ca/PTH; treat with phosphate/vit D, burosumab (anti-FGF23 mAb)

Syndrome	Ectopic mediator	Typical tumours	Key points
Others (rare)	GHRH (acromegaly), renin (hypertension), calcitonin, VIP, TSH	Carcinoids, islet cell, juxtaglomerular tumour	—

Haematologic paraneoplastic syndromes

Usually asymptomatic and self-limited; severity parallels tumour course. The most consequential is hypercoagulability.

Syndrome	Mediator	Associated cancers
Erythrocytosis	Erythropoietin	Renal cell (~3%), hepatoma (~10%), cerebellar haemangioblastoma (~15%)
Granulocytosis	G-CSF, GM-CSF, IL-6	Lung, GI, ovary, GU, Hodgkin's (no left shift)
Thrombocytosis	IL-6, thrombopoietin	Lung, GI, breast, ovary, lymphoma (marker of poorer prognosis)
Eosinophilia	IL-5	Lymphoma, leukaemia, lung
Thrombophlebitis / VTE	Procoagulants, tissue factor	Pancreatic, lung, GI, breast, ovary, GU, brain

- ▶ **Trousseau's syndrome** = migratory/recurrent superficial thrombophlebitis with visceral carcinoma, classically **pancreatic** cancer; may be the heralding sign of malignancy.
- ▶ Cancer-associated VTE risk is stratified by the **Khorana score** (site of cancer, platelets $\geq 350\,000/\mu\text{L}$, Hb $< 10\text{ g/dL}$ or use of ESAs, leucocytes $> 11\,000/\mu\text{L}$, BMI ≥ 35). Treat with LMWH or a DOAC (e.g., **apixaban**, noninferior to dalteparin).

Neurologic paraneoplastic syndromes (PNS) and autoimmune encephalitis

Disabling PNS occur in 0.5–1% of all cancer patients, but in 2–3% with SCLC/neuroblastoma and 30–50% with thymoma. In ~60% the neurologic syndrome **precedes** the cancer diagnosis; syndromes typically evolve subacutely. Antibodies are classified by their probability of an underlying tumour.

Antibody	Target	Classic syndrome	Tumour
Anti-Hu (ANNA-1)	intracellular	Encephalomyelitis, sensory neuronopathy	SCLC
Anti-Yo (PCA-1)	intracellular	Subacute cerebellar degeneration	Ovary, breast

Antibody	Target	Classic syndrome	Tumour
Anti-Ri (ANNA-2)	intracellular	Opsoclonus, cerebellar/brainstem	Breast, gynaecologic, SCLC
Anti-CRMP5 (CV2)	intracellular	Encephalomyelitis, chorea, optic neuritis, uveitis, neuropathy	SCLC, thymoma
Anti-Tr (DNER)	cell-surface	Cerebellar degeneration	Hodgkin's lymphoma
Anti-Ma2	intracellular	Limbic/hypothalamic/brainstem encephalitis	Testicular germ cell
Anti-amphiphysin	(synaptic)	Stiff-person syndrome	Breast, SCLC
Anti-NMDAR	cell-surface	Psychiatric prodrome → seizures, dyskinesias, dysautonomia, hypoventilation	Ovarian teratoma (young women)
Anti-VGCC	cell-surface	Lambert-Eaton myasthenic syndrome (LEMS) , cerebellar	SCLC
Anti-LGI1	cell-surface	Limbic encephalitis, hyponatraemia, faciobrachial dystonic seizures	Rarely thymoma
Anti-Caspr2	cell-surface	Morvan syndrome , neuromyotonia	Thymoma

- ▶ **Classic (“high-risk”) syndromes** — encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus, sensory neuronopathy, LEMS, gastrointestinal pseudo-obstruction, dermatomyositis.
- ▶ **Therapeutic dichotomy** — antibodies to **intracellular antigens** (Hu, Yo, Ri, CRMP5, Ma2) act via cytotoxic T cells, cause neuronal loss, and respond **poorly** to immunotherapy (focus on treating the tumour). Antibodies to **cell-surface/synaptic antigens** (NMDAR, LGI1, Caspr2, AMPAR, GABA-B) are **directly pathogenic** and **respond well** to tumour removal plus immunotherapy — first-line steroids, IVIg, plasma exchange; second-line **rituximab**, **cyclophosphamide**. ~85–90% of anti-NMDAR patients improve substantially.
- ▶ LEMS: proximal weakness with **post-tetanic facilitation** and autonomic features; if positive, screen for SCLC with CT/PET and continue surveillance ≥3 years.

Dermatologic and rheumatologic paraneoplastic syndromes

- ▶ **Acanthosis nigricans** (esp. gastric adenocarcinoma) and **tripe palms** (thickened velvety palms).
- ▶ **Sign of Leser-Trélat** — sudden eruption of multiple seborrheic keratoses (GI adenocarcinoma).
- ▶ **Erythema gyratum repens** (lung), **necrolytic migratory erythema** (glucagonoma), **Bazex syndrome / acrokeratosis paraneoplastica** (aerodigestive squamous cancers), **paraneoplastic pemphigus** (lymphoproliferative disease).

- ▶ **Dermatomyositis / polymyositis** (Gottron papules, heliotrope rash) — strongest cancer link with dermatomyositis, highest risk within the first 5 years.
- ▶ **Hypertrophic pulmonary osteoarthropathy (HPOA)** — triad of **digital clubbing, symmetrical large-joint arthropathy, and radiographic periostosis**; most often non-small-cell (adenocarcinoma) lung cancer.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Schematic of mechanisms of paraneoplastic syndromes** — central tumour cell with three labelled arrows: (1) *Ectopic hormone* → PTHrP, ADH, ACTH, IGF-II → target organs (bone/kidney, kidney, adrenal, muscle); (2) *Cytokines* → IL-6, G-CSF, IL-5, EPO → marrow (thrombocytosis, granulocytosis, eosinophilia, erythrocytosis); (3) *Onconeural antibodies / T cells* → CNS, dorsal root ganglion, neuromuscular junction. Label **eutopic vs ectopic** and “effects not due to mass/metastasis.”
- ▶ **Antibody–antigen location diagram** — two panels: *Intracellular antigens* (Hu, Yo, Ri, CRMP5) → cytotoxic T-cell attack → poor response; *Cell-surface antigens* (NMDAR, LGI1, VGCC) → antibody-mediated → good response to immunotherapy. Label the neuron, surface receptor, antibody, and T cell.

Clinical / Diagnostic significance

- ▶ **Recognition value** — atypical metabolic/neurologic features in a cancer patient, or an unexplained syndrome (hyponatraemia, hypercalcaemia, subacute cerebellar ataxia) in a patient without known cancer, should prompt a search for malignancy (CT/PET; testicular/pelvic USS or MRI for germ-cell tumours and teratomas).
- ▶ **Endocrine work-up** — suppressed PTH with raised PTHrP confirms HHM; ACTH >100 pg/mL with failure of high-dose dexamethasone suppression and absent petrosal:peripheral gradient indicates ectopic ACTH; IGF-II:IGF-I ratio >10:1 supports IGF-II hypoglycaemia.
- ▶ **Neurologic work-up** — only ~60–70% of CNS PNS and <20% of peripheral PNS have a detectable antibody; MRI (mesial temporal FLAIR change in limbic encephalitis) and CSF (lymphocytic pleocytosis, oligoclonal bands) support the diagnosis and exclude metastatic/leptomeningeal disease.
- ▶ **Management of HHM** — IV **0.9% saline 100–300 mL/h** for rehydration and calciuresis, then **bisphosphonate** (zoledronic acid/pamidronate) or **denosumab** (anti-RANKL; preferred in renal impairment or bisphosphonate-refractory cases); calcitonin or glucocorticoids as adjuncts; treat the tumour.
- ▶ **Management of SIADH** — fluid restriction, **vaptans** (tolvaptan) or demeclocycline; correct sodium slowly (0.5–1 mEq/L/h) to avoid osmotic demyelination.

High-yield exam pointers

- ▶ SCLC is the single commonest cause of paraneoplastic syndromes (SIADH, ectopic ACTH, LEMS, Hu/encephalomyelitis).
- ▶ Commonest **endocrine** PNS = **hypercalcaemia** (PTHrP); commonest cause of **paraneoplastic SIADH** = SCLC.
- ▶ **Ectopic ACTH** → hyperpigmentation, hypokalaemic metabolic alkalosis, *less* central obesity; ACTH not suppressed by high-dose dexamethasone.
- ▶ **Trousseau's syndrome** = migratory thrombophlebitis ↔ visceral (pancreatic) cancer.
- ▶ **Anti-Yo** → cerebellum (ovary/breast); **anti-Hu** → sensory neuronopathy/encephalomyelitis (SCLC); **anti-Ri** → opsoclonus; **anti-Ma2** → limbic/brainstem (testicular); **anti-Tr** → cerebellar (Hodgkin's).
- ▶ **Anti-NMDAR encephalitis** → young woman + **ovarian teratoma**; psychiatric → seizures → dyskinesias → autonomic instability; rituximab-responsive.
- ▶ **LEMS** → anti-VGCC, SCLC, proximal weakness with facilitation; **Lambert-Eaton precedes the cancer** in most.
- ▶ **Surface-antigen** antibodies respond to immunotherapy; **intracellular-antigen** antibodies do not — treat the tumour.
- ▶ Cutaneous clues: **Leser-Trélat**, **acanthosis nigricans**, **tripe palms**, **erythema gyratum repens**, **necrolytic migratory erythema** (glucagonoma); rheumatologic: **HPOA** (clubbing + periostosis), dermatomyositis.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Paraneoplastic Syndromes: Endocrinologic/Hematologic” and “Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis” (antibody classification, syndrome–tumour associations, Khorana score, management).
- ▶ **DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — Paraneoplastic syndromes and lung-cancer chapters (HPOA, dermatomyositis timing, dermatologic entities, hypercalcaemia/SIADH frequencies).
- ▶ **CMDT 2026** — “Cancer” chapter (hypercalcaemia of malignancy diagnosis and current management with saline, bisphosphonates, denosumab).



Paroxysmal nocturnal haemoglobinuria

Asked in: Paper IV Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Paroxysmal nocturnal hemoglobinuria (PNH) is an **acquired, clonal hematopoietic stem-cell disorder** caused by a somatic mutation in the X-linked *PIGA* gene, leading to

deficiency of the **glycosylphosphatidylinositol (GPI) anchor** and of the GPI-linked complement-regulatory proteins **CD55 and CD59** on the surface of blood cells. The result is a chronic, complement-mediated **intravascular hemolytic anemia** with recurrent exacerbations. The classic clinical triad is (1) **intravascular hemolysis**, (2) **a marked tendency to venous thrombosis**, and (3) **a variable degree of bone marrow failure (pancytopenia)** — a combination that makes PNH a uniquely recognisable entity. It is a rare disease (estimated prevalence **5–10 per million**, perhaps somewhat commoner in Southeast Asia and the Far East), affects men and women equally, is **never inherited/congenital**, and usually presents in young adults. It is the prime example of a *clonal but non-malignant* disorder.

Molecular pathogenesis — the PIGA mutation and GPI anchor

- ▶ The fundamental lesion is an **acquired somatic mutation of the PIGA gene (located on the X chromosome) in a hematopoietic stem cell*. PIGA encodes an enzyme needed for an early step in GPI biosynthesis*.
- ▶ Because the gene is X-linked, a single inactivating hit (one active X in each cell) abolishes function, producing a clone of progeny cells deficient in the GPI glycolipid.
- ▶ GPI is a glycolipid that, through a peptide bond, **anchors numerous proteins to the cell-surface membrane**; these proteins possess only an extracellular domain. Loss of GPI therefore removes a whole family of surface proteins, the critical ones being the **complement regulators CD55 and CD59**.
 - **CD55 (decay-accelerating factor)** — prevents assembly/accelerates decay of the C3 and C5 convertases, i.e., limits C3-fragment deposition.
 - **CD59 (membrane inhibitor of reactive lysis / protectin)** — the **most important** regulator; it blocks insertion of C9 polymers, preventing formation of the **membrane attack complex (MAC, C5b-9)**.
- ▶ The marrow becomes a **mosaic** of mutant (GPI-negative, “PNH”) and normal (GPI-positive) cells; the peripheral blood always contains both populations, and in most patients the PNH clone predominates.
- ▶ Rarely, PNH arises from **biallelic mutations of the autosomal PIGT gene (chromosome 20q) without a PIGA mutation; here GPI is made but cannot bind proteins, and the picture is complicated by a chronic inflammatory state**.

Mechanism of hemolysis — complement on an unprotected cell

- ▶ Hemolysis is **mainly intravascular** and results from the *intrinsic* hypersensitivity of CD55/CD59-deficient red cells to **activated complement**.
- ▶ **Alternative pathway** activation (continuous low-grade “tick-over”) drives the **chronic** baseline hemolysis; **classical pathway** activation (antigen–antibody) during **infection or inflammation** triggers the dramatic acute **exacerbations** (“paroxysms”).

- ▶ Without CD59, the MAC inserts freely into the membrane → lysis → **hemoglobinemia and hemoglobinuria**.
- ▶ Free plasma hemoglobin scavenges **nitric oxide**, producing smooth-muscle dystonia — **esophageal spasm/dysphagia, abdominal pain, erectile dysfunction**, and contributing to thrombotic risk and kidney damage.

Relationship with bone marrow failure (PNH–aplastic anemia syndrome)

- ▶ PNH and aplastic anemia (AA) are pathogenetically linked. AA is regarded as a T-cell-mediated organ-specific autoimmune attack on hematopoietic stem cells; the autoantigen in PNH may be the GPI molecule itself, so that **GPI-negative (PNH) stem cells are spared** the immune attack and undergo positive (negative against normal cells) selection* and clonal expansion.
- ▶ Thus PNH results from **two factors acting together: (i) failure of normal hematopoiesis and (ii) escape/expansion of the GPI-deficient clone**.
- ▶ **Clinical overlap:** many patients with overt PNH have antecedent (often unnoticed) BMF; a patient with PNH may evolve into frank AA, and a patient with AA may develop hemolytic PNH years later. Small GPI-deficient (PNH) clones are detectable by flow cytometry in **≥50% of patients with aplastic anemia** at presentation — a small clone (<2%) without reticulocytosis or thrombosis is **not** true PNH.
- ▶ Useful clinical categories: (a) **classic hemolytic PNH**, (b) **PNH in the setting of another marrow-failure disorder (AA/MDS)** — the “PNH-AA syndrome”, and (c) **subclinical PNH** (a small clone, no clinical hemolysis).

Clinical features

Component of the triad	Manifestations
Intravascular hemolysis	Episodic hemoglobinuria — classically “passing blood instead of urine”; reddish-brown urine typically in the first morning void (nocturnal hypoventilation lowers blood pH and facilitates hemolysis). Anemia, fatigue; NO depletion → dysphagia/esophageal spasm, abdominal pain, erectile dysfunction . Hemoglobinuria varies dramatically hour-to-hour.
Thrombosis (venous, characteristically unusual sites)	Most life-threatening complication and the leading cause of death. Hepatic vein → Budd-Chiari syndrome (acute hepatomegaly + ascites without liver disease should raise suspicion of PNH); mesenteric/abdominal veins (recurrent severe abdominal pain); cerebral veins (sagittal sinus) ; dermal vessels (painful nodules).

Component of the triad	Manifestations
Bone marrow failure / cytopenias	Anemia with neutropenia and/or thrombocytopenia signalling marrow failure; may evolve to overt aplasia.

- ▶ **Natural history** spans decades; with supportive care only, historical **median survival ~10–20 years**, death mainly from thrombosis, then infection (neutropenia) and hemorrhage (thrombocytopenia). **Transformation to AML is rare (~1–2%)**; rare spontaneous remissions occur.

Laboratory diagnosis

- ▶ **Hemolysis profile:** normo- to macrocytic anemia with **reticulocytosis** (up to ~20% / 400,000/ μ L); **LDH markedly elevated** (values in the thousands); unconjugated bilirubin mildly–moderately raised; **haptoglobin undetectable**.
- ▶ **Intravascular hemolysis markers:** **urine hemosiderin positive** (chronic loss), **hemoglobinuria** on dipstick (serial samples help because it fluctuates); **iron deficiency** is common from chronic urinary iron loss (may make the anemia microcytic).
- ▶ **Direct antiglobulin (Coombs) test is characteristically NEGATIVE** — a key point distinguishing PNH from autoimmune hemolytic anemia. (It can turn *positive* once a patient is on anti-C5 therapy because of C3 opsonisation.)
- ▶ **Flow cytometry = gold standard:** demonstrates a discrete population of cells deficient in CD55 and CD59 on red cells AND granulocytes/monocytes, giving a **bimodal distribution**. The FLAER assay (fluorescein-labelled proaerolysin, which binds the GPI anchor directly) on granulocytes/monocytes is **more sensitive**.
- ▶ **Diagnostic threshold:** do not diagnose PNH unless the GPI-deficient population is *substantial* — in first approximation **$\geq 5\%$ of red cells and $\geq 20\%$ of granulocytes**.
- ▶ **Older tests:** the **acidified-serum (Ham) test** is highly reliable; the **sucrose hemolysis test** is **unreliable** (both now superseded by flow cytometry).
- ▶ **Bone marrow:** usually **cellular with marked erythroid hyperplasia** $\pm$ mild dyserythropoiesis; may become **hypocellular/aplastic** at some stage.

Management

- ▶ **Supportive** (essential everywhere, as **complement inhibitors are very expensive/often inaccessible**): mandatory **folic acid ≥ 3 mg/day**; periodic serum iron with **iron replacement** as needed (may transiently increase hemolysis); transfusion of **leukocyte-depleted red cells**; treat/anticipate iron overload if transfusion-dependent.
- ▶ **Anticoagulation:** any patient with prior venous thrombosis (or a thrombophilia risk factor on screening) should receive **regular anticoagulant prophylaxis**; thrombolysis (tPA) for refractory thrombosis.

- ▶ **Glucocorticoids:** not indicated for chronic hemolysis (contraindicated long-term); a short prednisone course may help an inflammation-driven flare.
- ▶ **Complement inhibitors** (transform hemolysis, reduce transfusion need and thrombosis):

Agent	Target	Comment
Eculizumab	C5	Humanized anti-C5 mAb (introduced 2007); blocks C5 cleavage → no MAC → abolishes intravascular hemolysis; IV every 14 days. Residual <i>extravascular</i> hemolysis from C3 opsonisation persists (Coombs becomes positive).
Ravulizumab	C5	Longer-acting eculizumab derivative; IV every 8 weeks; fewer breakthrough episodes.
Pegcetacoplan	C3	Proximal blockade prevents both intravascular and extravascular hemolysis → can fully correct anemia (higher Hb than C5 blockade).
Iptacopan	Factor B	Oral; blocks alternative-pathway C3 convertase.
Danicopan	Factor D	Oral; add-on for inadequate response to C5 blockade.

- ▶ **Meningococcal risk:** terminal-complement blockade predisposes to **Neisseria meningitidis* infection — *vaccinate against serogroups ACWY and B** (plus antibiotic prophylaxis, e.g., penicillin) before starting.
- ▶ **Breakthrough hemolysis** can occur with incomplete blockade (more abrupt/severe with proximal C3 blockade because of the larger surviving PNH red-cell mass).
- ▶ **Allogeneic HSCT** is the only curative option — reserved for young patients with severe PNH or PNH-AA syndrome (complement inhibitors do not treat the marrow failure); immunosuppression with **antithymocyte globulin + ciclosporin** is an alternative for the AA component.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Complement cascade and the GPI-protected red cell (with drug targets).**
Labels: *Classical / Lectin / Alternative pathways* → C3 → C3 convertase → C5 convertase → C5 → C5b–C9 = Membrane Attack Complex (MAC); CD55 (DAF) blocking the convertases; CD59 (protectin) blocking MAC; GPI anchor tethering CD55/CD59;

Normal RBC (protected) vs PNH RBC (CD55/CD59 negative → lysis); drug arrows — Eculizumab/Ravulizumab at C5, Pegcetacoplan at C3, Iptacopan at factor B, Danicopan at factor D.

- ▶ **Diagram 2 — GPI anchor on the red-cell membrane.** Labels: *lipid bilayer, GPI glycolipid anchor, CD55, CD59, PIGA gene* → GPI biosynthesis; show **normal cell** (anchor + proteins present) vs PNH cell (anchor and proteins absent due to PIGA mutation).

Clinical / Diagnostic significance

- ▶ **Suspect PNH in:** Coombs-negative intravascular hemolytic anemia; hemolysis **with** unexplained cytopenia/pancytopenia or aplastic anemia; **venous thrombosis at unusual sites** (especially Budd-Chiari syndrome or abdominal/cerebral vein thrombosis) in a young patient; and unexplained iron-deficiency with hemoglobinuria.
- ▶ **LDH very high + haptoglobin absent + urine hemosiderin positive + DAT negative** is the classic biochemical signature; confirm with **flow cytometry** (CD55/CD59, FLAER).
- ▶ Screen all **aplastic anemia and hypoplastic MDS** patients for a PNH clone, and **monitor PNH patients** for evolving marrow failure.
- ▶ Recognising the **NO-depletion symptoms** (dysphagia, abdominal pain, erectile dysfunction) and **thrombotic risk** drives early complement inhibition and anticoagulation, which markedly improve quality of life and survival.

High-yield exam pointers

- ▶ PNH = **acquired clonal stem-cell disease**; somatic ***X-linked PIGA* mutation** → GPI-anchor deficiency → **loss of CD55 & CD59** → **complement-mediated** intravascular hemolysis**.
- ▶ **Triad:** hemolysis + **venous thrombosis** (leading cause of death) + **bone-marrow failure/pancytopenia**.
- ▶ **CD59** is the most important protector (blocks MAC); **CD55** accelerates convertase decay.
- ▶ **DAT/Coombs NEGATIVE** — distinguishes PNH from AIHA.
- ▶ **Diagnosis** = **flow cytometry** for GPI-deficient red cells *and* granulocytes; **FLAER** most sensitive; threshold **≥5% RBC / ≥20% granulocytes**; **Ham (acidified serum) test** classic, sucrose test unreliable.
- ▶ **First morning urine** is darkest (nocturnal acidosis); **LDH markedly raised, haptoglobin absent, urine hemosiderin positive**; iron deficiency common.
- ▶ **Budd-Chiari syndrome without liver disease** → think PNH.
- ▶ **Eculizumab (anti-C5, q2w) and ravulizumab (q8w)** abolish intravascular hemolysis; **pegcetacoplan (C3)/iptacopan (factor B)/danicopan (factor D)** also block extravascular hemolysis; **meningococcal vaccination mandatory** before complement blockade.

- ▶ **Allogeneic HSCT** is the only cure (for severe PNH / PNH-AA syndrome); **folic acid ≥ 3 mg/day** is mandatory supportive care; **AML transformation ~ 1 –2%**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Hemolytic Anemias” (Acquired/PNH section: PIGA, GPI anchor, CD55/CD59, complement cascade Figs 105-10/105-11, diagnosis, anti-complement therapy) and “**Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia**” (PNH–aplastic anemia relationship).
- ▶ **CMDT 2026** — “Blood Disorders” (Paroxysmal Nocturnal Hemoglobinuria) — essentials of diagnosis, FLAER assay, nitric-oxide–mediated symptoms, thrombosis sites, and current complement-inhibitor regimens including meningococcal prophylaxis.
- ▶ Standard nomenclature CD55 = *decay-accelerating factor* and CD59 = *membrane inhibitor of reactive lysis/protectin* is universally accepted textbook hematology (the functional roles are as described in Harrison).
- ▶ *Coverage note:* The assigned specialty text (**DeVita's Cancer: Principles & Practice of Oncology 12e*) *does not** substantively cover PNH (search matches were incidental, e.g., author names/“epigastric”); depth here is therefore drawn from Harrison 22e plus CMDT 2026, both of which cover PNH comprehensively.



Screening Strategies for Colorectal Cancer

Asked in: Paper II May 2019 — RGUHS MD General Medicine

Definition / Introduction — Screening for colorectal cancer (CRC) is the systematic application of tests to *asymptomatic, average-risk or increased-risk* individuals to detect either pre-malignant adenomatous/serrated polyps (so they can be removed) or early, curable cancers. CRC is an ideal target for screening because it is common, is fatal in nearly 50% of cases yet highly curable when localized, and arises from benign polyps that progress to cancer over many years through the *adenoma–carcinoma sequence*. Removal of these polyps has been shown to prevent the majority of cancers; consequently, the U.S. Preventive Services Task Force (USPSTF, 2021), American Cancer Society (ACS, 2018), ACG and US Multi-Society Task Force all endorse offering organized screening to **all adults aged 45–75 years**.

Rationale and risk stratification (who, and when to start)

- ▶ **Twin rationale:** (1) endoscopic removal of adenomatous polyps *prevents* cancer; (2) detection of localized, superficial cancers in asymptomatic people raises the surgical cure rate.
- ▶ **Starting age lowered to 45 years (USPSTF 2021)** because of the rising incidence of CRC in adults <50 years. Grade B at 45–49 years (qualified) and grade A at 50–75 years (strong).

- ▶ **76–85 years:** individualize (“C”) — consider overall health, life expectancy, prior screening and preferences. **>85 years:** discourage screening.
- ▶ Screening intensity is **risk-tiered**: average risk vs increased risk (family history, IBD/PSC) vs high risk (hereditary syndromes).

Risk category	Defining feature	When to begin / interval
Average risk	No personal/family history, no IBD	Age 45 y; modality-dependent interval (see below)
Single FDR, CRC at ≥ 60 y	One first-degree relative	Begin age 40 y; colonoscopy every 10 y (as average risk)
FDR with CRC/advanced adenoma < 60 y, or two FDRs	Stronger family history	Begin age 40 y or 10 y before youngest case; colonoscopy every 5 y
IBD (UC / Crohn colitis), PSC	Chronic colitis	Surveillance colonoscopy 8–10 y after symptom onset
FAP / MUTYH-associated	APC / biallelic MUTYH	Endoscopic surveillance from puberty; prophylactic colectomy
Lynch syndrome (HNPCC)	MMR gene variant	Colonoscopy every 1–2 y from age 25 y

Stool-based (non-invasive) tests

- ▶ **Guaiac faecal occult blood test (gFOBT, e.g. Hemoccult SENSА):** detects pseudoperoxidase activity of haem; **annual**. Affected by diet/medications. ~50% of proven CRCs give a negative test (intermittent bleeding); of asymptomatic “positives” <10% have cancer, 20–30% have benign polyps. Meta-analysis: **22% relative reduction** in CRC mortality with biennial testing (up to 32% with annual) — benefit emerges only after years of follow-up via downstream colonoscopy.
- ▶ **Faecal immunochemical test (FIT):** detects human globin; **annual**. Higher sensitivity than gFOBT with similar specificity and **not affected by diet or medication** — it has largely replaced gFOBT and is the *preferred* stool test (US Multi-Society Task Force, ACG). Pooled sensitivity ~74%, specificity ~94% for CRC; may detect proximal tumours less reliably.
- ▶ **Multi-target stool DNA test (mt-sDNA; Cologuard = FIT + methylated/mutated DNA markers):** every 1–3 years. Single-test sensitivity for CRC 92.3% vs 73.8% for FIT alone, and for large/serrated adenomas 42.4% vs 23.8%; but **lower specificity** → more false positives and follow-up colonoscopies. High sensitivity/specificity (>90%) for established adenocarcinoma but <50% sensitivity for advanced precancerous lesions.
- ▶ **Blood-based test (methylated SEPT9):** lower sensitivity and specificity than FIT, costlier — **not recommended as a first-line screening test**.

- **Key principle:** *any positive stool/blood/imaging test mandates colonoscopy*; a non-invasive test is only the first step of a two-step pathway.

Structural / visual (endoscopic and imaging) tests

Test	Interval	Strengths	Limitations
Colonoscopy	every 10 y	Examines <i>entire</i> colon; diagnostic + therapeutic (polypectomy); most sensitive	Bowel prep + sedation; perforation ~0.1% ($\approx 4/10\,000$), bleeding ~0.25%, death $\approx 2.9/100\,000$; operator-dependent
Flexible sigmoidoscopy	every 5 y (or 10 y + annual FIT)	No sedation, no full enema, fewer perforations ($\approx 1/10\,000$); RCT-proven ↓ incidence & mortality	Only rectosigmoid/descending colon; misses proximal lesions ($\approx 1.5\%$ have proximal advanced neoplasia despite normal scope)
CT colonography (virtual)	every 5 y	Sensitivity >95% for cancer, 86% for polyps ≥ 6 mm; option if colonoscopy declined/incomplete	Bowel prep; radiation; extracolonic findings (5–37%); flat/serrated lesions missed; positive → colonoscopy
Capsule colonoscopy	—	Non-invasive imaging of colon	Lower sensitivity (polyps >6 mm 64% vs 84%; CRC 74% vs 100%); FDA-approved only for unsuitable/incomplete colonoscopy

- **Sigmoidoscopy evidence:** meta-analyses of RCTs show an **18% relative reduction in incidence** and a **28% reduction in mortality**; benefit of a single screen persists >15 years. Any adenoma found at sigmoidoscopy → complete the examination with **full colonoscopy**.
- **Colonoscopy quality matters:** benefit is greater in the **distal** ($\approx 80\%$) than proximal colon ($\approx 40\text{--}60\%$); withdrawal time $\geq 7\text{--}9$ min and an adequate adenoma detection rate are key quality metrics.
- **Digital rectal examination (DRE)** is **NOT** an effective CRC screening test and is not recommended by any society.

Screening in high-risk / hereditary syndromes

- **Familial adenomatous polyposis (FAP):** autosomal dominant, APC gene ($\sim 90\%$); **MUTYH-associated polyposis** is autosomal recessive ($\sim 8\%$). Hundreds–thousands of adenomas; polyps by mean age 15 y, cancer often by 40 y, **inevitable by 50 y** if untreated. Management: genetic counselling/testing, endoscopic surveillance from puberty, and **prophylactic**

proctocolectomy/colectomy (usually before age 20 y); plus upper-GI endoscopy every 1–3 y for duodenal/peripapillary adenomas. *MUTYH-associated polyposis* — colonoscopic surveillance annually-to-biennially from age 25–30 y.

- ▶ **Lynch syndrome (HNPCC)**: autosomal dominant MMR gene defect (**MLH1, MSH2, MSH6, PMS2, EPCAM**) causing microsatellite instability; ~3% of all CRC, up to 17-fold risk; accelerated adenoma→cancer (1–2 y). **Universal tumour testing** (IHC for MMR proteins or MSI) is recommended for *all* CRCs. Carriers: **colonoscopy every 1–2 years from age 25 y** (or 5 y younger than youngest case); plus endometrial/ovarian surveillance from 30–35 y and consideration of risk-reducing hysterectomy ± BSO at 40 y.
- ▶ **IBD**: risk rises ~0.5–1% per year after the first decade; surveillance colonoscopy with biopsies begins 8–10 years after symptom onset (earlier with concurrent PSC).

Surveillance after polypectomy / curative resection

- ▶ After curative CRC resection: history, examination and **CEA** every 3–6 months for 2 years then 6-monthly to 5 years; CT chest/abdomen/pelvis 6–12 monthly in high-risk stage II / all stage III.
- ▶ **Colonoscopy 1 year** after resection (or after completing adjuvant therapy if not fully scoped pre-op); if clear, repeat **every 3–5 years** for metachronous lesions.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Adenoma–carcinoma sequence flow diagram**: *Normal colonic mucosa → APC loss → small adenoma → KRAS activation → large/advanced adenoma → TP53 / DCC loss → invasive carcinoma*, with a parallel arrow “polypectomy interrupts the sequence.” Label the multi-year timeline and the accelerated 1–2 year pathway in Lynch syndrome.
- ▶ **CRC screening algorithm**: Box “Average-risk adult, age 45 y” → two branches: *Stool-based (FIT annual / mt-sDNA q1–3 y)* and *Structural (colonoscopy q10 y / FS q5 y / CT colonography q5 y)*; any **positive non-invasive test → COLONOSCOPY**. Side box: “Increased/high risk → tailored earlier, more frequent colonoscopy.” Label start age 45, stop 75 (individualize 76–85).

Clinical / Diagnostic significance

- ▶ Choice of test is a shared decision — “*the best test is the one the patient will actually complete.*” FIT and colonoscopy are the preferred stool-based and structural modalities respectively.
- ▶ Unexplained **iron-deficiency anaemia** in any adult (except a menstruating multiparous woman) mandates full colonic evaluation — it is not a screening scenario but the commonest presentation of a right-sided cancer.
- ▶ Stool tests reduce mortality chiefly by triggering colonoscopy and polypectomy; their value is realized only when positives are followed up.

- ▶ **Primary prevention** adjuncts: regular **aspirin/NSAIDs** reduce adenoma/cancer incidence (individualized owing to bleeding risk); antioxidant vitamins and fibre supplements are *not* protective.

High-yield exam pointers

- ▶ **Start screening at age 45 y** (USPSTF 2021); continue to 75; individualize 76–85; discourage >85.
- ▶ **Average-risk menu:** FIT annual · gFOBT (Hemoccult SENSa) annual · mt-sDNA q1–3 y · flexible sigmoidoscopy q5 y · **colonoscopy q10 y** · CT colonography q5 y.
- ▶ **Colonoscopy = gold standard** (most sensitive, therapeutic); FIT = **preferred non-invasive test** (replaced gFOBT, diet-independent).
- ▶ **DRE is not a screening test.** Any positive non-invasive test → **colonoscopy**.
- ▶ **FAP:** APC, AD, colectomy before age 20 y; **MUTYH** is AR. **Lynch:** MMR genes, colonoscopy q1–2 y from age 25 y; universal MSI/IHC testing of all CRCs.
- ▶ **IBD/PSC:** surveillance colonoscopy 8–10 y after onset.
- ▶ Family history of CRC → begin at **age 40 y** or 10 y before youngest affected relative.
- ▶ Sigmoidoscopy misses the proximal colon; complete with colonoscopy if any adenoma found.
- ▶ Post-resection: colonoscopy at **1 year**, then q3–5 y.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Lower Gastrointestinal Cancers / Colorectal Cancer” (Table 86-3 screening strategies; stool, endoscopic and imaging modalities; hereditary syndromes) and “Prevention and Early Detection of Cancer” (Table 75-3 USPSTF/ACS recommendations; modality evidence — FOBT/FIT, sigmoidoscopy and colonoscopy mortality data, SEPT9, CT colonography).
- ▶ **CMDT 2026** — “Cancer” chapter, *Colorectal Cancer — Screening for Colorectal Neoplasms* (Table 44-12 average- and family-history-risk recommendations; FIT/gFOBT, mt-sDNA Cologuard/Cologuard Plus, colonoscopy, flexible sigmoidoscopy, CT and capsule colonography; post-resection surveillance) and “Gastrointestinal Disorders” chapter (FAP and Lynch syndrome surveillance and management).
- ▶ **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — corroborative oncologic background on hereditary CRC syndromes and the adenoma–carcinoma sequence.
- ▶ *Coverage note:* The corpus covers this topic well. Society guideline numbers cited are US-based (USPSTF/ACS/ACG); the corpus does not give India-specific (ICMR) CRC screening recommendations, so none are quoted.



Sickle cell anemia

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — Sickle cell anemia (SCA) is the **autosomal-recessive** hemoglobinopathy caused by *homozygosity* for the sickle β -globin gene (HbSS, $\alpha_2\beta S_2$). A single point mutation produces an abnormal hemoglobin (HbS) that **polymerizes when deoxygenated**, deforming the red cell into the classic sickle shape. The result is a **chronic hemolytic anemia** punctuated by **vaso-occlusive** events and progressive multi-organ damage. It is the most prevalent of the “sickle cell disease” (SCD) phenotypes and one of the commonest Mendelian disorders worldwide.

Molecular genetics, epidemiology & inheritance

- ▶ **Mutation:** point mutation in the β -globin gene (HBB, chromosome 11p15) — GAG→GTG in **codon 6**, substituting **valine for glutamic acid** ($\beta 6 \text{ Glu} \rightarrow \text{Val}$; Harrison numbers it residue 7 by counting the initiator methionine), generating βS . The mutant tetramer is $\alpha_2\beta S_2$ (HbS).
- ▶ **Inheritance:** autosomal recessive — homozygote ($\beta S/\beta S$) = sickle cell anemia; heterozygote ($\beta A/\beta S$) = **sickle cell trait**; compound heterozygotes (HbS- β -thal, HbSC, HbSE) give the broader sickle cell disease spectrum.
- ▶ **Heterozygote advantage:** HbS arose in Africa ~7,000–22,000 years ago and reached high frequency because carriers are relatively protected against *Plasmodium falciparum* malaria (balanced polymorphism).
- ▶ **HbS haplotypes** (Senegal, Benin, Bantu, Cameroon, **Arab-Indian**) modulate severity via their average HbF level — *Senegal* and *Arab-Indian* haplotypes have higher HbF and a milder, often Indian-relevant course.
- ▶ **Burden:** sickle cell trait affects 2–15% of emigrant populations and up to ~half the population in parts of Africa, India and the Middle East; carriers outnumber patients ~25:1. Median age of death in SCA is now in the **5th–6th decade** (CMDT: ~40–50 years).

Pathophysiology (the two interlinked sub-phenotypes)

- ▶ **Polymerization:** HbS behaves like HbA when oxygenated but on **deoxygenation** polymerizes into fibres; the process is exquisitely concentration-dependent — proportional to roughly the **30th power of intracellular Hb concentration**, so small rises in MCHC or cell dehydration markedly accelerate sickling.
- ▶ **Promoters of sickling:** hypoxia, acidosis, dehydration, hyperosmolarity, cold, infection and stasis. HbF **cannot enter the polymer** and therefore powerfully retards sickling (basis of HbF-inducing therapy).
- ▶ **Membrane injury:** repeated sickling causes K^+/Cl^- co-transport and Gardos-channel activation with cellular dehydration, phosphatidylserine externalization and oxidative damage → **irreversibly sickled cells (ISCs)** permanently deformed regardless of oxygenation.

- ▶ **Vaso-occlusion (viscosity arm):** rigid, adhesive sickle cells, leukocytes and platelets occlude the microvasculature → tissue ischemia/infarction and the acute painful episode.
- ▶ **Hemolysis (endothelial arm):** sickle red cells survive <20 days (normal ~120). **Intravascular hemolysis** depletes haptoglobin/hemopexin and releases free hemoglobin, heme and arginase, which scavenge **nitric oxide (NO)**, activate platelets/endothelium and drive vasoconstriction, a pro-inflammatory/pro-thrombotic state and **pulmonary hypertension, priapism, leg ulcers, stroke and nephropathy.**

Genotypes (classification of sickle hemoglobinopathies)

Genotype	Hb fractions (typical)	Clinical severity
Sickle cell trait (HbAS)	HbA 60–70%, HbS 30–40%	Benign; usually normal life expectancy
Sickle cell anemia (HbSS)	HbS >75%, HbF 2–15%, HbA2 ~3–4%, no HbA	Most severe; reference phenotype
HbS-β ⁰ thalassemia	HbS >75%, HbF 2–15%, HbA2 5–6%, no HbA ; low MCV	Clinically like HbSS
HbS-β ⁺ thalassemia	HbS 60–90%, HbA 5–40%, low MCV	~half the complication rate; spleen often palpable
HbSC disease	HbS ~50%, HbC ~50%	Milder; ↑ proliferative retinopathy , target cells
HbSE	HbS ~65%, HbE ~35%	Mild; often Asian/Indian ancestry
HbSS-α thalassemia	high HbA2, low MCV	~30% of HbSS; fewer strokes/leg ulcers, less PHT/renal disease

Clinical features & complications

- ▶ **Onset:** in the first year of life as protective HbF declines and the γ→β switch completes.
- ▶ **Constitutional:** chronic hemolytic anemia with **jaundice, pigment (calcium-bilirubinate) gallstones (~40%),** early splenomegaly then **autosplenectomy,** and **delayed puberty/growth.**
- ▶ **Acute painful (vaso-occlusive) episode:** commonest acute event — severe, often symmetrical/stereotyped pain in back, chest and long bones; lasts days–weeks; provoked by infection, dehydration, hypoxia, cold. **Dactylitis (hand-foot syndrome)** is the typical first presentation in infants.
- ▶ **Acute chest syndrome (ACS):** 2nd commonest acute event, occurs in >50% — fever, chest pain, cough, hypoxia and a **new pulmonary infiltrate**; causes include in-situ thrombosis, infection, **fat embolism from necrotic marrow** and hypoventilation; a leading cause of death.
- ▶ **Neurological:** **stroke/silent infarction in 10–15%** (ischemic in childhood, may be hemorrhagic in adults); neurocognitive decline.

- ▶ **Bone/joint:** osteonecrosis (avascular necrosis, esp. bilateral femoral heads, ~half of patients) and *Salmonella* > *Staphylococcus osteomyelitis*.
- ▶ **Genitourinary:** priapism (~30% of males); nephropathy in ~30% of adults (hyperfiltration → albuminuria → CKD); papillary infarction → hematuria and **hyposthenuria**.
- ▶ **Other:** leg ulcers (over the malleoli), proliferative **retinopathy**, **pulmonary hypertension** (5–10%, **poor prognosis**), hepatopathy/intrahepatic cholestasis.
- ▶ **Acute anemic crises:** aplastic crisis (parvovirus B19), **splenic sequestration** (children), hyperhemolytic and delayed hemolytic transfusion reactions, folate deficiency.
- ▶ **Infection:** functional **hyposplenism** → overwhelming infection with **encapsulated organisms** (*pneumococcus*, *Haemophilus*, *Salmonella*); a major cause of childhood death.

Diagnosis / investigations

- ▶ **CBC & film:** normocytic anemia (Hct usually 20–30%), ISCs, target cells, **nucleated RBCs**, **Howell-Jolly bodies** (hyposplenism), reticulocytosis (10–25%), leukocytosis ($12\text{--}15 \times 10^9/\text{L}$), reactive thrombocytosis; raised indirect bilirubin and LDH, low/absent haptoglobin.
- ▶ **Sickle solubility test:** rapid screen — positive in both trait and disease (cannot distinguish them).
- ▶ **Confirmatory:** **Hb electrophoresis / HPLC** — in HbSS, **HbS 85–98% with no HbA**; HbF often raised (**HbF 15–20% confers a milder course**). Differentiates HbSS from trait, HbSC and HbS- β -thal (see table).
- ▶ **DNA-based testing:** for definitive genotype, genetic counseling and antenatal diagnosis.
- ▶ **Screening:** newborn/cord-blood screening; **antenatal diagnosis** by chorionic villus sampling or cell-free fetal DNA; partner testing when either carries HbS/ β -thal trait.

Management

Modality	Mechanism / indication	Key detail
Hydroxyurea	Induces HbF (anti-polymerization); disease-modifying	Standard of care for all HbSS & HbS- β^0 ; start infants from ~9 months at ~20 mg/kg, titrate to max tolerated (CMDT 15–35 mg/kg/day); halves pain & ACS; mortality reduced ~49% at 17.5 yr
Voxelotor	Increases Hb-O ₂ affinity, inhibits HbS polymerization	1500 mg/day; raises Hb ~1 g/dL; reduces hemolysis (≥ 12 yr)
Crizanlizumab	Anti-P-selectin mAb ; blocks cell-endothelial adhesion	IV monthly; reduces painful episodes ~45%
L-glutamine	Reduces RBC oxidative stress	~25% fewer painful episodes, ~33% fewer hospitalizations

Modality	Mechanism / indication	Key detail
Transfusion / exchange	Severe anemia, stroke prevention/treatment, severe ACS, multiorgan failure, pre-op to Hb ~10 g/dL	Prefer automated red-cell exchange; antigen-match Rh (C, E/c, e) and K; avoid in routine pain
Allogeneic HSCT	Potentially curative	HLA-identical sibling event-free survival >95%; only ~15% have a matched donor; haploidentical improving
Gene therapy (ex vivo)	Two FDA-approved curative options	Lentiviral β A-T87Q (anti-sickling Hb) and CRISPR/Cas9 BCL11A disruption to de-repress HbF $\rightarrow$ 30–50% HbF/HbAT87Q, near-total VOC prevention

- **Acute painful episode:** identify/treat precipitant; IV opioids by PCA or fixed schedule (not “as-needed”) with breakthrough dosing; hydration with **half-normal saline (avoid over-hydration)**; VTE prophylaxis, incentive spirometry, laxatives/antihistamines; O₂ only if hypoxic; monitor first 48–72 h for evolving ACS.
- **Preventive package:** prophylactic penicillin (125 mg <3 yr, 250 mg $\geq$ 3 yr, twice daily until age 5), pneumococcal/Hib/meningococcal vaccination, folic acid 1 mg/day, transcranial Doppler screening annually ages 2–16 with transfusion for high-risk velocities, microalbuminuria screen by age 10 (ACE inhibitor/ARB for albuminuria, avoid NSAIDs), annual retinal screen from age 10.
- **Referral:** to a Comprehensive Sickle Cell Centre with multidisciplinary follow-up.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- “Pathophysiology of sickle cell disease” (Harrison Fig. 103-3): *Oxygenated HbS (solution) $\rightarrow$ Deoxygenation $\rightarrow$ HbS polymer / sickled RBC $\rightarrow$ branch into (1) Vaso-occlusion (endothelial + leukocyte/platelet adhesion $\rightarrow$ ischemia/pain/ACS) and (2) Hemolysis (RBC survival <20 days $\rightarrow$ free Hb + arginase $\rightarrow$ NO depletion $\rightarrow$ vasoconstriction, pulmonary HTN, platelet activation). Label: β S codon-6 GAG $\rightarrow$ GTG (Glu $\rightarrow$ Val), ISC (irreversibly sickled cell), Arginine $\rightarrow$ NO via NO synthase.*
- **Inheritance (Punnett) square:** two carrier parents (AS $\times$ AS) $\rightarrow$ 25% AA (normal), 50% AS (trait), 25% SS (disease). Label genotypes and 1-in-4 affected ratio.

Clinical / Diagnostic significance

- Distinguish trait vs disease: solubility test positive in both; electrophoresis/HPLC is decisive (trait HbA>HbS and asymptomatic; disease HbS>>HbA or no HbA).

- ▶ **HbF level** is the single best modifier of severity — the rationale for hydroxyurea and HbF-reactivating gene therapy.
- ▶ A febrile sickle patient is a **medical emergency** (hyposplenic sepsis); ACS and acute stroke mandate **exchange transfusion**.
- ▶ **Sickle cell trait** is largely benign but linked to exertional rhabdomyolysis/sudden death, hematuria, hyposthenuria, VTE and the rare aggressive **renal medullary carcinoma**.

High-yield exam pointers

- ▶ $\beta 6 \text{ Glu} \rightarrow \text{Val}$ (GAG $\rightarrow$ GTG), βS , tetramer $\alpha 2 \beta \text{S} 2$; autosomal recessive; chromosome 11.
- ▶ HbS polymerizes only when **deoxygenated**; polymerization $\propto \sim 30\text{th}$ power of Hb concentration; HbF **cannot polymerize** (protective).
- ▶ Heterozygote advantage against **falciparum malaria**.
- ▶ **Dactylitis (hand-foot syndrome)** = often the earliest manifestation in infants.
- ▶ **Acute chest syndrome** = leading cause of death; new infiltrate + hypoxia $\pm$ fat embolism from marrow.
- ▶ **Aplastic crisis** = parvovirus B19; osteomyelitis = **Salmonella**; smear shows **Howell-Jolly bodies** (autosplenectomy).
- ▶ **Hydroxyurea** is disease-modifying for all HbSS/HbS- β^0 (works by raising HbF; $\sim 49\%$ mortality reduction).
- ▶ Curative options: **HLA-matched sibling HSCT** (EFS $>95\%$) and **FDA-approved gene therapy** (lentiviral $\beta \text{A-T87Q}$ and CRISPR-edited BCL11A).
- ▶ **Penicillin prophylaxis + pneumococcal vaccine + TCD screening + folic acid** form the pediatric preventive bundle.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Disorders of Hemoglobin” (HbS mutation, polymerization, pathophysiology Fig. 103-3, genotype/Hb-fraction tables, complications, hydroxyurea/voxelotor/crizanlizumab/L-glutamine, transfusion, HSCT and gene therapy, preventive screening).
- ▶ **CMDT 2026** — “Blood Disorders” (**Sickle Cell Anemia & Related Syndromes**) (clinical findings, laboratory criteria, Hb-distribution Table 15-9, supportive care and current drug management).
- ▶ **DeVita's Cancer: Principles & Practice of Oncology, 12e** (hydroxyurea/ESCORT-HU and the sickle-cell-trait association of **renal medullary carcinoma**).

Coverage note: The corpus covers this topic richly; the cited HbF-percentage cut-off for a benign course (15–20%) and exact drug doses are taken verbatim from CMDT/Harrison. Harrison labels

the substituted residue “7” (counting the initiator methionine); the universally taught designation β6 is used here, both being the same valine substitution.



Spleen: Structure and Function

Asked in: Paper I Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — The **spleen** is the largest secondary lymphoid organ of the body and the major **reticuloendothelial (mononuclear phagocyte) organ**, lying in the left upper quadrant (LUQ) entirely within the rib cage. It is uniquely positioned in the **portal (low-pressure) circulation** and is functionally divided into **red pulp** (a blood-filtering compartment) and **white pulp** (lymphoid, immune compartment) — terms coined by *Malpighi*. It serves dual roles as a fastidious blood filter (quality control of red cells) and an immune organ (antibody synthesis and clearance of opsonised pathogens). The normal adult spleen weighs <250 g and is not normally palpable.

Development, gross anatomy and accessory spleens

- ▶ **Embryology:** arises from the **dorsal mesogastrium** at ~5 weeks' gestation as a series of *hillocks* (mesenchymal condensations) that coalesce and migrate to the LUQ. It is mesodermal in origin yet remains a lymphoid/RE organ.
- ▶ **Failure of the hillocks to fuse** leaves rests of splenic tissue → **accessory spleens (splenunculi)** in ~20% of persons; important to recognise, as they cause relapse after splenectomy for haematologic disease and must be sought (often hilar or pancreatic-tail).
- ▶ **Peritoneal attachments (ligaments):** *gastrosplenic* (gastrosplenic) *ligament* anchors spleen to the stomach (carries short gastric vessels), and the *splenorenal* (splenorenal) *ligament* anchors it to the left kidney (carries the splenic artery/vein and pancreatic tail).
- ▶ **Vascular supply:** the **splenic artery** (a branch of the coeliac trunk) carries ~150 mL/min of blood and ramifies into **central arterioles**; venous drainage is via the splenic vein into the portal system.
- ▶ **Normal dimensions:** weight <250 g (decreases with age); maximum **cephalocaudal diameter** 13 cm by **ultrasonography**, or maximum length 12 cm / width 7 cm by **radionuclide scan**.

Microscopic architecture — red pulp and white pulp

Compartment	Components	Principal function
White pulp	Periarteriolar lymphoid sheath (PALS) = T-cell zone sheathing central arteriole; primary follicles and secondary follicles with germinal centres = B-cell zones; surrounding marginal zone	Immune surveillance, antigen presentation, antibody synthesis, marginal-zone B-cell response to encapsulated organisms

Compartment	Components	Principal function
Marginal zone	Lymphoid zone at the white-pulp/red-pulp interface, rich in specialised B cells and macrophages	First contact with blood-borne antigens; T-independent responses to polysaccharide capsular antigens
Red pulp	Pulp cords (cords of Billroth) lined by RE/macrophages — anatomical “dead ends”; venous sinuses with slit-like inter-endothelial pores	Mechanical and immunologic filtration of erythrocytes; culling and pitting

- ▶ The “open” circulation / filtration mechanism: most blood leaving the central arterioles empties into the macrophage-lined cords. To re-enter the circulation, red cells must **squeeze through narrow slits in the cord lining into the sinuses** → venules. **Old, rigid, damaged or antibody-coated red cells are too poorly deformable to pass and are retained and destroyed** — this is the structural basis of red-cell quality control.
- ▶ The low portal pressure and slow transit minimise damage to normal erythrocytes while exposing abnormal cells to prolonged macrophage scrutiny.

Physiologic functions of the spleen

- ▶ 1. Quality control of erythrocytes (red pulp):
 - **Culling** — removal of senescent and defective red cells.
 - **Pitting** — removal of intra-erythrocytic inclusions without destroying the cell: **Howell-Jolly bodies (nuclear remnants)**, **Heinz bodies (denatured haemoglobin)**, **Pappenheimer/basophilic-stippling (siderotic) granules**, and intracellular parasites (e.g., malaria) are “pinched off” as the cell traverses the slits.
- ▶ 2. Immune function (white pulp): synthesis of **antibodies** (notably IgM by germinal-centre and marginal-zone B cells) and generation of immune responses to blood-borne pathogens; antigen presentation in PALS and follicles.
- ▶ 3. Clearance of opsonised material: removal of **antibody-coated bacteria and antibody-coated blood cells**, and of poorly opsonised **encapsulated organisms** and particulates from the circulation.
- ▶ 4. Reservoir/sequestration: the normal human spleen holds about **one-third of the total body platelet mass** plus a pool of **marginated neutrophils**, available to mobilise during bleeding or infection. (Unlike some animals, the *normal human spleen does not store or contract to autotransfuse red cells*.)
- ▶ 5. Extramedullary haematopoiesis (EMH): a latent fetal function reactivated when marrow cannot meet demand (e.g., myelofibrosis) — a cause of splenomegaly.

Splenomegaly — mechanisms and the concept of hypersplenism

- ▶ **Pathogenic mechanisms of enlargement** (a useful exam framework):
 - **Work hypertrophy / RE hyperplasia** — for removal of defective red cells (*hereditary spherocytosis, thalassemia, early sickle cell, haemoglobinopathies*).
 - **Immune hyperplasia** — response to infection (*infectious mononucleosis, subacute bacterial endocarditis, malaria*) or immune disease (*ITP, SLE, Felty's syndrome*).
 - **Congestive (passive congestion)** — portal hypertension (*cirrhosis, Budd-Chiari, splenic/portal vein obstruction, CHF*); chronic congestion = “*Banti's disease*.”
 - **Infiltration** — lymphomas, leukaemias, metastases (melanoma commonest), amyloidosis, and storage disorders (*Gaucher's, Niemann-Pick*).
 - **Extramedullary haematopoiesis** — myelofibrosis with myeloid metaplasia.
- ▶ **Hypersplenism** is a clinico-pathologic syndrome defined by: (1) **splenomegaly**, (2) **cytopenia(s) of one or more lineages**, (3) **normal or hyperplastic bone marrow**, and (4) **correction (or improvement) of cytopenias after splenectomy**. Cytopenias arise from increased pooling/destruction in congested cords or by immune mechanisms; red cells may become **spherocytic** from membrane loss during prolonged transit.
- ▶ **Massive splenomegaly** (spleen >8 cm below the costal margin or drained weight ≥ 1000 g) markedly narrows the differential: *chronic myeloid leukaemia, myelofibrosis with myeloid metaplasia, lymphomas, chronic lymphocytic leukaemia, hairy cell leukaemia, polycythaemia vera, Gaucher's disease, sarcoidosis, autoimmune haemolytic anaemia, diffuse splenic hemangiomatosis*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Schematic spleen unit** (Fig. 70-1): draw a central artery/arteriole with concentric zones — label **periarteriolar lymphoid sheath** (T-cell area), **primary follicle** (B-cell), **secondary follicle with germinal centre** (B-cell), **marginal lymphoid zone**, then the **red pulp** showing **pulp cords** (cords of Billroth, RE cells) as dead-ends and **pulp sinuses** with **sinusoidal pores** draining to the **splenic venous system**. Annotate the arrow: “stiff/old/damaged red cells cannot enter the sinuses — culled.”
- ▶ **Diagram 2 — Surface markings / palpation**: outline the LUQ spleen behind ribs 9–11; mark **Traube's space** (borders: *6th rib superiorly, left midaxillary line laterally, left costal margin inferiorly*) and show the line of bimanual palpation from the right lower quadrant towards the left costal margin.

Clinical / Diagnostic significance

- ▶ **Examination**: percussion (**Castell's sign**, **Nixon's method**, **Traube's space dullness**) is best done first, then **bimanual palpation** / ballottement / **Middleton manoeuvre** (palpation from above). Palpation sensitivity 56–71%, percussion 59–82%; both are unreliable in obesity or post-prandially. **Ultrasonography is the imaging investigation of choice** (normal craniocaudal

diameter ≤ 13 cm); CT/MRI better define focal lesions and infarcts; radionuclide scans demonstrate accessory splenic tissue.

- ▶ **Peripheral-smear clues to hyposplenism/post-splenectomy state:** Howell-Jolly bodies, Heinz bodies, basophilic stippling, target cells, acanthocytes, nucleated RBCs, anisocytosis and poikilocytosis; thrombocytosis (up to $1 \times 10^6/\mu\text{L}$) and leukocytosis (up to $25,000/\mu\text{L}$) transiently after splenectomy. Such changes appearing in a patient with an *intact* spleen suggest **splenic infiltration by tumour** interfering with culling/pitting.
- ▶ **Splenectomy — indications:** therapeutic control of symptomatic massive splenomegaly, traumatic/iatrogenic rupture, correction of cytopenias in hypersplenism or immune destruction (e.g., refractory ITP, hereditary spherocytosis, autoimmune haemolytic anaemia), and as effective secondary/tertiary therapy for hairy cell leukaemia, prolymphocytic leukaemia and splenic marginal-zone / mantle-cell lymphoma. Splenic marginal-zone lymphoma characteristically presents with massive splenomegaly and responds to splenectomy or rituximab (DeVita). The only real contraindication is **marrow failure where the spleen is the sole haematopoietic site**.
- ▶ **Overwhelming post-splenectomy infection (OPSI):** the gravest sequela. Susceptibility to **encapsulated organisms** — *Streptococcus pneumoniae* (most important), *Haemophilus influenzae* type b, *Neisseria meningitidis* — and to **Babesia** (avoid endemic areas) and *Capnocytophaga*. Overall sepsis risk $\sim 7\%$ over 10 years; **case-fatality of pneumococcal sepsis 50–80%**; risk highest in the **first 3 years** and in those aged <20 . Mechanism: failure to clear opsonised bacteria + impaired antibody response to **T-independent polysaccharide antigens**.
- ▶ **Prevention:** pneumococcal (PCV13/conjugate $\pm$ PPSV23), Hib and meningococcal vaccines, given ideally ≥ 2 weeks before elective splenectomy (repeat pneumococcal at ~ 5 years); patient education that **any unexplained fever is a medical emergency**; antibiotic standby.
Autosplenectomy occurs in sickle cell disease from repeated infarction — a palpable spleen after age 5 in SCD suggests a coexisting haemoglobinopathy.

High-yield exam pointers

- ▶ Spleen = largest **secondary lymphoid organ**; embryology = **dorsal mesogastrium, 5 weeks**; accessory spleens in $\sim 20\%$.
- ▶ **Red pulp = filter** (cords of Billroth + sinuses $\rightarrow$ *culling & pitting*); **white pulp = immunity** (PALS = T cells, follicles + marginal zone = B cells).
- ▶ **Pitting** removes inclusions $\rightarrow$ their reappearance (**Howell-Jolly bodies**) is the cardinal smear sign of hyposplenism.
- ▶ Normal weight <250 g; US **craniocaudad ≤ 13 cm**; spleen holds $\sim 1/3$ of body platelets.
- ▶ **Hypersplenism tetrad:** splenomegaly + cytopenia + hypercellular marrow + response to splenectomy.

- ▶ **Massive splenomegaly** (>1000 g / >8 cm): think CML, myelofibrosis, CLL, hairy cell leukaemia, lymphoma, PV, Gaucher's, kala-azar.
- ▶ **OPSI** by encapsulated organisms — vaccinate **2 weeks pre-elective splenectomy**; case-fatality 50–80%.
- ▶ **Traube's space dullness** and **Castell's sign** = bedside tests for splenomegaly; **ultrasound** is confirmatory.
- ▶ **Banti's syndrome** = congestive splenomegaly of portal hypertension; **autosplenectomy** = sickle cell disease.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Enlargement of Lymph Nodes and Spleen” (structure/function of the spleen, red/white pulp, culling and pitting, hypersplenism, massive splenomegaly, splenectomy and OPSI, vaccination); cross-referenced with Harrison's chapters on **non-Hodgkin's lymphoma / immune system** for white-pulp lymphoid architecture and marginal-zone B-cell biology.
- ▶ **DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — splenic marginal-zone lymphoma and the role of splenectomy in indolent B-cell neoplasms.
- ▶ *Coverage note:* This topic is **flagged thin** in the corpus — Harrison covers splenic **function, hypersplenism and splenectomy** in depth but gives only a **brief account of detailed histological/anatomical structure**; the white-pulp microanatomy (PALS, marginal zone, cords of Billroth) and surgical/peritoneal anatomy above are standard, universally-accepted textbook internal medicine/anatomy added for completeness and are faithful to the source where present (e.g., Fig. 70-1 labels). CMDT was not used (spec flag cmdt = false).



Stages in neutrophil development

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Granulopoiesis* is the bone-marrow production of neutrophils from the pluripotent haematopoietic stem cell (HSC) through a series of committed progenitors and morphologically recognisable precursors. In the normal adult, neutrophils are produced **only in the marrow**, where roughly three-fourths of nucleated cells are committed to leukocyte production. The system generates about 1.3×10^{11} **neutrophils per 80-kg person per day** and maintains a large marrow reserve that can be mobilised during inflammation. The entire journey from the first recognisable precursor to a mature segmented neutrophil takes **about 2 weeks**.

1. Progenitor hierarchy and lineage commitment

- ▶ Neutrophils and monocytes arise from a **common stem cell** under the control of **colony-stimulating factors (CSFs)** and **interleukins**; the minimum number of HSCs needed to sustain haematopoiesis is estimated at **400–500** at any time.
- ▶ Differentiation pathway (Harrison Fig. 101-2): **HSC** → **multipotent progenitor** → **common myeloid progenitor (CMP)** → **granulocyte-monocyte progenitor (GMP)** → **granulocyte progenitor** → **myeloblast**.
- ▶ **Soluble growth-factor regulation**: stem-cell factor (SCF) and IL-3 act early; GM-CSF and G-CSF drive granulocytic commitment and terminal maturation. G-CSF and GM-CSF are described as critical to the whole developmental process.
- ▶ **Transcription-factor control**: *C/EBPα* governs the granulocyte-monocyte branch point; *C/EBPε* (gene CEBPE) directs the granulocyte progenitor and specifically controls packaging of secondary-granule contents.

2. Morphologic maturation stages (the answer's core)

The morphologic sequence is **myeloblast** → **promyelocyte** → **myelocyte** → **metamyelocyte** → **band (stab) form** → **segmented (mature) neutrophil** (Harrison Fig. 67-2). The myeloblast is the first recognisable precursor.

Stage	Division	Key morphology	Granule event	Surface markers (cumulative)
Myeloblast	Yes (mitotic)	Large cell, prominent nucleoli , fine chromatin, agranular cytoplasm	No specific granules yet	CD33, CD13, CD15
Promyelocyte	Yes (mitotic)	Largest of the series; nucleolus still present	Primary (azurophil) granules appear	CD33, CD13, CD15
Myelocyte	Yes (last dividing cell)	Round/oval nucleus, no nucleolus; “dawn of neutrophilia”	Secondary (specific) granules appear	CD33, CD13, CD15, CD14, CD11b
Metamyelocyte	No (post-mitotic)	Kidney-bean / indented nucleus	Granule synthesis complete	CD33, CD13, CD15, CD14, CD11b
Band (stab) form	No	Sausage / band-shaped non-	—	+ CD10, CD16

Stage	Division	Key morphology	Granule event	Surface markers (cumulative)
		segmented nucleus		
Segmented neutrophil	No	Condensed multilobed nucleus (up to 4 lobes), clumped chromatin	—	CD33, CD13, CD15, CD14, CD11b, CD10, CD16

- ▶ **Two functional compartments:** the **proliferative (mitotic) pool** comprises the myeloblast, promyelocyte and myelocyte; the **myelocyte is the last cell capable of mitosis**. From the **metamyelocyte onward no cell division occurs** — these constitute the **post-mitotic maturation / storage pool**.
- ▶ As the band matures, the nucleus assumes a lobulated configuration; the physiologic role of the multilobed nucleus is uncertain but may permit the marked deformation needed for tissue migration and neutrophil extracellular trap (NET) formation.

3. Granule formation during maturation

Granule genesis is **stage-specific** and is the morphologic hallmark used to distinguish precursors:

- ▶ **Primary / azurophil granules** — synthesised at the **promyelocyte** stage; true lysosomes containing **myeloperoxidase, neutrophil elastase, cathepsin G, hydrolases, cationic proteins, bactericidal/permeability-increasing protein (BPI)** (kills gram-negative bacteria) and **defensins** (broad antimicrobial cysteine-rich peptides).
- ▶ **Secondary / specific granules** — synthesised at the **myelocyte** stage; contain **lactoferrin, vitamin B₁₂-binding protein, membrane components of the NADPH oxidase (NOX2), histaminase, the laminin receptor and receptors for chemoattractants and adherence factors (e.g., CR3/CD11b)**. They lack acid hydrolases, so are **not classic lysosomes**, and their contents are readily released extracellularly to modulate inflammation.
- ▶ (*Standard hematology adds a third, late tertiary/gelatinase granule pool; Harrison Ch. 67 itself describes only the primary and secondary granules.*)

4. Kinetics, marrow release and circulating pools

- ▶ **Transit time:** the proliferation phase **through the metamyelocyte** takes ~1 week, and the maturation phase **from metamyelocyte to mature neutrophil** takes another ~1 week.
- ▶ Marrow release is triggered by **IL-1, TNF- α , CSFs, complement fragments (C3a/C5a) and chemokines**, delivering cells to blood in an unstimulated state.
- ▶ **Anatomic distribution:** under normal conditions **~90% of the neutrophil pool is in the bone marrow, 2–3% in the circulation**, and the remainder in tissues.

- ▶ **Circulating pool** has two dynamic compartments: a **freely flowing pool** (~half the cells) and a **marginated pool** in contact with endothelium; *epinephrine* (exercise, stress) demarginates cells and can double the count in minutes, whereas *glucocorticoids* increase marrow release.
- ▶ **Lifespan**: circulating half-life is only **6–7 hours**; after entering tissues neutrophils survive **1–4 days** before apoptosis (prolonged by G-CSF and IFN- γ). Most are lost across the gut mucosa; senescent cells are cleared by lung and splenic macrophages.
- ▶ **Functional acquisition mirrors morphology**: adhesion and chemotactic machinery appears late — selectin ligand sialyl-Lewis^x (CD15s), L-selectin (CD62L) and the β_2 -integrins (CD11a/b/c with common CD18) become functional in the band/segmented stages, enabling rolling, tight adhesion and diapedesis only in the mature cell.

5. Disordered development — quick correlations

- ▶ **Neutropenia** can arise from *depressed production* (cytotoxic drugs, B₁₂/folate deficiency, congenital marrow failure), *peripheral destruction* (autoimmune, Felty syndrome) or *excess pooling*.
- ▶ **Neutrophilia** reflects increased production, increased marrow release, or **demargination** — the basis for the rapid rises seen with infection, glucocorticoids, epinephrine and exercise.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Maturation ladder** (label each stage left-to-right): *Myeloblast* → *Promyelocyte* → *Myelocyte* → *Metamyelocyte* → *Band form* → *Segmented neutrophil*. Annotate: “prominent nucleoli” (myeloblast); “primary/azurophil granules appear” (promyelocyte); “secondary/specific granules appear + last mitotic division” (myelocyte); “kidney-bean nucleus” (metamyelocyte); “band-shaped nucleus” (band); “multilobed (≤ 4 lobes)” (neutrophil). Bracket *Myeloblast–Myelocyte* as “mitotic / proliferative pool” and *Metamyelocyte–segmented* as “post-mitotic maturation–storage pool.”
- ▶ **Pool distribution pie/box**: three compartments labelled **Marrow ~90%**, **Circulating 2–3%** (freely flowing + marginated), **Tissue (remainder)**, with arrows for *G-CSF / steroids / endotoxin* (marrow release) and *epinephrine* (demargination).

Clinical / Diagnostic significance

- ▶ **Left shift**: appearance of immature forms (bands, metamyelocytes) in blood signals accelerated marrow release in infection/inflammation; a **leukemoid reaction** is persistent neutrophilia $\geq 30,000$ – $50,000/\mu\text{L}$ with **mature, non-clonal** cells (distinguishes from CML).
- ▶ **Maturation arrest** underlies several neutropenias: **severe congenital neutropenia** (*ELANE*-encoded neutrophil elastase, *HAX-1*/Kostmann), and **WHIM syndrome** (*CXCR4* mutation) shows marrow **myeloid arrest with hypersegmentation and myelokathexis**.

- ▶ **Acute promyelocytic leukaemia (APL)** is a clonal arrest at the **promyelocyte** stage; CML expands the entire granulocytic series across all maturation stages.
- ▶ **Nuclear clues: hypersegmentation (>5 lobes)** suggests **vitamin B₁₂/folate deficiency** (or WHIM); the **Pelger-Hüet anomaly** (LBR mutation) gives benign **bilobed “pince-nez”** nuclei that mimic bands; acquired *pseudo-Pelger-Hüet* occurs in MDS.
- ▶ **Cytoplasmic clues of toxicity: toxic granulation** (prominent azurophil granules), **Döhle bodies** (rough-ER aggregates) and cytoplasmic vacuoles indicate severe infection/sepsis (and COVID-19).
- ▶ **Absolute neutrophil count (ANC = bands + mature neutrophils)**: infection risk rises sharply <1000/ μ L; endogenous-flora control is lost <500/ μ L; the local inflammatory response is **absent** <200/ μ L.

High-yield exam pointers

- ▶ Sequence to memorise: Myeloblast → Promyelocyte → Myelocyte → Metamyelocyte → Band → Segmented neutrophil.
- ▶ **Promyelocyte = primary (azurophil/MPO-containing) granules; Myelocyte = secondary (specific/lactoferrin) granules; myelocyte is the last dividing cell.**
- ▶ Total marrow transit **~2 weeks** ($\approx$ 1 week proliferative + $\approx$ 1 week maturation); blood half-life 6–7 h; tissue survival 1–4 days.
- ▶ Distribution: **~90% marrow, 2–3% blood, rest tissues**; circulating = **freely flowing + marginated** halves.
- ▶ Marker progression: CD33/CD13/CD15 throughout; **CD14/CD11b from myelocyte; CD10/CD16 from band stage.**
- ▶ Daily output $\sim 1.3 \times 10^{11}$; G-CSF/GM-CSF are the master cytokines; C/EBP α and C/EBP ϵ the key transcription factors.
- ▶ Production $\sim 1.3 \times 10^{11}$ /day, regulated reserve mobilised by endotoxin/steroids; epinephrine causes demargination (pseudo-neutrophilia).

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Disorders of Granulocytes and Monocytes” (neutrophil maturation sequence, Fig. 67-2 stage/marker table, granule contents, marrow pools and kinetics, ANC thresholds, morphologic anomalies); “Hematopoietic Stem Cells” (progenitor hierarchy HSC→CMP→GMP and growth-factor/transcription-factor regulation, Fig. 101-2).
- ▶ **DeVita, Hellman & Rosenberg’s Cancer: Principles & Practice of Oncology, 12e** — consulted for myeloid-malignancy correlation (maturation-arrest leukaemias).

Coverage note (spec gap = true): Harrison 22e covers granulopoiesis and the full morphologic staging well within Ch. 67 and Ch. 101; DeVita (an oncology text) does **not** carry dedicated normal granulopoietic morphology, so the developmental detail here is drawn from Harrison. Classic “mitotic vs maturation-storage pool” terminology and the **tertiary/gelatinase granule** are universally accepted standard haematology but are only partially explicit in the corpus, so they are flagged rather than over-attributed.



Summarize the management of acute promyelocytic leukemia

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — Acute promyelocytic leukemia (APL) is the distinct subtype of acute myeloid leukemia (AML) defined by the balanced translocation **t(15;17)(q22;q12)** generating the **PML::RARA** fusion gene, whose chimeric protein blocks myeloid differentiation at the promyelocyte stage. It is both the most curable AML (≈85–90%+ long-term survival) *and* the most dangerous at presentation because of a life-threatening **disseminated intravascular coagulation (DIC)/hyperfibrinolysis** that causes early haemorrhagic death. The therapeutic revolution lies in two **differentiating/targeting** agents — **all-trans retinoic acid (ATRA, tretinoin) and arsenic trioxide (ATO)* — *which have converted APL into a largely chemotherapy-free, curable disease. APL is therefore managed as a medical emergency**: treat first on morphological suspicion, do not wait for genetic confirmation.

Why APL is managed differently — biology and diagnosis

- ▶ **PML::RARA** is both the diagnostic marker and the drug target. ATRA binds RARα and forces terminal differentiation of leukaemic promyelocytes; ATO degrades the PML::RARA oncoprotein, induces apoptosis, causes G1–S/G2–M arrest and has anti-angiogenic activity (per the DeVita drug data).
- ▶ **Hallmark morphology**: hypergranular promyelocytes with bundles of **Auer rods** (“faggot cells”); the microgranular (hypogranular) variant has a bilobed nucleus and high WBC.
- ▶ **Diagnostic confirmation**: rapid **PML::RARA RT-PCR** and/or **FISH** for t(15;17); immunophenotype typically **HLA-DR-negative**, **CD34-negative**, **CD33/CD13/myeloperoxidase strongly positive**.
- ▶ **Coagulopathy is the killer**: release of granule procoagulants/annexin-II-driven hyperfibrinolysis produces DIC; early death from intracranial or pulmonary haemorrhage is the main cause of treatment failure. Rare ATRA-resistant variants (e.g. **ZBTB16(PLZF)::RARA**, lacking classic t(15;17)) must be recognised because they respond poorly to ATRA/ATO.

Risk stratification (Sanz) — drives the regimen choice

The corpus splits APL for treatment into **low-risk** (presenting $\text{WBC} \leq 10 \times 10^9/\text{L}$) and **high-risk** ($\text{WBC} > 10 \times 10^9/\text{L}$), the latter requiring immediate cytoreduction. The widely used three-tier **Sanz score** refines this:

Risk group	Presenting WBC	Platelet count
Low	$\leq 10 \times 10^9/\text{L}$	$> 40 \times 10^9/\text{L}$
Intermediate	$\leq 10 \times 10^9/\text{L}$	$\leq 40 \times 10^9/\text{L}$
High	$> 10 \times 10^9/\text{L}$	any

- ▶ Low- and intermediate-risk are managed together as “**low/standard-risk**” and treated with chemotherapy-free ATRA + ATO.
- ▶ High-risk disease carries the greatest early-death risk (differentiation syndrome + haemorrhage) and warrants added cytoreductive chemotherapy.

Emergency supportive care (start immediately, before genetics)

- ▶ **Begin ATRA on clinical suspicion** of APL — it reduces the frequency of DIC and buys time while PCR/FISH is pending; the persistently high early-death rate is the rationale for not delaying.
- ▶ **Aggressive correction of coagulopathy:** transfuse to keep platelets $> 30\text{--}50 \times 10^9/\text{L}$ and fibrinogen $> 100\text{--}150 \text{ mg/dL}$ using platelets, cryoprecipitate and fresh frozen plasma; monitor PT/aPTT, fibrinogen and D-dimer at least twice daily until the coagulopathy resolves.
- ▶ **Avoid leukapheresis** in APL (worsens coagulopathy/precipitates fatal haemorrhage); avoid central lines/invasive procedures while coagulopathy persists.
- ▶ **Tumour-lysis prophylaxis:** hydration and allopurinol (rasburicase if marked hyperuricaemia/renal injury, avoiding G6PD deficiency).

Induction therapy — by risk group

Risk	Standard induction regimen	Key points
Low/standard-risk ($\text{WBC} \leq 10$)	ATRA $45 \text{ mg/m}^2/\text{day}$ PO + ATO 0.15 mg/kg/day IV until complete remission (chemotherapy-free)	ATRA + ATO proved superior to ATRA + idarubicin in EFS and OS (APL0406); CR approaches ~100% with excellent long-term survival
High-risk ($\text{WBC} > 10$)	ATRA + ATO plus cytoreductive chemotherapy — an anthracycline (idarubicin) or gemtuzumab ozogamicin	Immediate cytoreduction needed because of the rapidly rising WBC and severe differentiation-syndrome/haemorrhage risk after starting ATRA (APML4, AML17)

Risk	Standard induction regimen	Key points
		support ATO across all risk groups)

- ▶ The historical AIDA-type backbone (ATRA + idarubicin) remains an alternative where ATO is unavailable, but **ATRA + ATO is now standard of care** for low-risk disease and reduces cumulative chemotherapy toxicity.
- ▶ **Oral ATO** formulations (validated in China) are non-inferior to IV ATO in non-high-risk APL and improve convenience.

Differentiation (APL) syndrome — recognise and treat early

- ▶ **Onset:** typically within the **first 1–3 weeks** of ATRA (or ATO) therapy; caused by adhesion of differentiating neoplastic cells to pulmonary vascular endothelium and cytokine release.
- ▶ **Features:** unexplained **fever, fluid retention/weight gain, dyspnoea, chest pain, pulmonary infiltrates, pleural and pericardial effusions, hypoxaemia**, and rising leukocyte count; renal impairment in severe cases. **Mortality ≈10% if unrecognised.**
- ▶ **Management:** **dexamethasone 10 mg IV twice daily** at first suspicion, plus diuresis/supportive care and cytoreductive chemotherapy if hyperleukocytosis; **temporarily discontinue ATRA (and/or ATO)** only in severe cases (renal failure or ICU admission for respiratory distress) and resume once resolved.
- ▶ **Prophylaxis:** consider prednisone/dexamethasone prophylaxis especially in high-risk patients to blunt the syndrome.

Consolidation, maintenance and monitoring

- ▶ **Consolidation:** continue ATRA + ATO in repeating cycles after CR — e.g. ATO 0.15 mg/kg/day, 5 days/week for weeks 1–4 of an 8-week cycle × 4 cycles, with intermittent ATRA — to achieve **molecular (PCR-negative) remission.**
- ▶ **Maintenance:** with the chemotherapy-free ATRA + ATO regimen, prolonged maintenance is generally **not required**; in chemotherapy-containing (AIDA-type) protocols, maintenance uses ATRA ± 6-mercaptopurine + methotrexate, particularly for high-risk patients.
- ▶ **Measurable residual disease (MRD):** serial RT-PCR for PML::RARA is the standard tool — disappearance of the transcript predicts durable remission, while persistence or re-emergence reliably predicts **molecular relapse**, allowing pre-emptive re-treatment before overt relapse, especially in high-risk patients.
- ▶ **Drug monitoring:** ATO prolongs the **QT interval** — baseline and serial ECG, and aggressive repletion of **potassium and magnesium**; ATRA can cause headache/**pseudotumour cerebri**, dryness and hypertriglyceridaemia.

Relapsed/refractory disease

- ▶ ATO is highly active in relapse; for patients not previously exposed, ATO ± ATR-A (± gemtuzumab ozogamicin) can re-induce remission.
- ▶ Achieve a **second molecular remission**, then consolidate with **autologous HSCT** if PCR-negative, or **allogeneic HSCT** if PCR-positive/poor reserve. (In contrast to other AML subtypes, transplant is reserved for relapse, not first remission.)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Box 1 — Risk-adapted treatment algorithm (flow diagram):** “Suspected APL (faggot cells / coagulopathy)” → “Start ATRA + correct DIC immediately” → “Confirm PML::RARA (PCR/FISH)” → branch to **Low-risk** (WBC ≤10): ATRA + ATO and **High-risk** (WBC >10): ATRA + ATO + anthracycline/gemtuzumab → “Consolidation (ATRA+ATO cycles)” → “PML::RARA RT-PCR MRD monitoring” → “Molecular CR = cure / PCR re-emergence = pre-emptive salvage”. Side-arrow label: “Differentiation syndrome → dexamethasone 10 mg BD, hold ATRA if severe.”
- ▶ **Box 2 — Molecular target:** label **chromosome 15 (PML)** and **chromosome 17 (RARA)** → t(15;17) → **PML::RARA fusion protein** → blocked promyelocyte differentiation; arrows showing ATRA → differentiation and ATO → degradation of PML::RARA + apoptosis.

Clinical / Diagnostic significance

- ▶ APL is an **oncological emergency**: the leading preventable cause of death is **early haemorrhage from DIC**, so empirical ATRA and blood-product support precede genetic confirmation.
- ▶ **PML::RARA RT-PCR** is uniquely valuable both diagnostically and for MRD-directed therapy — APL is the paradigm of molecular monitoring in leukaemia.
- ▶ The cure of APL with **non-cytotoxic targeted differentiation therapy** is a landmark proof of concept in precision oncology; recognition of **ATRA-resistant RARA variants** prevents mismanagement.
- ▶ Vigilance for **differentiation syndrome** and **ATO-induced QT prolongation** is essential during induction.

High-yield exam pointers

- ▶ APL = AML with t(15;17) / PML::RARA; morphology = hypergranular promyelocytes with **faggot (multiple Auer-rod) cells**; immunophenotype HLA-DR-/CD34- **negative**.
- ▶ **Treat on suspicion** — start ATRA **immediately**; do not await cytogenetics; **avoid leukapheresis**.
- ▶ **Low-risk** = WBC ≤10 × 10⁹/L → **chemo-free ATRA** (45 mg/m²/d) + ATO (0.15 mg/kg/d); CR ~100% (APL0406 trial, superior to ATRA + idarubicin).
- ▶ **High-risk** = WBC >10 × 10⁹/L → **add anthracycline (idarubicin) or gemtuzumab ozogamicin** for immediate cytoreduction.

- ▶ **Differentiation syndrome:** first 1–3 weeks, fever/dyspnoea/effusions/infiltrates/hypoxaemia → dexamethasone 10 mg IV BD, hold ATRA if severe; ~10% mortality if missed.
- ▶ **DIC management:** keep fibrinogen >100–150 mg/dL and platelets >30–50 × 10⁹/L with cryoprecipitate/FFP/platelets.
- ▶ **ATO toxicity = QT prolongation** → monitor ECG, K⁺ and Mg²⁺; **ATRA toxicity = pseudotumour cerebri/headache, hypertriglyceridaemia, differentiation syndrome.**
- ▶ **MRD by PML::RARA PCR** directs cure (negativity) and pre-emptive salvage (re-emergence); relapse salvage uses **ATO-based re-induction** → **autologous HSCT (PCR-neg) or allogeneic HSCT (PCR-pos).**

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Acute Myeloid Leukemia” (Treatment of Acute Promyelocytic Leukemia section; t(15;17)/PML::RARA, ATRA + arsenic trioxide, APL/differentiation syndrome, DIC, PML-RARA PCR monitoring; content spans the ch109–ch110 page-bleed).
- ▶ **DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — “Management of Acute Leukemias” (Acute Promyelocytic Leukemia: ATRA/ATO, standard- vs high-risk, ATRA + ATO vs ATRA + idarubicin, oral ATO; APML4/AML17 trials) and the arsenic-trioxide drug profile (mechanism, induction/consolidation dosing, QT-prolongation/differentiation-syndrome toxicity).
- ▶ **CMDT 2026** — “Blood Disorders” (Acute Promyelocytic Leukemia: t(15;17)/PML-RARα, >90% curable with ATRA + ATO across induction/consolidation/maintenance; DIC; supportive care).

Coverage note: The corpus stratifies APL by a **low-risk** (WBC ≤10 × 10⁹/L) vs **high-risk** (>10 × 10⁹/L) dichotomy; the three-tier **Sanz** classification (adding a platelet >40 × 10⁹/L cut-off to define the intermediate group), the precise DIC transfusion thresholds (fibrinogen >100–150 mg/dL; platelets >30–50 × 10⁹/L), the dexamethasone 10 mg BID dose for differentiation syndrome, and the AIDA maintenance schedule (ATRA + 6-mercaptopurine + methotrexate) are universally accepted standard haematology included to satisfy the “summarize management” ask, consistent with the corpus framework.



Thrombocytopenia

Asked in: Paper IV May 2022 — RGUHS MD General Medicine

Definition / Introduction — Thrombocytopenia is a **platelet count <150,000/μL** (normal 150,000–450,000/μL). It results from one or more of three processes: (1) **decreased bone-marrow production,**

(2) sequestration (usually in an enlarged spleen), and (3) increased platelet destruction. It is the commonest cause of abnormal bleeding, ranging from incidental laboratory finding to life-threatening mucocutaneous and intracranial haemorrhage. The single most important first step in any thrombocytopenic patient is to review the peripheral blood smear and exclude *pseudothrombocytopenia*.

Pathophysiologic classification (three mechanisms)

Mechanism	Representative causes	Smear / marrow clue
Decreased production	Marrow aplasia, myelodysplasia, leukaemia/infiltration, chemotherapy, B12/folate deficiency, inherited disorders	Usually accompanied by ↓ RBC/WBC; marrow shows ↓ megakaryocytes
Sequestration	Splenomegaly (portal hypertension, infiltration)	Count rarely falls <40,000/μL from spleen alone; ~⅓ of platelets normally pooled in spleen
Increased destruction	Immune (ITP, drug-induced, HIT), consumptive (DIC, TTP/HUS)	Large/young platelets; marrow shows ↑ megakaryocytes

- ▶ **Thrombopoietin (TPO)**, made in the liver (↑ by interleukin-6), is the major regulator; falling platelet/megakaryocyte mass raises TPO and drives production. Platelet life-span is 7–10 days.
- ▶ **Pseudothrombocytopenia** is an *in vitro* artefact — EDTA-dependent platelet agglutination by antibodies (IgG > IgM/IgA) producing clumps on the smear. **Redraw in sodium citrate (blue top) or heparin (green top)**, or examine a finger-stick smear before diagnosing true thrombocytopenia.

Approach to the patient

- ▶ **History:** drug ingestion (prescription, over-the-counter, herbal — drugs are the commonest cause), prior platelet counts, family history, systemic illness, infection/HIV risk, pregnancy.
- ▶ **Examination:** spleen size (confirm with ultrasound — mild splenomegaly is easily missed), signs of chronic liver disease, and the bleeding pattern.
- ▶ **Bleeding–count correlation:** a count of ~5000–10,000/μL is needed to maintain microvascular integrity. **Petechiae** (pinpoint, non-blanching haemorrhages) first appear at sites of high venous pressure (ankles/feet) and signify *low platelet number, not dysfunction*. **Wet purpura** (haemorrhagic blood blisters on oral mucosa) and **retinal haemorrhage** herald risk of life-threatening bleeding.
- ▶ **Investigations:** CBC + smear first; if other cell lines are abnormal or the smear shows fragments, proceed to **bone marrow examination**. Marrow is indicated in isolated thrombocytopenia in patients >60 years or those failing initial therapy (myelodysplasia can present as isolated thrombocytopenia).

- ▶ The evaluation algorithm branches on whether Hb/WBC are normal or abnormal, and whether the smear shows normal morphology, platelet clumping (pseudothrombocytopenia), or fragmented RBCs (microangiopathy — DIC, TTP/HUS).

Common acquired causes

- ▶ **Infection-induced** — the commonest *non-iatrogenic* cause. Many viral/bacterial infections lower the count via both reduced production and reduced survival; may accompany DIC (especially gram-negative sepsis and severe COVID-19). HIV (early), infectious mononucleosis act through immune mechanisms; late HIV causes pancytopenia/dysplastic production.
- ▶ **Drug-induced** — the commonest cause overall. Two patterns: a **predictable dose-related marrow suppression** (chemotherapeutics), and **classic drug-dependent antibodies** that react with platelet antigens only when the drug is present (notably **quinine** and **sulfonamides**). Onset typically after ~21 days (median) of exposure or on re-exposure, resolving 7–10 days after withdrawal. *GpIIb/IIIa inhibitors* (abciximab, eptifibatide, tirofiban) can cause an abrupt drop **within 24 h** via naturally occurring cross-reacting antibodies. Drugs in Table 120-1 include amiodarone, carbamazepine, phenytoin, vancomycin, trimethoprim-sulfamethoxazole, ranitidine, ibuprofen, naproxen, ceftriaxone, ciprofloxacin and gold. *All drugs should be suspect and stopped/substituted where possible.*
- ▶ **Inherited thrombocytopenia** (uncommon) — autosomal dominant **macrothrombocytopenia** linked to the non-muscle myosin heavy chain **MYH9 gene** (*May-Hegglin anomaly*, *Sebastian*, *Epstein's* and *Fechtner syndromes*); characteristic **large platelets**. Always take a family history in unexplained thrombocytopenia.

Heparin-induced thrombocytopenia (HIT)

- ▶ An immune, prothrombotic reaction to **antibody against the platelet factor 4 (PF4)–heparin complex**, which activates platelets via the **FcγRIIa** receptor (also activates monocytes/endothelium). Distinct from other drug causes: thrombocytopenia is **rarely severe** (nadir rarely <20,000/μL) and, far from bleeding, it **markedly increases thrombosis** (HITT, in up to 50%).
- ▶ **Timing**: typically **5–14 days** after starting heparin; <5 days if exposed within the prior few weeks/months (pre-formed antibody). Occurs with both unfractionated (more common) and LMW heparin.
- ▶ **Diagnosis** — “4Ts” score: Thrombocytopenia, Timing of count fall, Thrombosis/sequelae, and other causes absent. Confirm with **PF4/polyanion immunoassay (ELISA)** — sensitive but low specificity (≈50% positive after cardiopulmonary bypass) — and the more specific **serotonin-release assay**. HIT remains a clinical diagnosis.
- ▶ **Treatment**: *stop all heparin immediately*; anticoagulate with a **non-heparin agent** — IV direct thrombin inhibitor **argatroban** (or bivalirudin), **fondaparinux**, or a **DOAC** (most experience

with rivaroxaban). **Avoid LMWH (cross-reacts) and avoid starting warfarin alone** (risk of venous limb gangrene from protein C/S depletion — overlap with a DTI/fondaparinux/DOAC after platelet recovery). Image for thrombosis ($\geq$ lower-limb duplex); anticoagulate **3–6 months** if thrombosis present.

- ▶ **VITT** (vaccine-induced immune thrombotic thrombocytopenia) — a rare spontaneous-HIT-like syndrome after the **adenoviral ChAdOx1-S/nCoV-19** vaccine, with very **high D-dimer** and thrombosis at unusual sites (cerebral venous sinuses); ~20% fatal; treat with **IVIgG + non-heparin anticoagulant**.

Immune thrombocytopenic purpura (ITP)

- ▶ Acquired immune-mediated platelet destruction (and impaired megakaryocyte release).
Children: acute, post-infectious, self-limited. **Adults:** chronic. **Secondary ITP** is associated with SLE, HIV, hepatitis C and (variably) *H. pylori*.
- ▶ **Clinical:** mucocutaneous bleeding (ecchymoses, petechiae, oral/GI/menorrhagia) with a very low count but otherwise **normal smear (often large platelets)**; wet purpura/retinal haemorrhage warn of severe bleeding.
- ▶ **Diagnosis of exclusion:** antiplatelet antibody testing is *not* useful (poor sensitivity/specificity). Test for HIV, HCV, SLE, immunoglobulins; **Coombs' test if anaemic** — ITP + autoimmune haemolytic anaemia = ***Evans syndrome***.
- ▶ **Treatment** (counts $>30,000/\mu\text{L}$ without bleeding need none — no excess mortality):
 - First line: **prednisone 1 mg/kg or dexamethasone 40 mg/day $\times$ 4 days; anti-Rh0(D) immune globulin 50–75 $\mu\text{g/kg}$ (*Rh-positive, non-splenectomised patients only*); IVIgG 1–2 g/kg over 1–5 days for rapid rise / severe bleeding.**
 - Second line: **rituximab** (anti-CD20; durable remission ~30%), **TPO-receptor agonists** — romiplostim (SC), eltrombopag / avatrombopag (oral), and **splenectomy** (now used less than TPO-RAs). Vaccinate against **encapsulated organisms** (pneumococcus, meningococcus, *H. influenzae*) before splenectomy.

Thrombotic microangiopathies — TTP & HUS

Both show **microangiopathic haemolytic anaemia (MAHA)** — thrombocytopenia + **schistocytes**, $\uparrow$ LDH, $\uparrow$ unconjugated bilirubin, $\downarrow$ haptoglobin, with microvascular thrombi. **PT and aPTT are characteristically normal** (this distinguishes them from DIC, where coagulopathy with prolonged PT/aPTT predominates).

Feature	TTP	HUS
Defect	Deficiency of / antibody to ADAMTS13 (cleaves VWF ultra-large multimers); activity $<10\%$ diagnostic	Mostly Shiga-toxin (<i>E. coli</i> O157:H7) post-diarrhoeal; atypical HUS = complement dysregulation

Feature	TTP	HUS
Classic features	Moschcowitz pentad (1924): MAHA, thrombocytopenia, renal failure , neurologic signs , fever	Acute renal failure , MAHA, thrombocytopenia; preceded by (bloody) diarrhoea, mainly children
Inherited form	Upshaw-Schulman syndrome	Atypical HUS (complement gene variants/anti-factor H)
Treatment	Plasma exchange (TPE) mainstay (mortality 85–100% → 10–30%); glucocorticoids (adjunct); rituximab ↓ relapse; caplacizumab (anti-VWF nanobody)	Mainly supportive ± dialysis (diarrhoeal mortality <5%); anticomplement therapy for aHUS; plasma exchange does not alter typical HUS

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Algorithm for evaluating the thrombocytopenic patient (Fig. 120-2):** Box “Platelet count <150,000/μL” → check “Haemoglobin and WBC” → branches *Normal* (→ “Peripheral blood smear”) and *Abnormal* (→ “Bone marrow examination”). Smear branches: “Platelets clumped → redraw in sodium citrate/heparin” (pseudothrombocytopenia); “Normal RBC morphology, platelets normal/large” → *Consider: drug-induced, infection-induced, idiopathic immune (ITP), congenital*; “Fragmented RBCs” → *Microangiopathic haemolytic anaemia (DIC, TTP)*.
- ▶ **Pathogenesis of TTP (Fig. 120-4):** label *Endothelial cell* → *ultra-large VWF multimers*; *ADAMTS13 protease* cleaving multimers in the normal state; in TTP — “No protease/inhibited ADAMTS13” → *persistent ultra-large VWF multimers* → *platelet aggregation and microvascular thrombosis*.

Clinical / Diagnostic significance

- ▶ Always **inspect the smear first** — it separates pseudothrombocytopenia, immune destruction (large platelets) and microangiopathy (schistocytes) at a glance and directs the entire work-up.
- ▶ **PT/aPTT** discriminate consumptive states: prolonged in **DIC**, normal in **TTP/HUS/ITP**.
- ▶ New thrombocytopenia + neurologic or renal signs + MAHA is **TTP until proven otherwise** — start plasma exchange empirically before ADAMTS13 confirmation, as it is rapidly fatal untreated.
- ▶ In a heparin-exposed patient with a falling count and new thrombosis, apply the 4Ts, stop heparin and switch to a non-heparin anticoagulant — do **not** transfuse platelets or start warfarin alone.
- ▶ **Platelet transfusion** is generally avoided/contraindicated in HIT and TTP (fuels thrombosis); reserve for marrow-failure bleeding and severe ITP haemorrhage.

High-yield exam pointers

- ▶ Threshold $<150,000/\mu\text{L}$; three mechanisms — **production, sequestration, destruction**.
- ▶ **Drugs = commonest cause overall; infection = commonest non-iatrogenic cause**. Quinine & sulfonamides classically cause drug-dependent antibodies.
- ▶ **Pseudothrombocytopenia** = EDTA artefact → redraw in citrate/heparin.
- ▶ **HIT**: PF4–heparin antibody, nadir rarely $<20,000/\mu\text{L}$, day 5–14, **causes thrombosis not bleeding**; avoid LMWH & warfarin-alone; use argatroban/fondaparinux/DOAC.
- ▶ **ITP**: diagnosis of exclusion; treat if bleeding or count $<30,000$; steroids/IVIgG/anti-D first line, TPO-RA/rituximab/splenectomy later; **Evans = ITP + AIHA**.
- ▶ **TTP**: ADAMTS13 $<10\%$, **Moschcowitz pentad**, *Upshaw-Schulman* = inherited; treat with **plasma exchange + caplacizumab/rituximab**.
- ▶ **HUS**: *E. coli* O157:H7, post-diarrhoeal, children, renal-predominant; aHUS = complement → anticomplement therapy.
- ▶ **PT/aPTT normal** in TTP/HUS/ITP but **prolonged in DIC** — a frequent discriminator question.
- ▶ MAHA labs: **schistocytes**, $\uparrow\text{LDH}$, $\uparrow\text{indirect bilirubin}$, $\downarrow\text{haptoglobin}$.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 120 “Disorders of Platelets and Vessel Wall”** (B.A. Konkle), covering definition, mechanisms, approach, drug/infection-induced thrombocytopenia, HIT/VITT, ITP, and TTP/HUS. The chapter's cross-referenced topics (general hemostasis approach, Ch 69; chemotherapy-induced cytopenia, Ch 78) were not separately provided but are summarised only at the level stated in Ch 120. Specific eculizumab naming for aHUS is given in the text only as “anticomplement therapy.” No coverage gap for the asked topic.



Tumour Lysis Syndrome

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Tumour lysis syndrome (TLS) is a life-threatening oncologic metabolic emergency characterised by the tetrad of **hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia**, caused by the rapid destruction of a large number of swiftly proliferating neoplastic cells with massive release of intracellular contents into the circulation. **Acidosis** may also develop and **acute renal failure occurs frequently**. It is the commonest disease-related metabolic emergency in haemato-oncology and is largely **preventable** — recognition of risk and prophylaxis are the most important steps in management.

Pathophysiology — the four metabolic derangements

- ▶ **Core mechanism:** Effective cytotoxic therapy (or rarely spontaneous necrosis) lyses tumour cells, dumping intracellular **potassium, phosphate and nucleic acids** into the blood faster than the kidney can clear them; the nucleic-acid purines are catabolised to **uric acid**.
- ▶ **Hyperuricaemia → uric acid nephropathy:** Turnover of nucleic acids raises serum uric acid. In the **acidic local environment** of the distal nephron, uric acid precipitates in the **tubules, medulla and collecting ducts**, causing obstructive uropathy and renal failure. **Lactic acidosis and dehydration** promote precipitation. **Uric acid crystals in urine** are strong evidence of uric acid nephropathy; the **urinary uric acid : creatinine ratio** is **>1** in acute hyperuricaemic nephropathy and **<1** in renal failure from other causes.
- ▶ **Hyperphosphataemia → hypocalcaemia:** Release of intracellular phosphate pools causes a **reciprocal fall in serum calcium**, producing **severe neuromuscular irritability and tetany**. **Calcium phosphate** precipitates in the renal interstitium and microvasculature (**nephrocalcinosis**), further impairing renal function.
- ▶ **Hyperkalaemia:** Potassium is the principal intracellular cation; massive cell destruction releases it abruptly. In the setting of renal failure, hyperkalaemia can rapidly become **life-threatening**, causing **ventricular arrhythmias and sudden death** — the most immediately lethal feature of TLS.
- ▶ **Renal injury is multifactorial:** both uric-acid and calcium-phosphate crystals are **directly toxic to tubular epithelium**, inducing local inflammatory and pro-oxidative responses; in addition, **soluble uric acid** causes a **crystal-independent** fall in renal blood flow through vasoconstriction and impaired autoregulation.

Aetiology and precipitating factors

Domain	Examples (Harrison 22e)
Classic high-risk tumours	Burkitt's lymphoma, acute lymphoblastic leukaemia (ALL), AML, other rapidly proliferating lymphomas
Lower-risk / occasional	Chronic leukaemias; rarely solid tumours; rarely spontaneous tumour necrosis
Drug triggers	Venetoclax (bcl-2 antagonist — notably increases TLS frequency in lymphoid neoplasms); glucocorticoids; hormonal agents (letrozole, tamoxifen); monoclonal antibodies (rituximab, obinutuzumab, ofatumumab, gemtuzumab)
Timing	Usually during or 1–5 days after chemotherapy; hyperuricaemia may already be present before treatment

Risk stratification and classification

- ▶ **Tumour-burden markers predict risk:** TLS likelihood (e.g. in Burkitt's lymphoma) relates to tumour burden and baseline renal function. Hyperuricaemia and high serum LDH (>1500 U/L), both correlating with total tumour burden, also correlate with the risk of TLS.
- ▶ **Pretreatment evaluation in at-risk patients:** complete blood count, serum chemistry (electrolytes, creatinine, calcium, phosphate, uric acid) and urinalysis. With abnormal baseline renal function, image the kidneys and retroperitoneum by sonography/CT to exclude obstructive uropathy, and watch urine output closely.
- ▶ **Pseudohyperkalaemia caveat:** very high leukocyte and platelet counts can artefactually raise serum potassium through cell lysis *after* the blood is drawn — follow plasma (not serum) potassium; in pseudohyperkalaemia there are no ECG changes.
- ▶ **Cairo–Bishop framework** (standard textbook classification — see Coverage note): **Laboratory TLS** = ≥ 2 of the metabolic abnormalities (raised uric acid, K^+ , phosphate; low calcium) within ~3 days before to 7 days after therapy; **Clinical TLS** = laboratory TLS plus an end-organ consequence — acute kidney injury (rising creatinine), cardiac arrhythmia/sudden death, or seizure.

Clinical features and investigations

- ▶ **Metabolic/renal:** oliguric or anuric acute renal failure, flank pain, haematuria (uric-acid stones/sludge).
- ▶ **Hyperkalaemia:** muscle weakness, paraesthesiae, peaked T waves, widened QRS, ventricular arrhythmias, cardiac arrest.
- ▶ **Hypocalcaemia (from hyperphosphataemia):** tetany, carpopedal spasm, paraesthesiae, neuromuscular irritability, seizures, prolonged QT.
- ▶ **Investigations:** serial uric acid, K^+ , phosphate, calcium, creatinine, urea, LDH; urinalysis for uric-acid crystals and uric acid : creatinine ratio; ECG for hyperkalaemic changes; renal/retroperitoneal imaging if obstruction suspected.

Prevention and management

Recognition of risk and prevention are the most important steps. The standard preventive approach is allopurinol plus aggressive hydration. Urinary alkalinisation with sodium bicarbonate is no longer recommended — though it increases uric-acid solubility, a high urinary pH decreases the solubility of xanthine, hypoxanthine and calcium phosphate, potentially increasing intratubular crystallisation.

Intervention	Mechanism / detail (Harrison 22e)	Notes
Aggressive IV hydration	Normal or ½-normal saline at 3000 mL/m ² /day	Cornerstone; maintains high urine output and dilutes solutes

Intervention	Mechanism / detail (Harrison 22e)	Notes
Allopurinol	Xanthine oxidase inhibitor — blocks <i>new</i> uric acid formation	300 mg/m ² /day; IV form if oral not tolerated; does not remove pre-formed uric acid
Febuxostat	Potent non-purine selective xanthine oxidase inhibitor	Fewer hypersensitivity reactions than allopurinol; no dose adjustment in mild–moderate renal impairment; superior uric-acid control vs allopurinol in intermediate-to-high-risk haematologic malignancy; preferred in allopurinol allergy and/or renal failure
Rasburicase (recombinant urate oxidase)	Converts poorly soluble uric acid → readily soluble allantoin (urate oxidase is absent in primates)	Acts within hours; 0.2 mg/kg IV daily; for high-risk prophylaxis and established hyperuricaemia, especially with renal failure
Renal replacement therapy	Removes K ⁺ , phosphate, uric acid and fluid	Haemodialysis preferred ; consider early ; haemofiltration gives gradual continuous removal

- ▶ **Rasburicase cautions:** contraindicated in G6PD deficiency (cannot detoxify the hydrogen peroxide end-product of the urate-oxidase reaction → haemolysis); causes **ex vivo degradation of uric acid** in the test tube at room temperature, giving **spuriously low uric acid** values — **blood samples must be cooled immediately** to deactivate the enzyme.
- ▶ **Escalation (Fig. 80-4 algorithm):** After 24–48 h, if **uric acid >8.0 mg/dL** or **creatinine >1.6 mg/dL**, correct treatable (obstructive) renal failure and **start recombinant urate oxidase 0.2 mg/kg IV daily**; if no improvement, **delay chemotherapy or start dialysis**. If **uric acid <8.0 mg/dL** and **creatinine <1.6 mg/dL**, proceed with chemotherapy and monitor chemistry every 6–12 h.
- ▶ **Indications for urgent haemodialysis:** K⁺ >6.0 meq/L; uric acid >10 mg/dL; creatinine >10 mg/dL; phosphate >10 mg/dL or rising; symptomatic hypocalcaemia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathophysiology flow diagram** — Labels: *Cytotoxic chemotherapy / rapid tumour cell lysis* → release of K⁺, phosphate, nucleic acids (purines); purines → *xanthine oxidase* → **uric acid**; arms to **Hyperkalaemia** (ventricular arrhythmia, sudden death), **Hyperphosphataemia** → **reciprocal Hypocalcaemia** (tetany; calcium-phosphate nephrocalcinosis), **Hyperuricaemia** (uric-acid crystal precipitation in tubules → uric-acid

nephropathy) → converging on **Acute Kidney Injury**. Mark drug blockade points:
Allopurinol/Febuxostat at xanthine oxidase; **Rasburicase** converting uric acid → **allantoin**.

- ▶ **Management algorithm box** (after Fig. 80-4) — Labels: *Hydrate (saline 3000 mL/m²/day)* → *Allopurinol 300 mg/m²/day* → *Monitor chemistry* → decision node at 24–48 h (**uric acid 8.0 / creatinine 1.6 mg/dL**) → *Rasburicase* → *Dialysis*, with the dialysis-threshold list (**K⁺ >6, uric acid >10, creatinine >10, phosphate >10, symptomatic hypocalcaemia**).

Clinical / Diagnostic significance

- ▶ TLS is **largely preventable**; identifying the high-risk patient (bulky, chemo-sensitive haematologic malignancy; high LDH; pre-existing renal impairment) and instituting hydration plus a hypouricaemic agent before therapy is the key intervention.
- ▶ **Hyperkalaemia is the most immediately fatal** disturbance — continuous cardiac monitoring and prompt treatment are mandatory.
- ▶ The **urinary uric acid : creatinine ratio (>1)** helps distinguish acute hyperuricaemic nephropathy from other causes of renal failure.
- ▶ Choice of hypouricaemic agent is risk-adapted: **allopurinol** for prevention in lower risk, **rasburicase** for high-risk prophylaxis and established hyperuricaemia (especially with renal failure), **febuxostat** where allopurinol is contraindicated or renal function is impaired.
- ▶ **Early dialysis** rather than delayed dialysis improves outcome once defined biochemical thresholds are crossed.

High-yield exam pointers

- ▶ TLS tetrad: **hyperuricaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia** ± acidosis ± acute renal failure.
- ▶ Classic culprits: **Burkitt's lymphoma, ALL, AML**; drug trigger to remember — **venetoclax** (bcl-2 antagonist).
- ▶ Onset **during or 1–5 days after** chemotherapy; high LDH >1500 U/L flags high tumour burden/risk.
- ▶ Standard prophylaxis = **aggressive hydration (3000 mL/m²/day) + allopurinol (300 mg/m²/day)**; **bicarbonate urinary alkalinisation is no longer recommended**.
- ▶ **Rasburicase** converts uric acid → **allantoin**; **contraindicated in G6PD deficiency**; **cool the sample** to avoid spuriously low uric acid.
- ▶ **Febuxostat** = non-purine selective xanthine oxidase inhibitor; useful in **allopurinol allergy / renal impairment**.
- ▶ **Pseudohyperkalaemia** with high WBC/platelets — follow **plasma K⁺**; no ECG changes.

- ▶ **Dialysis thresholds:** K^+ >6 meq/L, uric acid >10, creatinine >10, phosphate >10 (or rising), symptomatic hypocalcaemia — **haemodialysis preferred.**

SOURCE & COVERAGE

Harrison 22e — Ch 80 “Oncologic Emergencies” (Tumor Lysis Syndrome section and Fig. 80-4 management algorithm). **Coverage note:** All metabolic mechanisms, at-risk tumours/drugs, LDH/risk markers, drug doses and dialysis thresholds are grounded in Ch 80. The **Cairo–Bishop laboratory-vs-clinical TLS classification** (and its specific cut-offs/timing window) is universally accepted standard internal medicine but is **not** stated in the provided Harrison chapter text; it has been included for completeness and flagged here.



Unstable hemoglobin

Asked in: Paper IV Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Unstable hemoglobins are rare inherited hemoglobin variants in which a globin mutation makes the hemoglobin tetramer structurally unstable, so it denatures and precipitates within the red cell. They are also called **congenital Heinz body hemolytic anemias**. The usual clinical expression is **nonspherocytic hemolytic anemia** with jaundice, reticulocytosis, pigmenturia, and often splenomegaly, but severity ranges from almost silent hemolysis to recurrent crises.

Classification and examples

- ▶ **Place in hemoglobin disorders:** Harrison classifies them under **hemoglobinopathies** with abnormal physical, chemical, or functional properties, specifically among hemoglobins that oxidize readily; the phenotype is **hemolytic anemia and jaundice**.
- ▶ **Genetic basis:** mutations affect alpha- or beta-globin and disturb the **tertiary or quaternary structure** of the hemoglobin molecule. Many cases arise from a **new mutation**, so absence of a family history does not exclude the diagnosis.
- ▶ **Common structural mechanisms:**
 - Introduction of **proline into an alpha helix**, disrupting normal globin folding.
 - Replacement by a **polar amino acid in the hydrophobic interior** of the globin molecule, destabilizing the heme pocket or globin contacts.
 - Interface mutations that weaken tetramer stability and promote denaturation.
- ▶ **Number of variants:** Harrison notes **156 unstable hemoglobin variants** have been described; most are rare and family-specific.
- ▶ **Important examples from Harrison:**

- **Hemoglobin Köln:** beta 99 Val -> Met; found in multiple families and a classic unstable beta-chain variant.
- **Hemoglobin Hasharon:** alpha 47 Asp -> His; described particularly in Ashkenazi Jews.
- **Hemoglobin Zurich:** beta 63 His -> Arg; notable because it may show **oxidant drug-induced hemolysis**.
- ▶ **Laboratory expression of the variant:** in many heterozygotes the abnormal hemoglobin forms about 20-35% of total hemoglobin, but **hyperunstable variants may be undetectable** on routine fractionation and may mimic a thalassemic phenotype.

Pathogenesis of Heinz-body hemolysis

- ▶ Normal hemoglobin keeps heme protected within a stable globin pocket; unstable variants unfold more easily, especially under oxidative stress.
- ▶ The unstable hemoglobin **precipitates intracellularly** as **Heinz bodies**, which are intraerythrocytic aggregates of denatured hemoglobin.
- ▶ Heinz bodies damage the red-cell membrane and reduce deformability. When such cells traverse splenic cords and sinusoids, macrophages remove the inclusions by **pitting**.
- ▶ Pitting produces characteristic **bite cells** and **blister cells**. Repeated pitting and membrane injury shorten red-cell survival, causing mainly **extravascular hemolysis** in the spleen.
- ▶ During more severe episodes, there may also be intravascular hemolysis with **pigmenturia**, low haptoglobin, hemoglobinemia, hemoglobinuria, or later urinary hemosiderin.
- ▶ Oxidant stress, infection, fever, and selected oxidant drugs can increase denaturation, explaining episodic worsening on a background of chronic compensated hemolysis.

Clinical features

- ▶ **Presentation:** lifelong or incidentally detected **Coombs-negative nonspherocytic hemolytic anemia**; some patients present in childhood, while mild variants are detected only during family studies or after a hemolytic episode.
- ▶ **Symptoms:** fatigue, exertional dyspnea, pallor, intermittent jaundice, dark urine after hemolytic stress, or abdominal discomfort from splenomegaly or gallstones.
- ▶ **Signs:** pallor, icterus, **splenomegaly**, and occasionally hepatomegaly. Growth and development are usually normal in mild disease.
- ▶ **Baseline severity:** Harrison describes the associated disease as **usually mild** and often not requiring transfusion; adult hemoglobin may be only mildly reduced, roughly in the **9-14 g/dL** range in typical tabulated cases.
- ▶ **Crises:** acute worsening may follow oxidant drugs, intercurrent infection, or any stress increasing oxidative injury. Hb Zurich is the exam example for drug-triggered hemolysis.

- **Complications of chronic hemolysis:** unconjugated hyperbilirubinemia, pigment gallstones, folate demand from chronic reticulocytosis, episodic hemoglobinuria, and rarely transfusion-related iron burden if severe disease is repeatedly transfused.

Laboratory diagnosis

- **CBC and reticulocytes:** normocytic or mildly macrocytic anemia because of reticulocytosis; leukocyte and platelet counts are usually normal unless hypersplenism coexists.
- **Hemolysis profile:** increased reticulocyte count, indirect bilirubin, and LDH; reduced haptoglobin; urine hemoglobin or hemosiderin if intravascular hemolysis has occurred.
- **Peripheral smear:** polychromasia with **bite cells/blister cells**. Spherocytes are not the defining abnormality, helping separate it from hereditary spherocytosis or autoimmune hemolysis.
- **Heinz body demonstration:** Heinz bodies are **not seen on ordinary Wright-Giemsa smears**. Use a **supravital stain** such as brilliant cresyl blue, cresyl violet, crystal violet, or methyl violet to show dark globular inclusions of denatured hemoglobin.
- **Stability testing:** heat-stability testing by heating blood to 50°C or incubation with **isopropanol** precipitates unstable hemoglobins; Harrison emphasizes that these tests need careful controls.
- **Hemoglobin analysis:** HPLC or capillary electrophoresis may detect a variant peak; however, a negative HPLC does not exclude a **hyperunstable** variant because the abnormal hemoglobin may be rapidly degraded.
- **Molecular confirmation:** DNA sequencing of alpha- and beta-globin genes is definitive and is important for family studies and genetic counseling.
- **Family study:** evaluate parents, siblings, and children with CBC, reticulocyte count, smear, hemoglobin fractionation, and targeted mutation testing once the proband mutation is known.

Differential diagnosis

Disorder	Key overlap	Differentiating points
G6PD deficiency	Oxidant-triggered hemolysis, Heinz bodies, bite cells	X-linked; normal blood between attacks in many patients; enzyme assay low between episodes but may be falsely normal soon after hemolysis because of reticulocytosis
Hereditary spherocytosis	Jaundice, splenomegaly, gallstones	Spherocytes and raised MCHC; membrane disorder rather than hemoglobin instability; Heinz bodies are not the key lesion
Autoimmune hemolytic anemia	Hemolysis, jaundice, splenomegaly	Direct antiglobulin test positive; spherocytes common; acquired and immune-mediated

Disorder	Key overlap	Differentiating points
Thalassemia syndromes	Chronic inherited anemia; abnormal hemoglobin studies	Microcytosis and target cells dominate; defect is reduced globin synthesis, not unstable tetramer precipitation; hyperunstable Hb may mimic thalassemia and needs DNA testing
Sickle cell disease	Hemolysis and pigment gallstones	HbS polymerization with vaso-occlusion; sickled cells and characteristic HbS fraction on HPLC
M hemoglobins / methemoglobinemia	Abnormal hemoglobin with cyanosis	Main feature is slate-gray cyanosis/methemoglobin, not Heinz-body hemolysis; treatment usually unnecessary for inherited M hemoglobins
PNH	Coombs-negative hemolysis, hemoglobinuria	Acquired clonal disorder; thrombosis and cytopenias may occur; flow cytometry shows CD55/CD59 deficiency

Management and counseling

- ▶ **General principle:** most unstable hemoglobins need **supportive care**, not disease-specific drug therapy.
- ▶ **Avoid triggers:** avoid known oxidant drugs whenever possible, especially in patients with previous drug-triggered hemolysis or Hb Zurich-like variants. Practical avoid-list includes dapsone, primaquine-type antimalarials, nitrofurantoin, phenazopyridine, rasburicase, methylene blue, sulfonamides, pegloticase, and quinolones when safer alternatives exist.
- ▶ **During acute hemolysis:** stop the trigger, treat infection, maintain hydration and urine output, monitor hemoglobin, bilirubin, LDH, renal function, and urine pigment, and transfuse packed red cells only for symptomatic or severe anemia.
- ▶ **Chronic care:** folate replacement is reasonable when chronic reticulocytosis is present; monitor for gallstone symptoms and splenic enlargement.
- ▶ **Transfusion:** Harrison notes disease is usually mild and **does not require transfusion**. Repeated transfusion should be avoided unless clearly indicated because it adds alloimmunization and iron-overload risk.
- ▶ **Splenectomy:** not routine. Consider only in selected severe, transfusion-dependent or hypersplenic cases after hematology review; if performed, give appropriate pneumococcal, meningococcal, and Haemophilus influenzae type b vaccination and fever education.

- ▶ **Genetic counseling:** explain autosomal codominant/inherited hemoglobin-variant behavior, possible de novo mutation, variable expression, and the value of DNA-confirmed diagnosis before reproductive counseling.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis flow diagram:** globin mutation -> unstable Hb tetramer -> intracellular denaturation -> Heinz bodies -> splenic pitting -> bite/blister cells -> extravascular hemolysis -> jaundice, splenomegaly, reticulocytosis, pigmenturia.
- ▶ **Peripheral smear diagram:** label normal RBC, Heinz body on supravital stain, bite cell after splenic pitting, blister cell, reticulocyte/polychromasia.

Clinical / Diagnostic significance

- ▶ Think of unstable hemoglobin in **Coombs-negative nonspherocytic hemolytic anemia** with Heinz bodies, especially when G6PD assay is normal or attacks are familial/recurrent.
- ▶ A routine smear can miss the diagnosis because Heinz bodies require **vital/supravital staining**.
- ▶ HPLC can be misleading: some variants appear as 20-35% abnormal hemoglobin, while **hyperunstable variants may be absent** because they precipitate or degrade rapidly.
- ▶ Drug history is essential; oxidant drugs may convert compensated hemolysis into a crisis.
- ▶ Do not label all bite-cell hemolysis as G6PD deficiency. A normal G6PD level away from crisis plus positive heat/isopropanol instability testing should redirect work-up toward unstable Hb.
- ▶ DNA sequencing is the most reliable final test and prevents unnecessary immune, marrow, liver, and cardiopulmonary work-ups.

High-yield exam pointers

- ▶ Write the synonym: **congenital Heinz body hemolytic anemia**.
- ▶ Core lesion: structurally unstable Hb -> **precipitated denatured Hb** -> Heinz bodies.
- ▶ Heinz bodies need **brilliant cresyl blue/cresyl violet/crystal violet/methyl violet** supravital staining.
- ▶ Smear clue after splenic pitting: **bite cells and blister cells**.
- ▶ Harrison examples: **Hb Köln, Hb Hasharon, Hb Zurich**.
- ▶ Hb Zurich is the classic unstable Hb susceptible to **oxidant drug-induced hemolysis**.
- ▶ Diagnosis: hemolysis labs + supravital stain + **heat 50°C/isopropanol instability test** + HPLC/capillary electrophoresis + globin gene sequencing.
- ▶ Routine HPLC may miss **hyperunstable** variants.
- ▶ Most cases are mild: avoid oxidants, folate if chronic hemolysis, transfuse only when clinically necessary.

SOURCE & COVERAGE

Harrison 22e — “Disorders of Hemoglobin”; Harrison 22e — “Interpreting Peripheral Blood Smears” and “Hemolytic Anemias”; CMDT 2026 — “Blood Disorders”. Coverage note: the specified DeVita’s Cancer 12e heme-malignancy text was grepped but has no substantive benign unstable-hemoglobin coverage, so this thin topic is grounded mainly in Harrison and CMDT.



Vitamin B12 (Cobalamin) Deficiency

Asked in: Paper IV Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Vitamin B12 (cobalamin) deficiency is a state of inadequate tissue cobalamin resulting in **megaloblastic anaemia** (ineffective erythropoiesis with defective DNA synthesis) and a characteristic **neuropsychiatric syndrome**, most importantly *subacute combined degeneration* of the cord. Cobalamin is a cobalt-containing corrin-ring vitamin synthesised solely by micro-organisms; humans depend entirely on **food of animal origin**. Because body stores (2–3 mg) last 3–4 years, deficiency develops insidiously and is usually due to **malabsorption** (chiefly pernicious anaemia) rather than dietary lack — except in vegans. The hallmark is that *neurological damage may be irreversible and can occur even with a normal blood count*, making early recognition critical.

Biochemistry, sources and physiology of absorption

- ▶ **Structure/forms** — cobalt atom at the centre of a corrin ring. Active coenzyme forms: **adenosylcobalamin (ado-B12)**, mitochondrial cofactor for *L-methylmalonyl-CoA mutase*; **methylcobalamin**, cytoplasmic/plasma cofactor for *methionine synthase*. Hydroxocobalamin is the therapeutic precursor form.
- ▶ **Dietary sources & requirement** — meat, fish, eggs and dairy; plant foods are devoid of B12. Western diet supplies 5–30 µg/day; **daily requirement** ~1–3 µg; body stores 2–3 mg (mainly liver), sufficient for 3–4 years.
- ▶ **Two cobalamin-dependent reactions** — (1) methylmalonyl-CoA → succinyl-CoA (ado-B12); a block raises **methylmalonic acid (MMA)**. (2) homocysteine + 5-methyl-THF → methionine (methylcobalamin); a block raises **homocysteine** and regenerates THF.
- ▶ **The “methylfolate trap”** — in B12 deficiency, methionine synthase fails, so 5-methyl-THF accumulates in plasma while intracellular folate polyglutamates fall (THF starvation). This impairs thymidylate synthesis (dUMP→dTMP), producing the *common final pathway of megaloblastosis* shared by folate and B12 deficiency, and explains why large doses of folic acid partially correct the anaemia (but **not** the neuropathy) of B12 deficiency.

Step	Mechanism
Release from food	Gastric acid + pepsin free B12; it binds haptocorrin (HC / TC I) from saliva
Pancreatic phase	Trypsin digests HC; B12 transferred to intrinsic factor (IF)
Intrinsic factor	Glycoprotein from gastric parietal cells (fundus/body); gene at 11q13
Ileal uptake	IF-B12 binds cubilin receptor on ileal enterocyte; trafficked via amnionless (AMN)
Transport	After ~6 h, B12 enters portal blood on transcobalamin II (TC II); delivered to tissues via TC II receptor + megalin
Enterohepatic cycle	0.5–5 µg enters bile/day and is reabsorbed (intact in vegans → slow deficiency; lost in malabsorption → faster)

Causes of B12 deficiency

- **Inadequate intake (dietary)** — **vegans/strict vegetarians**; large at-risk group are Indian Hindus (subnormal levels in up to 50% of young Indian vegans, though frank megaloblastic anaemia is uncommon as the enterohepatic cycle is intact).
- **Malabsorption** — the commonest mechanism:

Site	Causes
Gastric	Pernicious anaemia (autoimmune, commonest severe cause); total/partial gastrectomy; congenital IF deficiency; food-cobalamin malabsorption (atrophic gastritis, PPIs, bariatric surgery)
Intestinal	Stagnant-loop syndrome (bacterial overgrowth — jejunal diverticulosis, blind loop, stricture, fistula); ileal resection (≥ 1.2 m terminal ileum)/Crohn disease; Imerslund-Gräsbeck syndrome (cubilin/AMN mutation, selective malabsorption + proteinuria); tropical sprue; fish tapeworm (<i>Diphyllobothrium latum</i>); gluten-induced enteropathy
Other	Zollinger-Ellison syndrome; chronic pancreatitis; HIV; TC II deficiency (congenital)

- **Drugs / toxic** — **metformin** (lowers TC I); prolonged PPI use; colchicine, neomycin; **nitrous oxide** (N₂O) irreversibly oxidises methylcobalamin and inactivates methionine synthase (megaloblastosis after prolonged anaesthesia; myeloneuropathy in those exposed/abusing N₂O).

Pernicious anaemia (the key autoimmune cause)

- ▶ **Definition** — severe lack of IF due to **autoimmune atrophic gastritis** of the gastric body/fundus.
- ▶ **Epidemiology** — incidence ~120/100,000 (UK); M:F ≈ 1:1.6; **median onset 70–80 years**; commoner in those of African ancestry and blood group A.
- ▶ **Associations** — other organ-specific autoimmune disease: **autoimmune thyroid disease**, vitiligo, type 1 diabetes, Addison disease, hypoparathyroidism; increased risk of **gastric carcinoma** and gastric carcinoid.
- ▶ **Serology** — IF antibodies: “blocking” (type I, ~55%, prevents B12–IF binding) and “binding” (type II, ~35%); **parietal-cell antibody** (~90%, directed at gastric H⁺/K⁺-ATPase, but non-specific). **Raised serum gastrin, low pepsinogen I.**
- ▶ **Histology** — atrophy of all layers of body/fundus, loss of parietal and chief cells, intestinal metaplasia; antrum spared.

Clinical features

- ▶ **Anaemia** — insidious; symptoms often mild relative to severe anaemia (good adaptation). Pallor, mild **icterus/lemon-yellow tint** (haemolysis + ineffective erythropoiesis), fatigue.
- ▶ **Epithelial/GI** — **glossitis** (beefy, smooth red tongue), angular cheilosis, anorexia, weight loss, diarrhoea; reversible **melanin hyperpigmentation**.
- ▶ **Neuropsychiatric** — **subacute combined degeneration (SACD)**: symmetrical demyelination of the posterior columns and lateral (pyramidal) tracts of the cervico-thoracic cord.
 - Earliest: distal **paraesthesiae** and peripheral neuropathy.
 - Posterior column: loss of **vibration and proprioception**, sensory ataxia, **positive Romberg sign**, **Lhermitte sign**.
 - Pyramidal: spastic weakness, **hyperreflexia**, extensor plantars (the combination of absent ankle jerks with extensor plantars is classic).
 - Higher centres: dementia, depression, psychosis (“megaloblastic madness”), optic atrophy, anosmia.
 - Autonomic: postural hypotension, impotence, bladder/bowel incontinence.
 - *Crucial point*: neurological disease may occur with a **normal CBC and normal MCV** and is potentially reversible only if treated within ~6 months.
- ▶ **Other** — infertility, recurrent fetal loss; raised homocysteine is a (weak) vascular/thrombotic risk factor.

Investigations and diagnosis

- ▶ **Peripheral smear** — **oval macrocytes**, marked anisopoikilocytosis, **MCV usually >100 fL** (110–140 fL), **hypersegmented neutrophils (>5 lobes)**; leucopenia and thrombocytopenia in severe cases; **reticulocytopenia**.

- ▶ **Bone marrow** — hypercellular, **megaloblastic** erythroid hyperplasia with **nuclear–cytoplasmic asynchrony** (open “sieve-like” chromatin with mature haemoglobinised cytoplasm), **giant metamyelocytes/giant bands**, hyperpolyploid megakaryocytes.
- ▶ **Ineffective erythropoiesis** (“intramedullary haemolysis”) — raised **unconjugated bilirubin**, very high LDH, low haptoglobin, raised urine urobilinogen.
- ▶ **Confirmatory biochemistry:**

Test	Comment
Serum cobalamin	Normal ~118–148 to 738 pmol/L; deficiency usually <74 pmol/L (<100 ng/L); borderline 74–148 pmol/L. <i>False-normal in up to 50% of PA sera due to IF antibodies interfering with assay</i>
Serum MMA	Raised — relatively specific for B12 deficiency (normal in folate deficiency); also raised in renal failure
Serum homocysteine	Raised in both B12 and folate deficiency (less specific; also up in renal disease, B6 deficiency, hypothyroidism)
Tests for cause	IF + parietal-cell antibodies, serum gastrin (↑) and pepsinogen I (↓) for PA; gastric endoscopy; coeliac serology; check iron status (coexistent iron + B12 deficiency in 15–20% of elderly may mask macrocytosis)

- ▶ The Schilling test is **obsolete** (radioactive B12 unavailable).

Treatment

- ▶ **Parenteral** (standard for severe deficiency / PA / neuropathy) — **hydroxocobalamin** preferred (better retention): six **1000 µg IM** doses at 3–7-day intervals to replenish stores, then **1000 µg IM every 3 months** for maintenance. (Cyanocobalamin, used in the US, needs higher/more frequent dosing — e.g. 1000 µg IM monthly.) CMDT regimen: 100–1000 µg IM/SC, daily for 1 week → weekly for 1 month → monthly.
- ▶ **Oral/sublingual** — high-dose **1000–2000 µg/day** cyanocobalamin or methylcobalamin is effective even in PA, as ~1% is absorbed passively independent of IF; requires good compliance and monitoring; preferred for food-cobalamin malabsorption.
- ▶ **Lifelong therapy** for PA, total gastrectomy and ileal resection. Treat/screen patients on long-term PPIs or after bariatric surgery.
- ▶ **Critical caveats:**
 - Always **exclude/correct B12 deficiency before giving folic acid** — folate monotherapy may correct the anaemia but **precipitate or worsen SACD**.

- **Hypokalaemia** and a transient rise in platelets may occur in the first days of treatment (brisk haematopoiesis); monitor in severe anaemia.
- Expect **reticulocytosis at 5–7 days**; blood picture normalises by ~2 months. Transfusion is rarely needed (give packed cells slowly if essential).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Subacute combined degeneration** — spinal cord cross-section: draw a cord transverse section and shade/label the **posterior (dorsal) columns** — **fasciculus gracilis & cuneatus** and the **lateral corticospinal (pyramidal) tracts** as the demyelinated regions; label *“posterior + lateral column demyelination; anterior columns spared.”*
- ▶ **Cobalamin absorption pathway**: stomach (parietal cell → **intrinsic factor**; haptocorrin from saliva) → duodenum (**pancreatic trypsin** frees B12 from HC → binds IF) → **terminal ileum (cubilin/AMN receptor)** → portal blood on **transcobalamin II** → tissues/liver store. Label each box.

Clinical / Diagnostic significance

- ▶ A raised MCV with **hypersegmented neutrophils** on a routine count is often the first clue — pursue B12/folate before labelling “anaemia of chronic disease.”
- ▶ **MMA + homocysteine** distinguish true tissue deficiency from a borderline serum B12 and detect deficiency despite normal levels; **MMA is the more specific marker**.
- ▶ In any patient with **unexplained myelopathy, sensory ataxia, dementia or psychosis**, check B12 — neurology can present without anaemia.
- ▶ Diagnosing **pernicious anaemia** mandates one-time gastroscopy (gastric atrophy, carcinoma/carcinoid surveillance) and screening for associated autoimmune endocrinopathy.
- ▶ The therapeutic trap to avoid in exams: **never treat megaloblastic anaemia with folic acid alone** until B12 is replete.

High-yield exam pointers

- ▶ Body stores last **3–4 years**; only source is **animal food**; commonest cause of severe deficiency is **pernicious anaemia (autoimmune)**.
- ▶ **MMA raised in B12 deficiency, NOT in folate deficiency**; homocysteine raised in both.
- ▶ PA antibodies: IF antibody = specific but ~50% sensitive; parietal-cell antibody = sensitive (90%) but non-specific.
- ▶ Neurology = **subacute combined degeneration** → posterior + lateral columns; absent ankle jerks + extensor plantars + positive Romberg/Lhermitte.
- ▶ Smear: **oval macrocytes + hypersegmented neutrophils**; marrow: megaloblasts with **nuclear–cytoplasmic asynchrony**, giant metamyelocytes.

- ▶ Treat with **hydroxocobalamin IM**; give **folate only after B12 corrected**; watch for **hypokalaemia** and **reticulocytosis** on day 5–7.
- ▶ **Nitrous oxide** inactivates methionine synthase → can precipitate acute B12 myeloneuropathy.
- ▶ **Metformin** and long-term PPIs are recognised drug causes; screen at-risk patients.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Megaloblastic Anemias” (Hoffbrand) and “Vitamin and Trace Mineral Deficiency and Excess.”
- ▶ **CMDT 2026** — “Blood Disorders: Vitamin B12 Deficiency” (current diagnostic thresholds and treatment regimens).
- ▶ *Coverage note:* The spec-listed specialty text (DeVita's *Cancer: Principles & Practice of Oncology*) addresses haematologic **malignancies**, not benign nutritional/megaloblastic anaemia, so it does not cover this topic; Harrison's dedicated haematology chapter by A.V. Hoffbrand is the authoritative subspecialty source used here, supplemented by CMDT for management.



Agents Causing Occupational Cancers — Types of Cancer, Industrial Sources of Exposure, and Prevention

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — *Occupational cancers* are malignancies whose development is causally attributable to exposure to physical, chemical or biological **carcinogens encountered in the workplace**. They are the prototype of *preventable* cancer because the causative agent is identifiable, often a “complete carcinogen” (acting as both initiator and promoter), and the route of exposure is amenable to engineering and regulatory control. Occupational and environmental exposures are estimated to contribute up to ~10% of all lung cancers, and a substantial fraction of bladder cancer and virtually all mesothelioma. They characteristically show a **long latency (often decades)** between first exposure and tumour, and risk that rises with intensity and duration of exposure.

Principal occupational carcinogens — cancer caused and industrial source

Carcinogen	Type of cancer caused	Industrial use / setting of exposure
Asbestos	Bronchogenic carcinoma; pleural & peritoneal mesothelioma; laryngeal	Mining, milling, insulation, construction, shipbuilding/ship repair, pipe-fitting, brake linings
Aromatic amines (benzidine, 2-naphthylamine — “dyes”)	Bladder (urothelial) carcinoma	Dye, rubber, paint, textile and aluminium industries

Carcinogen	Type of cancer caused	Industrial use / setting of exposure
Benzene	Acute myeloid (myelocytic) leukaemia	Petrochemical, rubber, shoe/leather, solvent, petrol industries
Vinyl chloride monomer	Hepatic angiosarcoma	PVC plastic polymerisation
Arsenic (inorganic)	Skin, lung, liver (angiosarcoma), bladder, kidney	Smelting, microelectronics, wood preservatives, pesticides/herbicides; contaminated deep-well water
Chromium (hexavalent)	Lung, nasal sinus	Chrome plating, pigment/dye manufacture, stainless-steel welding, tanning
Nickel dust	Lung, nasal sinus	Nickel refining, electroplating, alloy and battery manufacture
Polycyclic aromatic hydrocarbons (coal tar, soot, pitch)	Skin — scrotal SCC (chimney sweeps); lung	Coke ovens, coal-tar/pitch, roofing, soot (chimney sweeping), aluminium production
Crystalline silica	Lung carcinoma (on a background of silicosis)	Sandblasting, quarrying, stone-cutting, foundry, ceramics, artificial-stone benchtops
Radon gas / radon daughters	Lung carcinoma	Underground uranium and hard-rock mining; indoor accumulation
Beryllium	Lung carcinoma (highly suspect)	Alloy processing for nuclear power/weapons, aerospace, electronics
Ionising radiation	Leukaemia, thyroid, breast, bone, lung, soft tissue (many)	Radiology/radiography, nuclear industry, radium-dial painting
Diesel exhaust	Lung carcinoma (miners)	Mining, transport, professional drivers
Wood dust / formaldehyde	Sinonasal adenocarcinoma; nasopharyngeal	Furniture and cabinet making, joinery
Nitrogen / sulphur mustard gas	Lung, head & neck, nasal sinus	Chemical-weapon and munitions manufacture
Ultraviolet (sunlight)	Non-melanoma skin cancer; melanoma	Outdoor work (farming, fishing, construction)

Key carcinogen groups — clinical detail

- ▶ **Asbestos** — the single most important occupational carcinogen. All fibre types cause disease; it produces **asbestosis** (diffuse interstitial fibrosis, usually after ≥ 10 years of exposure, presenting ≥ 15 years later), **pleural plaques** (a radiographic marker of exposure, not impairment), bronchogenic carcinoma and **mesothelioma**. **>80% of mesotheliomas are attributable to asbestos**, so documented mesothelioma in an exposed worker is *compensable*. Smoking and asbestos act **multiplicatively** for lung (not mesothelioma) risk.
- ▶ **Aromatic amines** — *benzidine* and *2-naphthylamine* are excreted in urine and concentrated in the bladder, producing urothelial carcinoma in dye, rubber and paint workers; **schistosomiasis* (*S. haematobium*)* is the parallel infective cause of (squamous) bladder cancer in endemic regions such as Egypt.
- ▶ **Benzene** — a myelotoxin causing aplastic anaemia and **acute myeloid leukaemia**; also implicated in myelodysplasia.
- ▶ **Vinyl chloride** — the classic cause of **hepatic angiosarcoma**, a rare sentinel tumour highly specific for occupational exposure (arsenic and thorotrast are the other causes).
- ▶ **Crystalline silica** — silicosis carries an increased risk of lung cancer and of **tuberculosis** (“silicotuberculosis”); *eggshell* calcification of hilar nodes is a clue. Resurgent in **artificial-stone (engineered quartz) benchtop** workers.
- ▶ **Arsenic** — chronic exposure produces **palmar/plantar hyperkeratosis, hyperpigmentation and Mees’ lines**, with skin, lung, liver (angiosarcoma), bladder and kidney cancers.
- ▶ **Polycyclic aromatic hydrocarbons** — the historical *Percival Pott* observation of scrotal squamous-cell carcinoma in chimney sweeps (soot) is the first described occupational cancer.
- ▶ **Beryllium** — causes chronic granulomatous lung disease (diagnosed by the **beryllium lymphocyte proliferation test, BeLPT**) and is a suspect lung carcinogen.

Prevention — primary, secondary and tertiary

Primary prevention (most important — “hierarchy of controls”):

- ▶ **Elimination / substitution** of the carcinogen — e.g., asbestos replaced by synthetic mineral fibres (fibreglass, refractory ceramic fibres); ban/restrict known agents.
- ▶ **Engineering controls** — enclosure of process, **local exhaust ventilation**, closed systems (vinyl chloride polymerisation), **wet methods** and dust suppression for silica.
- ▶ **Administrative controls** — limiting exposure duration, job rotation, restricted-area zoning, worker education and a documented **occupational history**.
- ▶ **Personal protective equipment (PPE)** — respirators, protective clothing (least effective; last line).
- ▶ **Regulation** — enforce permissible exposure limits / threshold limit values, and *ALARA* (“as low as reasonably achievable”) for ionising radiation.

- ▶ **Smoking cessation** — essential because tobacco is **multiplicative** with asbestos and additive/multiplicative with radon; importantly, β -carotene supplementation **increased** lung cancer in asbestos-exposed smokers (CARET trial), so antioxidant chemoprevention is *not* advised.

Secondary prevention (early detection / surveillance):

- ▶ Periodic **chest radiograph, HRCT and pulmonary function tests** in dust-exposed workers; **low-dose CT** screening in eligible high-risk smokers.
- ▶ **Urine cytology / haematuria surveillance** in aromatic-amine-exposed workers; **biological monitoring** (e.g., urinary arsenic, BeLPT for beryllium).
- ▶ Recognition of pleural plaques and pre-employment/periodic medical examination.

Tertiary prevention: early definitive treatment, rehabilitation, and **workers' compensation / medico-legal certification** (mesothelioma, asbestosis, silicosis are notifiable, compensable diseases). Population-level measures include vaccination against oncogenic infections (HBV, HPV) and IARC carcinogen classification with national registries.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ “**Carcinogen → target organ**” **body map**: a human silhouette with labelled arrows — *Asbestos → lung & pleura (mesothelioma); Aromatic amines → urinary bladder; Benzene → bone marrow (AML); Vinyl chloride → liver (angiosarcoma); Arsenic → skin; PAH/soot → scrotal skin (SCC); Wood dust/Ni/Cr → nasal sinuses; Radon/silica/diesel → lung.*
- ▶ **Hierarchy of controls (inverted pyramid)**: top-to-bottom labels — *Elimination → Substitution → Engineering controls → Administrative controls → PPE* (annotate “most effective” at top, “least effective” at bottom).

Clinical / Diagnostic significance

- ▶ A meticulous **occupational and environmental history** is essential in any patient with lung fibrosis, an unexplained malignancy, haematuria or cytopenia — exposure may be remote and bystander (e.g., shipyard painters/electricians, household contacts of asbestos workers).
- ▶ **Sentinel tumours** point directly to specific exposures: hepatic angiosarcoma → vinyl chloride/arsenic; pleural mesothelioma → asbestos; scrotal SCC → soot/PAH; sinonasal adenocarcinoma → wood dust/nickel.
- ▶ Investigations: HRCT and PFT (pneumoconioses), pleural biopsy/thoracoscopy with calretinin/WT-1 for mesothelioma, cystoscopy + urine cytology (bladder), bone-marrow study (benzene/AML), BeLPT (beryllium).
- ▶ Recognising an occupational cause carries **public-health duty** — notification, workplace inspection, screening of co-workers and statutory compensation.

High-yield exam pointers

- ▶ Asbestos → lung cancer + **pleural/peritoneal mesothelioma**; >80% mesotheliomas are asbestos-related; smoking multiplies lung (not mesothelioma) risk.
- ▶ **Aromatic amines (benzidine, 2-naphthylamine)** → **bladder cancer** (dye/rubber/paint industry).
- ▶ Benzene → AML; Vinyl chloride → hepatic angiosarcoma; Arsenic → skin/lung/bladder + Mees' lines.
- ▶ PAH/soot → **scrotal SCC** (Pott, chimney sweeps) — the first recognised occupational cancer.
- ▶ **Chromium & Nickel** → lung and nasal-sinus cancer; Radon & diesel exhaust → lung cancer (miners).
- ▶ Silica → lung cancer + **increased TB risk** (silicotuberculosis); artificial-stone workers are a re-emerging group.
- ▶ Prevention pyramid: **Elimination > Substitution > Engineering > Administrative > PPE**; plus smoking cessation, exposure limits and surveillance.
- ▶ β -carotene **harms** asbestos-exposed smokers (CARET) — do not use as chemoprevention.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Prevention and Early Detection of Cancer” (Table of Suspected Carcinogens), “Occupational and Environmental Lung Disease” (categories of occupational exposure and respiratory responses), “Heavy Metal Poisoning” (arsenic), and “Cancer Genetics” (chimney-sweep/soot historical note).
- ▶ **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — bladder-cancer epidemiology (aromatic amines in painting/rubber/aluminium industries; arsenic; *S. haematobium*) and sinonasal/formaldehyde occupational associations.
- ▶ **CMDT 2026** — “Occupational Pulmonary Diseases” (pneumoconioses table; list of industrial pulmonary carcinogens; asbestos as cocarcinogen with tobacco; mesothelioma).

Coverage note: The corpus covers occupational carcinogens richly but in a *scattered* fashion (carcinogen→cancer table in the cancer-prevention chapter; industrial sources in the occupational-lung and heavy-metals chapters; bladder/aromatic-amine and formaldehyde detail in DeVita). The structured **hierarchy-of-controls** prevention framework and the **Percival Pott** eponym are standard, universally accepted occupational-medicine teaching (Harrison confirms the chimney-sweep observation and asbestos-fibre substitution; the formal control hierarchy is not given verbatim).



Presenting Clinical Features, Serum Markers and Surveillance Recommendations for Pancreatic Carcinoma

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Pancreatic carcinoma denotes malignant neoplasia of the pancreas, of which **ductal adenocarcinoma (PDAC)** of the exocrine pancreas is by far the commonest and most lethal subtype (overall 5-year survival $\approx 13\%$). About **75% arise in the head** and 25% in the body/tail. Its posterior retroperitoneal location and absence of early symptoms mean most patients present late — only 10–20% have resectable disease, $>30\%$ present locally advanced and $>50\%$ metastatic. This answer covers the presenting clinical features, the serum/tumour markers used in diagnosis and monitoring, and the current surveillance recommendations for high-risk individuals.

Presenting clinical features (history)

- ▶ **Painless obstructive jaundice** — the classic presentation of a **head-of-gland** tumour obstructing the distal common bile duct; clinically visible once bilirubin >2 mg/dL, accompanied by dark urine, **pale/clay-coloured stools** and **pruritus** (bile-salt deposition). Jaundice is present in $\sim 75\%$ of periampullary tumours.
- ▶ **Abdominal pain** ($\sim 40\text{--}70\%$) — typically dull **mid-epigastric “boring” pain radiating to the back** from retroperitoneal invasion of the splanchnic (coeliac) nerve plexus; exacerbated by eating or lying flat and relieved by sitting forward (the latter often signifies extrapancreatic, inoperable spread).
- ▶ **Weight loss and cachexia** ($\sim 50\%$) with loss of muscle mass; $\geq 5\%$ **weight loss** in the year preceding diagnosis occurs in $\sim 75\%$ of patients.
- ▶ **New-onset or unexpectedly worsening diabetes mellitus** (type 3c), often with concomitant weight loss, or an unexplained rise in HbA1c in the preceding 1–2 years — may herald the cancer (new diabetes after age 45 is a recognised clue).
- ▶ **Steatorrhea / malabsorption** ($\sim 15\%$) from exocrine insufficiency and pancreatic-duct obstruction — bulky, malodorous, greasy stools.
- ▶ **Fatigue** ($\sim 30\%$), **pruritus** ($\sim 30\%$), **anorexia**, and **new-onset depression** ($\sim 40\%$) — the depression association, though reported, remains debated.
- ▶ **Acute pancreatitis** without an alternative cause, especially in patients ≥ 40 years, may occasionally be the first presentation.

Eponymous and examination signs

Sign	Finding	Significance
Courvoisier’s sign	Palpable, non-tender, distended gallbladder with painless jaundice	Suggests malignant distal biliary obstruction (vs stone disease); accurate $\sim 50\%$ of the time
Trousseau’s syndrome/sign	Migratory superficial thrombophlebitis $\pm$ DVT/PE and arterial thrombi	Reflects the cancer-associated hypercoagulable state

Sign	Finding	Significance
Virchow's node	Palpable left supraclavicular lymph node (thoracic duct drainage)	Sign of advanced/metastatic disease
Sister Mary Joseph's nodule	Subcutaneous periumbilical metastatic nodule	Indicates peritoneal metastasis
Blumer's shelf / ascites / hepatomegaly	Peritoneal & hepatic spread	Late, incurable disease

- ▶ Other late signs: a hard fixed epigastric mass, splenomegaly or gastric varices (splenic vein occlusion), and silvery stools (combined biliary obstruction + ampullary bleeding) in **ampulla of Vater** tumours.

Serum and tumour markers

- ▶ **CA19-9 (carbohydrate antigen 19-9)** — the principal and only FDA-approved serum marker, though for monitoring, not screening/early detection.
 - **Biology:** a high-molecular-weight glycolipid that is a **sialylated derivative of the Lewis (a) blood-group antigen**, shed by tumour mucins. ~8–15% of people are **Lewis-antigen “non-secretors”** and cannot express CA19-9 → falsely normal levels.
 - **Performance:** sensitivity ~70%, specificity ~87%; **false elevations** occur in biliary obstruction/cholestasis, cholangitis, and acute/chronic pancreatitis — so CA19-9 should ideally be measured **after the bilirubin has normalised**.
 - **Prognostic/monitoring role:** higher pre-operative levels correlate with higher stage and unresectability; a **CA19-9 ≥ 500 U/mL (IAP) or ≥ 1000 U/mL (MD Anderson)** defines *biologically borderline* disease; **failure of an elevated level to fall after resection** predicts poor survival (post-operative CA19-9 ≥ 180 U/mL: HR ≈ 3.58 in RTOG 97-04). Falling levels on neoadjuvant therapy indicate response.
- ▶ **CEA (carcinoembryonic antigen)** and **CA125** — drawn as baseline adjuncts; **CA125 is especially useful in the Lewis-negative non-secretors** with undetectable CA19-9. Serial trends of all three guide therapeutic decisions.
- ▶ **Routine bloods:** mild anaemia, cholestatic liver enzyme pattern (raised conjugated bilirubin, ALP), occasionally raised lipase/amylase, raised HbA1c/glucose. **Plasma chromogranin A** is elevated in pancreatic neuroendocrine tumours (a differential), but is falsely raised by PPIs.
- ▶ Emerging “liquid biopsy” markers (ctDNA, cell-free DNA methylation, circulating tumour cells) are investigational and not yet standard.

Diagnostic workup (for completeness)

- ▶ **Multiphase (pancreatic-protocol) contrast-enhanced CT** is the first-line imaging — defines the tumour, vascular (SMA/SMV/portal/coeliac/hepatic) relationships, resectability and metastases; EUS is more sensitive for small tumours and guides biopsy.
- ▶ **MRI/MRCP** is an alternative; **PET-CT** detects occult metastases but is not routine staging.
- ▶ **Tissue diagnosis by EUS-guided FNA/core biopsy** (sensitivity ~90%) — also enables molecular profiling (KRAS, microsatellite/MMR status, BRCA/PALB2).
- ▶ **Staging** uses the AJCC 8th-edition TNM system; disease is grouped as resectable, borderline resectable, locally advanced (unresectable) and metastatic.

Surveillance / screening recommendations

- ▶ **Average-risk (general) population: do NOT screen** — low prevalence makes CA19-9/imaging screening inefficient (unacceptable false-positive rate); the **USPSTF recommends against** population screening.
- ▶ **High-risk individuals warrant surveillance** (per the **International Cancer of the Pancreas Screening — CAPS — Consortium**). Eligible groups:
 - **Hereditary syndromes regardless of family history:** *Peutz-Jeghers syndrome* (STK11/LKB1), *familial atypical multiple-mole melanoma* (p16/CDKN2A), and *hereditary pancreatitis* (PRSS1).
 - **Germline pathogenic-variant carriers** in **ATM, BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6 or TP53** *plus* at least one affected first- or second-degree relative.
 - **Familial pancreatic cancer** — kindreds with ≥ 1 first-degree and ≥ 1 additional relative with PDAC.
- ▶ **Modality: annual surveillance** alternating/combining **endoscopic ultrasound (EUS) and MRI/MRCP** (low radiation, detect cystic precursors and small solid lesions). Enrolment on a prospective registry with genetic counselling is advised.
- ▶ **Age to start:** generally **age 50, or 10 years before** the youngest affected relative's age at diagnosis; earlier in selected syndromes — **age 40** for *CDKN2A* or *PRSS1* carriers, **age 35** for *Peutz-Jeghers syndrome*, and **within ~20 years of onset** of hereditary pancreatitis.
- ▶ **Risk magnitude (justifies surveillance):** one first-degree relative $\uparrow$ risk ~4.6-fold, two ~6.4-fold, ≥ 3 ~32-fold; syndromic fold-risks — *Peutz-Jeghers* 76–140 $\times$, hereditary pancreatitis ~53 $\times$, FAMMM/p16 15–22 $\times$, Lynch 9–36 $\times$, ATM ~6 $\times$, BRCA2 3.5–10 $\times$.
- ▶ **Cystic-lesion surveillance:** incidental cysts ≤ 2 cm are low-risk — MRI at 1 year then every 2 years; EUS-FNA if a cyst reaches ≥ 2 cm or develops high-risk features. **Main-duct IPMNs** and **mucinous cystic neoplasms** are resected; branch-duct IPMNs with “worrisome features” (cyst ≥ 3 cm, mural nodule, main-duct dilatation, raised CA19-9) need closer EUS evaluation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Pancreas anatomy and tumour spread:** Draw the pancreas (head with uncinate process, neck, body, tail) crossing the L2 vertebra, labelling **common bile duct, ampulla of Vater, duodenal C-loop, superior mesenteric artery (SMA), superior mesenteric vein (SMV)–portal vein confluence, coeliac axis, splenic vessels**; show a head tumour obstructing the CBD (jaundice) and arrows to **Virchow's (left supraclavicular) node** and **Sister Mary Joseph's (periumbilical) nodule**.
- ▶ **Diagram 2 — CA19-9 biology/utility box:** Label “sialylated Lewis(a) antigen,” “Lewis-negative non-secretors (8–15%) → false-normal,” “false-high in cholestasis/pancreatitis,” and the monitoring cut-offs ($\geq 500/\geq 1000$ U/mL = biologically borderline; rising post-op = poor prognosis).

Clinical / Diagnostic significance

- ▶ **Painless jaundice + Courvoisier-positive gallbladder** in an older patient should prompt urgent imaging for periampullary/pancreatic-head cancer.
- ▶ **CA19-9 is a monitoring and prognostic tool, not a screening test** — always interpret against bilirubin and Lewis status; use CEA/CA125 when CA19-9 is uninformative.
- ▶ **New-onset diabetes with weight loss after age 45–50** is a recognised early clue — consider occult PDAC.
- ▶ **Trousseau's syndrome** mandates anticoagulation (LMWH or a DOAC) and should trigger an occult-malignancy search.
- ▶ Identifying a **BRCA1/2 or PALB2** germline variant changes management (PARP inhibitor + platinum sensitivity) and triggers family cascade testing and surveillance.

High-yield exam pointers

- ▶ **PDAC = commonest, most lethal pancreatic cancer; 75% in head; KRAS mutated in 90–95%** (also CDKN2A >90%, TP53 ~75%, SMAD4 ~50%).
- ▶ **Classic triad to write:** painless obstructive jaundice + Courvoisier-positive gallbladder + epigastric pain radiating to back.
- ▶ **Four eponyms:** Courvoisier (gallbladder), Trousseau (migratory thrombophlebitis), Virchow (L supraclavicular node), Sister Mary Joseph (umbilical nodule).
- ▶ **CA19-9 = sialylated Lewis(a) antigen;** ~8–15% Lewis-negative non-secretors give false-normal values; raised by cholestasis/pancreatitis; sensitivity ~70%, specificity ~87%.
- ▶ **No screening in average-risk population (USPSTF against).**
- ▶ **High-risk surveillance = annual EUS + MRI** from age 50 (or 10 years before youngest affected relative); earlier in CDKN2A/PRSS1 (40), Peutz-Jeghers (35).
- ▶ **Diagnosis:** pancreatic-protocol CT + EUS-FNA; **stage by AJCC 8th-edition TNM.**

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Pancreatic Cancer” (clinical features, eponymous signs, CA19-9/CEA/CA125 serum markers, germline syndromes and fold-risks, high-risk MRI/EUS screening).
- ▶ **DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 12e** — “Cancer of the Pancreas” (presenting-symptom frequencies, CA19-9 biology and prognostic cut-offs, CAPS Consortium screening eligibility, gene panel and start ages, biological/conditional staging).
- ▶ **CMDT 2026** — “Carcinoma of the Pancreas & Ampulla of Vater” (CA19-9 sensitivity/specificity, current high-risk surveillance schedule and start ages, cystic-lesion surveillance).



Vitamin K-Dependent Coagulation Factors and the Impact of Anticoagulant Drugs

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — The **vitamin K-dependent factors** are a group of plasma proteins whose biological activity requires post-translational **γ-carboxylation** of glutamic acid residues, a reaction for which **vitamin K** is an obligatory cofactor. They comprise the procoagulant zymogens **factors II** (prothrombin), **VII**, **IX** and **X** and the natural anticoagulants **protein C** and **protein S** (plus protein Z and the non-haemostatic Gla proteins of bone, kidney, lung and placenta). γ-Carboxylation confers the ability to bind **calcium** and assemble on **anionic phospholipid membranes** — without it these proteins are inert. This single biochemical step is the pharmacological target of **vitamin K antagonists** (**warfarin**), and it explains the wider impact of all anticoagulant classes on haemostasis.

The vitamin K-dependent factors and the carboxylation reaction

- ▶ **Procoagulant factors: II** (prothrombin), **VII**, **IX**, **X** — easily recalled by the mnemonic “1972” (factors IX, VII, X, II).
- ▶ **Anticoagulant (regulatory) proteins: Protein C** and its cofactor **Protein S**; also **Protein Z**.
- ▶ **Non-coagulation Gla proteins: osteocalcin** (bone) and **matrix Gla protein** — Harrison notes vitamin K-dependent proteins also occur in bone, lung, kidney and placenta.
- ▶ **Mechanism:** Vitamin K is the cofactor for **γ-glutamyl carboxylase (GGCX)**, which converts **glutamate (Glu)** → **γ-carboxyglutamic acid (Gla)** on these proteins. The Gla residues chelate Ca^{2+} , allowing the factor to dock onto phospholipid surfaces (e.g. activated platelets) and participate in cascade complexes.

- ▶ **The vitamin K cycle:** carboxylation oxidises reduced vitamin K (hydroquinone) to **vitamin K epoxide**; **vitamin K epoxide reductase (VKORC1)** regenerates the reduced form so the cofactor can be reused. Dietary vitamin K is often limiting, making this recycling essential.
- ▶ **Plasma half-lives (clinically pivotal):** **factor VII shortest (~6 h) → PT prolongs first**; factor X ≈ 24 h; **prothrombin ≈ 72 h (longest)**; protein C and protein S are also short-lived.
- ▶ **Genetic disease:** inherited mutations of **GGCX** or **VKORC1** cause combined deficiency of *all* vitamin K-dependent factors (activity 1–30%), a congenital bleeding disorder responsive to vitamin K₁ (5–20 mg) or PCC.

Why this matters: PT/INR, deficiency and the newborn

- ▶ Because PT is sensitive to **II, VII and X**, vitamin K deficiency or warfarin **prolongs the PT/INR before the aPTT**.
- ▶ **Acquired vitamin K deficiency** — causes: poor intake, **broad-spectrum antibiotics** (suppress gut flora), malabsorption/cholestasis (fat-soluble vitamin), chronic liver disease.
- ▶ **Distinguishing from liver failure:** **Factor V is NOT vitamin K-dependent** and is made only in hepatocytes — *low FVII with normal FV = vitamin K deficiency*; *low FV = hepatocellular failure*.
- ▶ **Haemorrhagic disease of the newborn** (vitamin K deficiency bleeding) — prevented by routine neonatal vitamin K; neonates also have physiologically low protein C (relevant to warfarin necrosis).
- ▶ **Treatment of deficiency:** vitamin K₁ (phytonadione) **10 mg parenteral** restores factors in 8–24 h; the SC route is avoided (erratic absorption); for urgent correction give **FFP or 4-factor PCC**.

Impact of anticoagulant medications — overview

Class	Example(s)	Molecular target	Effect on vit-K factors / monitoring
Vitamin K antagonist	Warfarin	Inhibits VKORC1 → ↓ functional II, VII, IX, X, protein C/S	Directly lowers vit-K factors; monitor PT/INR
Unfractionated heparin	Heparin	Activates antithrombin → inhibits IIa & Xa (1:1)	No effect on synthesis; monitor aPTT / anti-Xa
LMWH	Enoxaparin, dalteparin	Antithrombin-mediated, predominantly anti-Xa	Usually no monitoring; anti-Xa if needed
Pentasaccharide	Fondaparinux	Antithrombin-mediated, pure anti-Xa	No routine monitoring
Direct oral – IIa	Dabigatran	Reversible direct thrombin (IIa) inhibitor	Fixed dose; aPTT/dTT qualitative

Class	Example(s)	Molecular target	Effect on vit-K factors / monitoring
Direct oral – Xa	Rivaroxaban, apixaban, edoxaban	Reversible direct factor Xa inhibitor	Fixed dose; anti-Xa if needed

Warfarin — the vitamin-K-antagonist in depth

- ▶ **Mechanism:** a racemic R/S mixture; the **S-enantiomer** is more potent and is metabolised by CYP2C9. By blocking VKOR it prevents regeneration of reduced vitamin K, so the liver secretes under-carboxylated, inactive factors (PIVKA).
- ▶ **Pharmacology:** rapidly/almost completely absorbed, peak ~90 min, **half-life 36–42 h**, >97% albumin-bound.
- ▶ **Delayed onset:** the antithrombotic effect awaits clearance of pre-formed factors and depends on fall in factor X and prothrombin ($t_{1/2}$ 24 and 72 h) — hence **overlap with a parenteral anticoagulant** (heparin/LMWH/fondaparinux) for ≥ 5 days and until INR is therapeutic for ≥ 2 days.
- ▶ **Pharmacogenomics:** **CYP2C9/3 and VKORC1 variants increase sensitivity and bleeding risk; FDA labelling advises lower initiation doses in carriers. Starting dose 5–10 mg*.*
- ▶ **Monitoring:** PT standardised as $INR = (\text{patient PT} / \text{mean normal PT})^{ISI}$; target **INR 2.0–3.0** for most indications, 2.5–3.5 for mechanical (especially mitral) valves. Diet, drugs and disease alter response → frequent monitoring.
- ▶ **Adverse effects:**
 - **Bleeding** (commonest; rises sharply when INR exceeds range).
 - **Warfarin-induced skin necrosis** — 2–5 days after starting, well-demarcated necrotic lesions on thigh/buttock/breast; due to a transient **procoagulant state from rapid fall of short-lived protein C** → microvascular thrombi. **Protein C/S-deficient patients** must be bridged with a parenteral anticoagulant and started low.
 - **Teratogenicity** — crosses the placenta causing **warfarin embryopathy**; contraindicated in pregnancy (but safe in breastfeeding).
- ▶ **Reversal:** asymptomatic high INR → **vitamin K 1 mg PO/IV**; serious bleeding → **vitamin K 5–10 mg slow IV plus 4-factor prothrombin complex concentrate** (contains all four vitamin K-dependent procoagulants; normalises INR faster than FFP).

Impact of the other anticoagulant classes

- ▶ **Heparin (UFH):** binds **antithrombin** (a serpin), accelerating inhibition of **thrombin and factor Xa** equally (anti-Xa:anti-IIa 1:1); also releases TFPI. Parenteral, monitored by aPTT/anti-Xa. Complications: bleeding, **heparin-induced thrombocytopenia (HIT)** — an IgG/PF4 immune

prothrombotic syndrome 5–14 days in, more common than with LMWH — and **osteoporosis**.
Reversed fully by protamine sulfate (≈ 1 mg per 100 U heparin).

- ▶ **LMWH (enoxaparin)**: mean MW ~ 5000 ; chains mostly too short to bridge thrombin $\rightarrow$ **predominant anti-Xa activity**; better bioavailability, less HIT/osteoporosis, renally cleared (caution if CrCl < 30). **Protamine gives only partial ($\sim 60\%$) reversal**.
- ▶ **Fondaparinux**: synthetic pentasaccharide, **pure antithrombin-mediated anti-Xa**, $t_{1/2}$ 17 h, once-daily SC; does **not cause HIT** and is **not reversed by protamine** (contraindicated if CrCl < 30).
- ▶ **DOACs**: **dabigatran** (direct IIa) and **rivaroxaban/apixaban/edoxaban** (direct Xa). Predictable fixed dosing, no routine monitoring, fewer interactions/intracranial bleeds than warfarin (but more GI bleeding at higher doses); cleared partly renally (dabigatran 80%). **Contraindicated in pregnancy**.
- ▶ **DOAC reversal**: vitamin K and FFP are ineffective. Specific antidotes — **idarucizumab** (antibody fragment, 5 g IV) for dabigatran; **andexanet alfa** (decoy Xa) for rivaroxaban/apixaban. If unavailable, 4-factor PCC 25–50 U/kg. Activated charcoal if ingestion < 4 h.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **The vitamin K cycle (Warfarin's site of action)**: draw the closed cycle with labels — *Glutamate (Glu)* $\rightarrow$ (via γ -glutamyl carboxylase + O_2 + CO_2) $\rightarrow$ *γ -Carboxyglutamate (Gla)* on factors II, VII, IX, X, protein C, protein S; *Reduced vitamin K (hydroquinone)* $\rightarrow$ oxidised to *Vitamin K epoxide* $\rightarrow$ regenerated by **VKORC1 (vitamin K epoxide reductase)**; mark Warfarin $\perp$ blocking VKORC1.
- ▶ **Coagulation cascade with anticoagulant targets**: Tissue factor/VIIa $\rightarrow$ IXa $\rightarrow$ Xa $\rightarrow$ prothrombin (II) $\rightarrow$ thrombin (IIa) $\rightarrow$ fibrinogen $\rightarrow$ fibrin; arrows showing warfarin $\downarrow$ synthesis of II/VII/IX/X, heparin–antithrombin on IIa & Xa, LMWH/fondaparinux on Xa, rivaroxaban/apixaban/edoxaban on Xa, dabigatran on IIa.

Clinical / Diagnostic significance

- ▶ PT/INR is the bedside readout of vitamin K–dependent procoagulant function — used to diagnose vitamin K deficiency, monitor warfarin and assess hepatic synthetic capacity.
- ▶ **Mixing study corrects** in vitamin K deficiency (factor deficiency) but not when an inhibitor is present.
- ▶ **FV vs FVII discrimination** separates vitamin K deficiency from liver failure.
- ▶ **Bridging principle**: never start warfarin alone in active/high-risk thrombosis (delayed onset + transient hypercoagulability) — overlap with a parenteral agent.
- ▶ **Procedure planning**: hold DOACs 1–2 days (longer if renal impairment); reverse warfarin with vitamin K + 4F-PCC for emergency surgery.

High-yield exam pointers

- ▶ Vitamin K-dependent factors = II, VII, IX, X (procoagulant) + protein C, protein S (anticoagulant) — mnemonic “1972”.
- ▶ Vitamin K is cofactor for γ -glutamyl carboxylase; recycled by VKORC1 — warfarin blocks VKORC1.
- ▶ Factor VII (shortest $t_{1/2}$) $\rightarrow$ PT/INR rises first; prothrombin ($t_{1/2}$ 72 h) longest.
- ▶ Warfarin skin necrosis = early fall of short-lived protein C (worse in protein C/S deficiency).
- ▶ Warfarin is teratogenic; DOACs and warfarin both contraindicated in pregnancy — LMWH/UFH are the pregnancy anticoagulants.
- ▶ Reversal map: warfarin $\rightarrow$ vitamin K + 4F-PCC; UFH $\rightarrow$ protamine (full); LMWH $\rightarrow$ protamine (partial); dabigatran $\rightarrow$ idarucizumab; rivaroxaban/apixaban $\rightarrow$ andexanet alfa.
- ▶ Low FVII + normal FV = vitamin K deficiency; low FV = liver failure.
- ▶ Target INR 2.0–3.0 (2.5–3.5 for mechanical valves); always overlap warfarin and parenteral anticoagulant ≥ 5 days.

SOURCE & COVERAGE

- ▶ Harrison’s Principles of Internal Medicine, 22e — “Coagulation Disorders” (vitamin K cycle, γ -carboxylation, GGCX/VKORC1, vitamin K deficiency, factor half-lives, FV vs FVII) and “Antiplatelet, Anticoagulant, and Fibrinolytic Drugs” (warfarin mechanism/pharmacology/INR/reversal; heparin, LMWH, fondaparinux; DOACs and their antidotes).
- ▶ CMDT 2026 — “Disorders of Hemostasis, Thrombosis, & Antithrombotic Therapy” (vitamin K deficiency management, phytonadione dosing, protamine neutralisation, DOAC perioperative handling).
- ▶ Coverage note: The spec-listed specialty text *DeVita’s Cancer Principles & Practice* does not substantively cover this coagulation/anticoagulation topic (only a tangential note that progestational agents raise plasma warfarin levels); depth here derives from Harrison and CMDT. Protein Z, osteocalcin/matrix Gla protein, the “1972” mnemonic, PIVKA and protamine 1 mg/100 U are standard textbook haematology included for completeness.

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Dermatology & psychiatry

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Bipolar disorder

Asked in: Paper IV Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Bipolar disorder is a chronic, recurrent **mood disorder** characterised by unpredictable swings of mood, energy and activity between **mania (or hypomania)** at one pole and **depression** at the other, separated by periods of relative euthymia. It is a *major affective (mood) disorder* distinguished from major depressive disorder by the presence, current or past, of at least one **manic or hypomanic episode**. It affects ~1.5% of the population, has a strong genetic loading (monozygotic concordance approaching 80%), typically begins between 20–30 years of age, and carries a very high lifetime risk of suicide and psychosocial disability.

Epidemiology and classification (Bipolar spectrum)

- ▶ **Prevalence:** Bipolar I ~1.0–1.5% (lifetime ~3.3% and Bipolar II ~1.1% in the NESARC survey); cross-national bipolar *spectrum* ~2.4%. Cyclothymic disorder ~0.4–2.5%.
- ▶ **Onset:** typically ~20 years (often late adolescence); men tend to have onset ~4–5 years earlier and more **manic** episodes, women more **depressive** episodes and rapid cycling.
- ▶ **Sex ratio:** overall ~1:1 (unlike MDD which is ~2:1 female), but women predominate in Bipolar II, mixed/dysphoric mania and rapid cycling; pure (unipolar) mania is commoner in men.

Subtype	Defining requirement	Key feature
Bipolar I	≥1 lifetime manic episode (≥1 week, or any duration if hospitalised)	Depressive/hypomanic episodes usual but not required
Bipolar II	≥1 hypomanic episode + ≥1 major depressive episode ; <i>never</i> a full manic episode	Depression-predominant; high suicide/comorbidity risk
Cyclothymic disorder	≥2 years (≥1 year in children) of fluctuating hypomanic and depressive symptoms that <i>never</i> meet full episode criteria	Chronic, temperamental; 15–50% convert to Bipolar I/II
Substance/medication-induced & due to another medical condition	Manic/hypomanic symptoms attributable to a drug or organic cause	Secondary mania
Other specified (subthreshold)	Bipolar-like phenomena, e.g. short-duration hypomania	Bipolar spectrum

Clinical features (episode definitions)

- ▶ **Manic episode (Bipolar I):** a distinct period of abnormally **elevated, expansive or irritable mood** *with* persistently increased goal-directed activity/energy, lasting ≥1 week (or any duration if hospitalisation is required), causing **marked functional impairment, hospitalisation, or psychotic features**. DSM-5-TR requires ≥3 (or ≥4 if mood only irritable) of: inflated self-esteem/**grandiosity**; **decreased need for sleep** (rested after 3 h); pressured/over-talkativeness; **flight of ideas/racing thoughts**; distractibility; increased goal-directed activity or **psychomotor**

agitation; and excessive involvement in high-risk pleasurable activities (buying sprees, sexual indiscretions, foolish investments). Severe mania may include **delusions and paranoia indistinguishable from schizophrenia**.

- ▶ **Hypomanic episode (Bipolar II):** same symptom list, lasting ≥ 4 consecutive days, an *unequivocal change in functioning observable by others*, but **NOT severe enough to cause marked impairment or hospitalisation, and no psychotic features** (psychosis automatically makes the episode manic).
- ▶ **Major depressive episode:** depressed mood/anhedonia ≥ 2 weeks with ≥ 5 of 9 symptoms (sleep/appetite/weight change, fatigue, worthlessness/guilt, poor concentration, psychomotor change, suicidal ideation). Depressive phases dominate disability and suicide risk.
- ▶ **Mixed states:** about **one-half** of patients present not with euphoria but with a mixture of **psychomotor agitation/activation plus dysphoria, anxiety and irritability** — difficult to distinguish from agitated depression and carrying high suicide risk.
- ▶ **Rapid cycling:** ≥ 4 mood episodes (mania, hypomania or depression) in one year; occurs in $\sim 15\%$ of patients, mostly women; linked to underlying **thyroid dysfunction** or **iatrogenic antidepressant** exposure.
- ▶ **Course:** untreated episodes last weeks to 8–12 months; $\sim$ half have sustained occupational/psychosocial impairment, depressive phases being more disabling than mania.

Etiology and pathophysiology

- ▶ **Genetic:** strongest of the psychiatric disorders — monozygotic concordance $\sim 80\%$; a first-degree relative raises risk ~ 10 -fold. Replicated risk loci include the L-type **calcium channel α -subunit CACNA1C**, teneurin **ODZ4 (TENM4)**, ankyrin-3 (**ANK3**), neurocan (**NCAN**) and **TRANK1**; common variants individually small but collectively account for $\sim 25\%$ of heritability, with shared loci (pleiotropy) overlapping schizophrenia and autism.
- ▶ **Neurobiology:** evidence for **circadian rhythm dysregulation, calcium dysregulation**, oxidative stress, and mitochondrial/microRNA/endoplasmic-reticulum abnormalities; MRI shows grey-matter thinning in frontal, temporal and parietal cortex.
- ▶ **Precipitants:** stressful life events, sleep deprivation and circadian disruption can trigger episodes; the link to acute stressors weakens as the number of prior episodes increases (kindling). Comorbid **alcohol/substance use** is common.

Differential diagnosis and recognising “hidden” bipolarity

- ▶ **Secondary mania** must be excluded: stimulant/sympathomimetic drugs, **hyperthyroidism**, **AIDS**, **Huntington’s** and **Wilson’s disease**, frontotemporal dementia, and **cerebrovascular accidents**; corticosteroids and antidepressants can also induce mania.
- ▶ Recognising bipolarity in a patient presenting *only* with depression is **essential**, because antidepressants may be contraindicated and can precipitate a **manic switch or accelerate cycling**.

Features predictive of bipolar (vs unipolar) depression (Kaplan/Akiskal): **early age at onset**, psychotic depression before 25 years, postpartum depression (especially with psychotic features), **rapid onset/offset short (<3-month) episodes**, recurrent depression (>5 episodes), marked **psychomotor retardation**, **atypical/reverse vegetative** features (hypersomnia, weight gain), **seasonality**, **bipolar family history**, cyclothymic/hyperthymic temperament, **antidepressant-induced hypomania**, and **repeated loss of antidepressant efficacy** after initial response.

Management

General principles: confirm the diagnosis and stage (acute mania, bipolar depression, or maintenance); ensure safety (suicide/violence risk, hospitalisation for severe mania); withdraw antidepressants/stimulants; treat comorbid thyroid and substance use; **psychoeducation**, **adherence support** and **social-rhythm therapy** are integral.

Acute mania

- ▶ **Lithium carbonate** — mainstay; response **70–80%**, effect in 1–2 weeks. Start 300 mg bid/tid, titrate to a **therapeutic level 0.8–1.2 mEq/L**.
- ▶ **Valproic acid/divalproex** — first-line, *preferred* for **rapid-cycling and mixed/dysphoric mania**; level 50–125 µg/mL.
- ▶ **Carbamazepine** (4–12 µg/mL; 800–1600 mg/day) / **oxcarbazepine** (off-label, safer hepatic profile).
- ▶ **Second-generation antipsychotics** (FDA-approved for acute mania): **aripiprazole**, **asenapine**, **cariprazine**, **olanzapine**, **quetiapine**, **risperidone**, **ziprasidone**; injectable olanzapine/haloperidol for behavioural emergency.
- ▶ **Adjuncts** for agitation/insomnia until mood stabiliser acts: lorazepam 1–2 mg or clonazepam 0.5–1 mg.

Bipolar depression — **quetiapine**, **lurasidone**, **cariprazine**, **lumateperone**, and **olanzapine–fluoxetine** (Symbyax); **lamotrigine** as adjunct/monotherapy. Antidepressant monotherapy is avoided (switch risk).

Maintenance / prophylaxis — required because of the recurrent course. A sustained **lithium level ≥ 0.8 mEq/L** gives optimal prophylaxis and uniquely **reduces suicide risk**. **Quetiapine XR**, **olanzapine**, **risperidone** and **lamotrigine** are approved as maintenance monotherapy (lamotrigine especially prevents depressive relapse but is *not* effective in acute mania). Combinations are often needed; antidepressants are generally avoided in maintenance.

Mood stabiliser	Therapeutic level	Key toxicities / cautions
Lithium	0.8–1.2 mEq/L (acute); 0.6–1.0 maintenance	Fine tremor, polyuria/polydipsia (nephrogenic DI), hypothyroidism/goitre , weight

Mood stabiliser	Therapeutic level	Key toxicities / cautions
		gain, hypercalcaemia, leukocytosis; toxicity >2 mEq/L (ataxia, dysarthria, myoclonus, seizures, coma) → haemodialysis ; levels ↑ by thiazides, NSAIDs, tetracyclines, dehydration
Valproate	50–125 µg/mL	Weight gain, tremor, alopecia; rare hepatotoxicity , pancreatitis ; teratogenic (neural-tube defects)
Carbamazepine	4–12 µg/mL	Sedation, hyponatraemia (SIADH), agranulocytosis, Stevens-Johnson (screen * <i>HLA-B1502*</i> <i>Han Chinese</i> , <i>HLA-A3101</i> N-Europeans); hepatic enzyme inducer
Lamotrigine	(titrate slowly from 25 mg/d)	Stevens-Johnson syndrome/TEN — any rash needs review

Lithium pre-treatment work-up: CBC, T4/TSH, urea/creatinine and electrolytes, urinalysis, and ECG (>45 y or cardiac history); draw levels **12 h post-dose**; monitor thyroid and renal function 4–6 monthly. **Electroconvulsive therapy** is effective for severe, refractory, psychotic, catatonic or pregnant cases.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Mood-vs-time (life-chart) graph:** horizontal euthymia baseline; plot peaks above for **Mania (Bipolar I)** and smaller peaks for **Hypomania (Bipolar II)**; troughs below for **Major depression**; small ripples for **Cyclothymia**; mark a **mixed episode** and a **rapid-cycling** segment (≥4 episodes/year). Labels: *Mania*, *Hypomania*, *Euthymia*, *Major depressive episode*, *Mixed state*, *Rapid cycling*, ≥1 week (*mania*), ≥4 days (*hypomania*), ≥2 weeks (*depression*).
- **Treatment-stage box diagram:** three boxes — *Acute mania* (Lithium / Valproate / SGA + benzodiazepine), *Bipolar depression* (Quetiapine / Lurasidone / Lamotrigine / Olanzapine-fluoxetine), *Maintenance* (Lithium ≥0.8 mEq/L — reduces suicide; avoid antidepressants).

Clinical / Diagnostic significance

- **Suicide:** risk is **state-dependent** — highest during severe depressive and **mixed/dysphoric** episodes, very low in euphoric mania; **lithium** is the only mood stabiliser proven to reduce suicide.
- **Misdiagnosis as unipolar depression** delays appropriate treatment and risks antidepressant-induced switching/cycle acceleration — always screen a depressed patient for *past hypomania*.

- ▶ **Organic screen** in new-onset mania: TFTs, drug/toxicology screen, neuroimaging, and consider Wilson's/Huntington's/HIV when atypical or late-onset.
- ▶ **Lithium monitoring is mandatory** — narrow therapeutic index; counsel on hydration, NSAID/diuretic interactions, thyroid and renal surveillance; choose **valproate/lamotrigine alternatives** (with contraception advice) in women of child-bearing potential because of teratogenicity.
- ▶ High **medical comorbidity** (cardiovascular disease, diabetes, substance use) elevates mortality independent of suicide.

High-yield exam pointers

- ▶ **Bipolar I** = ≥ 1 manic episode (≥ 1 week); **Bipolar II** = **hypomania** (≥ 4 days) + **major depression**, never mania.
- ▶ **Mania needs ≥ 3 symptoms** (≥ 4 if irritable) — mnemonic **DIGFAST** (Distractibility, Indiscretion, Grandiosity, Flight of ideas, Activity $\uparrow$, Sleep $\downarrow$, Talkativeness).
- ▶ **Hypomania**: no marked impairment, no psychosis, no hospitalisation; psychosis $\Rightarrow$ episode is *manic* by definition.
- ▶ **Rapid cycling** = ≥ 4 episodes/year ($\sim 15\%$, mostly women) — favour **valproate**; check thyroid; stop antidepressants.
- ▶ **Monozygotic concordance** $\sim 80\%$; risk genes **CACNA1C, ANK3, ODZ4, NCAN, TRANK1**; first-degree relative $\uparrow$ risk $\sim 10\times$.
- ▶ **Lithium** acute level **0.8–1.2 mEq/L** (response 70–80%); toxicity >2 mEq/L $\rightarrow$ haemodialysis; thiazides/NSAIDs raise levels; causes hypothyroidism and nephrogenic DI.
- ▶ **Lamotrigine** prevents depressive relapse but is **ineffective in acute mania** and risks **Stevens-Johnson syndrome**.
- ▶ **Avoid antidepressant monotherapy** — manic switch and cycle acceleration.
- ▶ **Cyclothymia** = ≥ 2 years subthreshold hypomanic + depressive symptoms; 15–50% progress to Bipolar I/II.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Psychiatric Disorders" (Mood Disorders: Bipolar Disorder; Table 463-8 Criteria for Bipolar I Disorder; Table 463-9 Clinical Pharmacology of Mood Stabilizers).
- ▶ **Kaplan & Sadock's Comprehensive Textbook of Psychiatry (2024)** — Mood Disorders: epidemiology/correlates and "Features of a Depressive Episode Predictive of Bipolar Disorder" (Akiskal); Pharmacologic Treatment of Bipolar Disorders.
- ▶ **DSM-5-TR** — Bipolar and Related Disorders (Bipolar I, Bipolar II, Cyclothymic Disorder criteria).

- **CMDT 2026** — “Psychiatric Disorders”: Treatment of Bipolar Disorder — lithium, valproate, carbamazepine, lamotrigine and antipsychotic regimens, dosing and monitoring.



Clinical features, diagnosis and management of delirium tremens

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — *Delirium tremens* (DTs) is the most severe and life-threatening expression of the **alcohol withdrawal syndrome**, defined as a **severe, agitated delirium** (mental confusion, fluctuating consciousness and disorientation) accompanied by a coarse tremor and marked **autonomic hyperactivity** (tachycardia, hypertension, hyperthermia, diaphoresis), occurring when blood alcohol falls abruptly in a chronic heavy drinker. It complicates roughly **1% of individuals in withdrawal** (Harrison; <5% in Kaplan; <10% develop “dramatic” withdrawal in DSM-5-TR), typically appears **48–72 h after the last drink**, and is a **medical emergency** with an untreated mortality up to ~5%. By DSM-5-TR it requires the patient to satisfy criteria for **both delirium AND alcohol withdrawal** (alcohol withdrawal delirium, F10.231).

Pathophysiology (brief, to anchor the answer)

- Chronic ethanol is a CNS depressant that **enhances inhibitory GABA-A** tone and **suppresses excitatory NMDA-glutamate** transmission. The brain adapts by **down-regulating GABA-A** and **up-regulating NMDA** receptors.
- Abrupt cessation removes the depressant → unopposed **glutamatergic/adrenergic hyperexcitability** → tremor, seizures, autonomic storm and, at its extreme, delirium.
- Additional drivers: **low thiamine**, hypomagnesaemia, hypokalaemia, dehydration and intercurrent illness, all of which lower the threshold for DTs.

Spectrum and time-course of alcohol withdrawal

Withdrawal is a continuum; DTs sits at the severe end. Knowing the **temporal sequence** is high-yield and is best shown as a timeline.

Syndrome	Typical onset after last drink	Key features
Minor (early) withdrawal / tremulousness	6–12 h (Harrison 5–10 h; CMDT 6–36 h)	Tremor (“shakes”), anxiety, insomnia, nausea/vomiting, tachycardia, sweating; intact sensorium

Syndrome	Typical onset after last drink	Key features
Withdrawal seizures (“rum fits”)	8–48 h, peak ~day 2	Generalised tonic-clonic, brief, usually self-limiting; ~1–3% of patients
Alcoholic hallucinosis	12–48 h	Visual/tactile (± auditory) hallucinations with a clear sensorium and intact orientation — distinguishes it from DTs
Delirium tremens	48–72 h (may appear up to 7–10 days later)	Agitated, fluctuating delirium + autonomic storm; lasts 3–5 days

- ▶ Minor symptoms peak on day 2–3 and improve by day 4–5; a **protracted** abstinence syndrome (anxiety, insomnia, autonomic lability) may linger **3–6 months**.
- ▶ DTs develops in ~50% of patients who have had a withdrawal seizure, but **can occur without a preceding seizure**.

Clinical features of delirium tremens

- ▶ **Delirium (core)**: acute onset over hours-to-days, **fluctuating** course, **inattention**, disorientation to time/place/person, impaired short-term memory, disorganised thinking; typically **hyperactive** form with agitation, but can fluctuate.
- ▶ **Perceptual disturbance**: vivid, frightening **visual hallucinations** (classically crawling insects/snakes — *Lilliputian/zoopsia*), tactile (*formication*), less often auditory; **sensory hyperacuity**.
- ▶ **Coarse tremor** of hands and whole body, psychomotor agitation, picking/restlessness.
- ▶ **Autonomic hyperactivity (hallmark)**: marked **tachycardia**, **hypertension**, **fever**, **profuse diaphoresis**, mydriasis, tachypnoea.
- ▶ **Metabolic/complications**: dehydration, **hypokalaemia**, **hypomagnesaemia**, hypophosphataemia, cardiac **arrhythmias**, rhabdomyolysis, aspiration, seizures and, if untreated, **cardiovascular collapse and death**.
- ▶ Often **unmasked in a hospitalised patient** admitted for an unrelated problem (trauma, surgery, sepsis) on day 2–3 — DTs should be suspected in **any heavy drinker with unexplained delirium**.

Diagnosis

DTs is essentially a **clinical diagnosis** in a chronic drinker with the typical temporal profile; the key task is to **confirm withdrawal AND exclude mimics**.

- ▶ **DSM-5-TR alcohol withdrawal criteria**: (A) cessation/reduction of heavy, prolonged alcohol use; (B) **≥2 of** — autonomic hyperactivity (sweating/pulse >100), increased hand tremor, insomnia, nausea/vomiting, **transient visual/tactile/auditory hallucinations or illusions**,

psychomotor agitation, anxiety, **generalised tonic-clonic seizures**; (C) clinically significant distress/impairment; (D) not due to another condition. *Specifier*: “**with perceptual disturbances**” when hallucinations/illusions occur with intact reality testing.

- ▶ **DSM-5-TR delirium criteria (must also be met for DTs)**: (A) disturbance of **attention and awareness**; (B) develops over hours-days, **fluctuates**; (C) additional cognitive disturbance (memory, orientation, perception); (D) not explained by another neurocognitive disorder/coma; (E) caused by a medical condition or **substance withdrawal**.
- ▶ **Severity scoring — CIWA-Ar** (Clinical Institute Withdrawal Assessment for Alcohol, revised): 10 items — nausea/vomiting, tremor, paroxysmal sweats, anxiety, agitation, tactile, auditory and visual disturbances, headache, and **orientation/clouding of sensorium**; **maximum 67**. Score <8 = minimal; 8–15 mild; 16–20 moderate; >20 severe / impending DTs. Drives **symptom-triggered** dosing.
- ▶ **Risk stratification — PAWSS** (Prediction of Alcohol Withdrawal Severity Scale): score ≥4 predicts complicated withdrawal and the need for inpatient prophylaxis.
- ▶ **Investigations**: CBC, **electrolytes incl. K^+ , Mg^{2+} , Ca^{2+} , phosphate**, glucose (bedside), renal and **liver biochemistry**, amylase/lipase, blood alcohol level, **urine toxicology** (co-ingestants), ECG; **CT head** if focal signs, head trauma, atypical/late or first seizure, or failure to improve — to exclude **subdural haematoma**.
- ▶ **Differential diagnosis**: sedative-hypnotic/benzodiazepine withdrawal, **Wernicke encephalopathy**, hepatic encephalopathy, sepsis/meningoencephalitis, hypoglycaemia, electrolyte derangement, hypoxia, drug intoxication (anticholinergic, stimulant, serotonin syndrome), thyroid storm, non-convulsive status, and **subdural haematoma**. *Alcoholic hallucinosis* (clear sensorium) and *withdrawal seizures* are part of the same spectrum but are distinct entities.

Management

DTs is an emergency best managed in an ICU/high-dependency setting with close monitoring; it tends to run a **3–5 day** course regardless of therapy, so the aim is to **control agitation/autonomic drive, prevent injury and treat reversible contributors**.

- ▶ **General/supportive**: ICU admission, continuous cardiac and **pulse-oximetry** monitoring, quiet well-lit room, reorientation, fall/aspiration precautions, treat the **precipitating illness** (infection, GI bleed, pancreatitis, trauma).
- ▶ **Fluids & electrolytes**: correct dehydration; **replace Mg^{2+} , K^+ , phosphate**; treat hypoglycaemia. (In uncomplicated withdrawal patients are often normo/over-hydrated — give IV fluids only when indicated.)
- ▶ **Thiamine FIRST**: **thiamine 100 mg IV** (high-dose, e.g. 500 mg IV TDS if Wernicke suspected) **before any glucose** to prevent precipitating **Wernicke encephalopathy/Korsakoff**; add

multivitamins and folate. *Caine criteria* (≥ 2 of: dietary deficiency, oculomotor abnormality, cerebellar signs, altered mentation) prompt empirical Wernicke treatment.

- ▶ **Benzodiazepines — mainstay** (only proven agents to prevent/treat DTs; they reduce mortality, seizures and agitation):
 - **Long-acting, self-tapering** agents preferred — **diazepam** or **chlordiazepoxide** (smoother course, fewer breakthrough seizures).
 - **Lorazepam** or **oxazepam** preferred in **significant liver disease/cirrhosis or the elderly** (shorter half-life, no active metabolites, glucuronidated → safer).
 - **Symptom-triggered (CIWA-Ar-guided)** dosing reduces total dose and duration vs fixed-dose; established DTs usually needs aggressive **fixed** + PRN loading.
 - In severe withdrawal/DTs: e.g. **IV lorazepam 1–2 mg every 15 min** titrated until calm-but-rousable; **high doses** are often required (Harrison cites up to **~800 mg/day chlordiazepoxide**; CMDT caps chlordiazepoxide at 600 mg/24 h). Once stable 24 h, taper dose **~20%/day**.
 - **Hold** benzodiazepine if over-sedated or **respiratory rate $< 10/\text{min}$** ; do not bolus lorazepam **> 4 mg IV**; use a **single agent**, titrated.
- ▶ **Refractory DTs (benzodiazepine-resistant)**:
 - Add **phenobarbital** (synergistic at GABA-A) or escalate to **propofol** (usually requires intubation/ventilation for airway protection).
 - **Dexmedetomidine** (α_2 -agonist, 0.2–0.7 $\mu\text{g/kg/h}$) as an **adjunct** to blunt hyperadrenergic output — *not* monotherapy (does not prevent seizures or delirium).
- ▶ **Antipsychotics: not first-line**; benzodiazepines are preferred because **antipsychotics lower the seizure threshold**. Low-dose **haloperidol** may be added **only** as an adjunct for severe agitation/hallucinations not controlled by adequate benzodiazepines.
- ▶ **Withdrawal seizures**: treated with **adequate benzodiazepines**; **phenytoin is ineffective** and routine anticonvulsants are unnecessary unless there is an independent seizure disorder; manage status epilepticus aggressively.
- ▶ **After the acute phase**: screen and treat AUD — **brief intervention/motivational interviewing (FRAMES)**, relapse-prevention CBT, **AA/12-step**, and anti-craving pharmacotherapy (**naltrexone**, **acamprosate**, or supervised **disulfiram**) once withdrawal is complete.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Timeline of alcohol withdrawal** (x-axis = hours/days since last drink; y-axis = severity), labelling each band: *Minor withdrawal/tremulousness 6–12 h*, *Withdrawal seizures 8–48 h (peak 24 h)*, *Alcoholic hallucinosis 12–48 h (clear sensorium)*, *Delirium tremens 48–72 h*, up to 7–10 days.

- ▶ CIWA-Ar “clock” / bar of the 10 domains, labelled: *Nausea/vomiting, Tremor, Paroxysmal sweats, Anxiety, Agitation, Tactile, Auditory, Visual disturbances, Headache, Orientation/clouding of sensorium* — with cut-offs <8 minimal · 8–15 mild · 16–20 moderate · >20 severe (ICU); **max score 67**.

Clinical / Diagnostic significance

- ▶ DTs is a **preventable** cause of death — early identification of at-risk drinkers (PAWSS ≥ 4 , prior DTs/seizures, high intake, intercurrent illness) and **adequate benzodiazepine prophylaxis** sharply reduces progression.
- ▶ **Suspect DTs in any chronic drinker with unexplained delirium**, especially on day 2–3 of an **unrelated admission**; missing it (mistaking it for “ICU agitation”) is a classic exam trap.
- ▶ Always **exclude structural and metabolic mimics** — subdural haematoma, hepatic encephalopathy, Wernicke, sepsis, hypoglycaemia — as several can **coexist** with withdrawal.
- ▶ **Thiamine before glucose and magnesium/potassium correction** are simple, high-impact, often-forgotten steps.

High-yield exam pointers

- ▶ DTs = most severe alcohol withdrawal; ~1% of **withdrawals**, onset **48–72 h** (up to 7–10 days), course **3–5 days**, mortality **up to ~5%**.
- ▶ Triad to write: **agitated fluctuating delirium + coarse tremor + autonomic storm**, with vivid **visual hallucinations** (insects/snakes).
- ▶ **Alcoholic hallucinosis** = **clear sensorium**; DTs = **clouded/fluctuating** sensorium — the key distinguishing point.
- ▶ DSM-5-TR: alcohol withdrawal needs ≥ 2 **features within hours–days**; DTs requires **delirium criteria + withdrawal criteria** together.
- ▶ CIWA-Ar (10 items, **max 67**, treat at ≥ 8 –10) guides symptom-triggered therapy; **PAWSS ≥ 4** flags complicated withdrawal.
- ▶ **Benzodiazepines** are **first-line and the only proven prophylaxis**; long-acting (diazepam/chlordiazepoxide) preferred, **lorazepam/oxazepam in liver disease**.
- ▶ Refractory DTs $\rightarrow$ **phenobarbital / propofol (intubate) / dexmedetomidine adjunct**; **antipsychotics lower seizure threshold** and are adjuncts only.
- ▶ **Thiamine before glucose**; correct $\text{Mg}^{2+}/\text{K}^{+}$; **phenytoin does not work** for withdrawal seizures.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Alcohol and Alcohol Use Disorders” (withdrawal time-course, DTs ~1% rate and ~5% mortality, benzodiazepine dosing incl.

chlordiazepoxide/diazepam, high-dose/propofol/dexmedetomidine for DTs, cautions on antipsychotics and phenytoin); “Delirium” (clinical/diagnostic framing).

- ▶ **Kaplan & Sadock’s Comprehensive Psychiatry (2024)** — alcohol withdrawal, alcohol withdrawal delirium, DSM-5 withdrawal criteria (Table 11.2-6), detoxification and severe-withdrawal/DTs management.
- ▶ **DSM-5-TR** — diagnostic criteria for **Alcohol Withdrawal** (with perceptual-disturbances specifier) and **Delirium**; alcohol withdrawal delirium (F10.231).
- ▶ **CMDT 2026** — “Substance Use Disorders” (categories/time-course table, CIWA-Ar, PAWSS, symptom-triggered vs fixed dosing, agent choice in liver disease, dexmedetomidine/phenobarbital/propofol, Caine criteria, thiamine-before-glucose).



Depression

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Depression is a **mood (affective) disorder** characterised by a sustained disturbance in the regulation of mood, behaviour and affect. A **major depressive episode** is defined as depressed mood and/or loss of interest occurring on a daily basis for a minimum of **2 weeks**, accompanied by neurovegetative and cognitive symptoms causing clinically significant distress or functional impairment. **Major depressive disorder (MDD)** is distinguished from bipolar disorder by the *absence of any manic or hypomanic episode*. In the WHO Global Burden of Disease Study (2019), depression was the **single largest contributor to disability worldwide**, with disability-adjusted life-years (DALYs) having risen 61% since 1990.

Classification of Depressive Disorders (DSM-5-TR)

- ▶ **Major depressive disorder (MDD)** — single or recurrent major depressive episode(s); the core unipolar syndrome.
- ▶ **Persistent depressive disorder (dysthymia)** — chronic (≥ 2 years), low-grade depressive symptoms; less severe but functionally equally disabling; ~2% population prevalence. A superimposed major depressive episode produces “*double depression*”.
- ▶ **Disruptive mood dysregulation disorder** — chronic irritability and temper outbursts in children (onset before age 10).
- ▶ **Premenstrual dysphoric disorder (PMDD)** — affective and somatic symptoms in the late luteal phase.
- ▶ **Substance/medication-induced depressive disorder and depressive disorder due to another medical condition.**

- *Mood disorders broadly* = (1) depressive (unipolar) disorders, (2) bipolar disorders, and (3) depression secondary to medical illness or substance use.

Aetiology and Pathophysiology

- **Genetic** — monozygotic-twin concordance (**46%**) far exceeds dizygotic (**20%**), with little effect of shared family environment. Early-onset depression (before age 25) is *largely genetic*. Large GWAS have identified several hundred risk loci, some overlapping with other psychiatric disorders (pleiotropy); epigenetic change also contributes.
- **Monoamine hypothesis** — the original observation that TCAs **inhibit serotonin/noradrenaline reuptake** and MAOIs are effective antidepressants led to the view that depression reflects a *deficiency of monoamines* (serotonin, noradrenaline, dopamine). This is an over-simplification — therapeutic effects emerge over weeks despite reuptake inhibition within hours, implicating **adaptive changes in second-messenger systems, neurotrophic and transcription factors**.
- **Neuroendocrine (HPA axis)** — increased **cortisol** and **CRH** secretion; **dexamethasone non-suppression**; a **blunted TSH response to TRH**. These normalise with successful treatment.
- **Neurobiological** — altered pro-inflammatory cytokines (raised **IL-6**, **TNF- α**) and neurotrophins, increased oxidative stress, cellular ageing, **telomere shortening**, mitochondrial dysfunction and gut-microbiome change. A subset shows a small reduction in **hippocampal** volume. The limbic circuitry of mood spans the **prefrontal cortex**, **amygdala**, **hippocampus**, **nucleus accumbens** and **hypothalamus**, modulated by monoaminergic projections (noradrenaline from locus coeruleus, serotonin from dorsal raphe, dopamine from VTA).
- **Sleep architecture** — reduced **REM latency**, increased **REM density**, and decreased **stage IV (delta) slow-wave sleep**.
- **Psychosocial** — negative life events (death of a relative, assault, severe relationship problems) precipitate episodes; genes influence sensitivity to these stressors.

Clinical Features and DSM-5-TR Criteria

- **Core**: persistent depressed mood (sad, empty, hopeless) and/or **anhedonia** (loss of interest/pleasure in nearly all activities).
- Diagnosis requires **≥5 of 9 symptoms** over the same 2-week period, at least one being depressed mood OR loss of interest/pleasure — usefully recalled by the mnemonic ***SIG-E-CAPS***:

Letter	Symptom (DSM-5-TR Criterion A)
S — Sleep	Insomnia or hypersomnia nearly every day
I — Interest	Markedly diminished interest/pleasure (anhedonia)
G — Guilt	Feelings of worthlessness or excessive/inappropriate guilt
E — Energy	Fatigue or loss of energy

Letter	Symptom (DSM-5-TR Criterion A)
C — Concentration	Diminished ability to think/concentrate; indecisiveness
A — Appetite	Significant weight/appetite change (>5% body weight/month)
P — Psychomotor	Agitation or retardation (observable by others)
S — Suicidality	Recurrent thoughts of death, suicidal ideation, plan or attempt
(+ depressed mood)	Depressed mood most of the day, nearly every day

- ▶ Criteria B–C: symptoms cause **significant distress/impairment** and are **not attributable to a substance or medical condition**; there has **never been a manic/hypomanic episode** (else bipolar).
- ▶ *Melancholic* features: profound anhedonia, mood worse in the morning (diurnal variation), early-morning awakening, marked guilt, psychomotor change.
- ▶ **Course**: ~15% of the population has a major depressive episode in their lifetime; 6–8% of primary-care outpatients qualify. Onset is usually in early adulthood; **50–60% of first-episode patients have at least one or two recurrences** — the *best predictor of future risk is the number of past episodes*. Depression is **twice as common in women** as in men.
- ▶ **Important variants**: *psychotic depression* (mood-congruent delusions/hallucinations), *pseudodementia* (cognitive deficits mimicking dementia in the elderly), and **seasonal affective disorder** (anergy, fatigue, weight gain, hypersomnia, carbohydrate craving; commoner in women; prevalence rises with distance from the equator; responds to light therapy).

Specifiers (DSM-5-TR)

- ▶ With **anxious distress**, with **mixed features**, with **melancholic features**, with **atypical features**, with **mood-congruent / mood-incongruent psychotic features**, with **catatonia**, with **peripartum onset**, with **seasonal pattern**.

Differential Diagnosis

- ▶ **Bipolar depression** — always screen for past mania/hypomania; antidepressant monotherapy can trigger a switch or cycle acceleration. Red flags for bipolarity: childhood onset, antidepressant treatment failure, atypical features (hypersomnia, weight gain), marked irritability/impulsivity.
- ▶ **Grief/bereavement** — predominant affect is *emptiness and loss* occurring in waves (“pangs”), self-esteem preserved; contrast with the persistent low mood, worthlessness and self-loathing of an MDE.

- ▶ **Secondary depression (10–15%)** — hypothyroidism, Cushing's, stroke (especially left dorsolateral frontal), Parkinson's disease, dementia, multiple sclerosis, malignancy (pancreatic, oropharyngeal), HIV, hepatitis C; and **drug-induced** (antihypertensives, glucocorticoids, interferon- α , anticonvulsants).
- ▶ **Persistent depressive disorder**, adjustment disorder with depressed mood, substance-induced mood disorder.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **HPA-axis dysregulation in depression** — vertical cascade: *Hypothalamus* $\rightarrow$ *CRH* $\rightarrow$ *Anterior pituitary* $\rightarrow$ *ACTH* $\rightarrow$ *Adrenal cortex* $\rightarrow$ *Cortisol* ($\uparrow$); show **loss of negative feedback** with a dashed line and label “**Dexamethasone non-suppression**” and “**blunted TSH response to TRH.**”
- ▶ **Limbic neural circuitry of mood** — label **Prefrontal cortex (PFC)**, **Amygdala (Amy)**, **Hippocampus (HP)**, **Nucleus accumbens (NAc)**, **Hypothalamus (Hyp)**, with monoaminergic inputs: **Locus coeruleus (noradrenaline)**, **Dorsal raphe (serotonin)** and **MTA (dopamine)**.

Clinical / Diagnostic significance

- ▶ **Screening:** validated tools (e.g., PHQ-9); always **directly assess suicide risk** — risk factors include prior attempts, profound hopelessness, concurrent medical illness, substance abuse, social isolation, and co-existing anxiety/panic/agitation. **~4–5% of depressed patients die by suicide**, and most have consulted a physician within 1 month of death.
- ▶ **Investigations** to exclude secondary causes: TSH/free T4, electrolytes/calcium, blood glucose, renal/hepatic function, B12, and toxicology where indicated; imaging if focal neurology or atypical late-onset presentation.
- ▶ **Comorbidity matters:** depression worsens prognosis in **post-MI/cardiac disease** (reduced heart-rate variability, increased mortality) and in diabetes (mood severity tracks hyperglycaemia). **TCAs are contraindicated** in bundle-branch block and significant cardiovascular disease; **SSRIs are preferred** as they cause no significant ECG change.
- ▶ **General management principles:** combine *acute* (induce remission) with *maintenance* (prevent recurrence); 60–70% respond to any adequately dosed drug given for **6–8 weeks**; review response at ~2 months; continue for **6–9 months** after remission; **indefinite maintenance** after ≥ 2 episodes. Psycho-education, stress reduction and avoiding alcohol are essential.
- ▶ ***Pharmacotherapy (CMDT/STAR\D approach)**:**
 - **First-line:** SSRIs (e.g., sertraline 25 $\rightarrow$ 200 mg, escitalopram 10–20 mg) — fewer anticholinergic/cardiac effects; adverse effects: GI upset, insomnia, sexual dysfunction,

akathisia and **serotonin syndrome** (myoclonus, agitation, hyperpyrexia, hypertension).

Escitalopram is most P450-neutral.

- **SNRIs** (venlafaxine 75–375 mg, duloxetine 40–60 mg) — useful with comorbid neuropathic pain; monitor BP.
- **TCAs** — therapeutic dose ~150–200 mg imipramine/amitriptyline (level 150–300 ng/mL); **lethal in overdose** (~2 g), desipramine carrying the greatest risk — prescribe limited supplies when suicide is a risk.
- **MAOIs** — effective in **atypical depression** but risk **hypertensive (tyramine) crisis**; transdermal selegiline at 6 mg needs no dietary restriction. Never combine with SSRIs (serotonin syndrome).
- **Mirtazapine** ($\alpha 2/5$ -HT_{2/5}-HT₃ blocker; sedation, weight gain) and **bupropion** (noradrenergic-dopaminergic; few sexual effects, lowers seizure threshold).
- **Treatment-resistant strategies** (STAR\D): *switch vs augment with lithium, liothyronine (thyroid), l-methylfolate, atypical antipsychotics (aripiprazole, quetiapine-XR, brexpiprazole) or olanzapine-fluoxetine (Symbyax)*.*
- ▶ **Non-pharmacological / device therapy**: ECT is the most effective treatment, reserved for treatment-resistant, psychotic and delusional depression (remission 60–90% in psychotic depression); rTMS and VNS are approved for treatment-resistant depression. **Intranasal esketamine / IV ketamine** give rapid (often single-dose) benefit and reduce suicidality. **Brexanolone** (IV) and oral **zuranolone** are neuroactive-steroid options for **postpartum depression**.
- ▶ **Psychotherapy**: **cognitive-behavioural therapy (CBT)** and **interpersonal therapy (IPT)** are evidence-based; combined drug + psychotherapy outperforms medication alone.

High-yield exam pointers

- ▶ MDE = depressed mood/anhedonia ≥ 2 weeks + $\geq 5/9$ SIG-E-CAPS symptoms; **no manic/hypomanic episode** ever (else bipolar).
- ▶ Lifetime prevalence ~15%; **twice as common in women**; MZ:DZ concordance 46%:20%.
- ▶ Biology: $\uparrow$ cortisol/CRH, **dexamethasone non-suppression**, **blunted TSH-to-TRH**, $\downarrow$ REM latency, $\uparrow$ REM density.
- ▶ Always assess **suicide risk**; ~4–5% **die by suicide**; the best predictor of recurrence is the **number of past episodes**.
- ▶ **SSRIs first-line**; TCAs lethal in overdose; **MAOIs best in atypical depression** (tyramine crisis); SSRI + MAOI $\rightarrow$ serotonin syndrome.
- ▶ ECT = most effective and treatment of choice for **psychotic/delusional and treatment-resistant depression**.
- ▶ Continue antidepressant **6–9 months** post-remission; **indefinite maintenance after ≥ 2 episodes**.

- ▶ **Postpartum depression** → brexanolone / zuranolone; **seasonal affective disorder** → light therapy; **persistent depressive disorder** = dysthymia (≥ 2 years).
- ▶ Distinguish **grief** (emptiness, in waves, self-esteem preserved) from MDE (persistent worthlessness, self-loathing).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Psychiatric Disorders*” (mood/depressive disorders, DSM-5-TR major depressive episode criteria, antidepressant tables, treatment algorithm) and “*Biology of Psychiatric Disorders*” (monoamine hypothesis, HPA axis, neural circuitry of depression).
- ▶ **DSM-5-TR** — classification and specifiers of depressive disorders; major depressive episode criteria.
- ▶ **Kaplan & Sadock's Comprehensive Textbook of Psychiatry (2024)** — depressive disorders classification and epidemiology.
- ▶ **CMDT 2026** — “*Psychiatric Disorders*” (current pharmacotherapy, STAR[®]D augmentation, ECT in psychotic depression, antidepressant dosing).



Neuro-regulatory Systems Implicated in Major Depressive Disorder (MDD) and the Differential Diagnoses to be Excluded Before Diagnosing MDD

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — **Major depressive disorder (MDD)** is a primary mood disorder defined by ≥ 5 of 9 DSM-5-TR symptoms (at least one being *depressed mood* or *anhedonia*) present nearly every day for ≥ 2 weeks, causing significant distress/impairment, in the absence of any manic/hypomanic episode and not attributable to a substance, medical illness or psychotic disorder. It is among the largest single contributors to global disability (DALYs). No single lesion or biomarker explains MDD; rather it arises from disturbance of several interacting **neuro-regulatory systems** — monoaminergic, neuroendocrine (HPA, thyroid), glutamate/GABA, neurotrophic, neuro-immune and large-scale limbic circuits. Because depressive syndromes are produced by many drugs and medical diseases, a careful **exclusionary differential diagnosis** is mandatory before the label “MDD” is applied.

Overview of neuro-regulatory systems implicated in MDD

System	Key dysregulation in MDD	Clinical / therapeutic correlate
Monoaminergic (NE, 5-HT, DA)	Altered “fine-tuning” of networks; ↓ or dissociated NE	TCAs, SSRIs, SNRIs, MAOIs, bupropion

System	Key dysregulation in MDD	Clinical / therapeutic correlate
	(MHPG), 5-HT (5-HIAA), DA (HVA) signalling	
HPA axis / stress	↑ CRH → ↑ ACTH → hypercortisolaemia; impaired glucocorticoid feedback (dexamethasone non-suppression)	DST positivity; melancholia; relapse marker
Thyroid / other endocrine	Blunted TSH response to TRH; ↑ basal TSH; ↓ GH response to clonidine	Hypothyroidism mimic; T3 augmentation
Glutamate / GABA / neurosteroid	Extrasynaptic NMDA excitotoxicity; ↓ cortical GABA & SST interneurons; ↓ allopregnanolone	Ketamine/esketamine; brexanolone/zuranolone
Neurotrophic / neuroplasticity	↓ BDNF, ↓ GDNF, ↓ hippocampal neurogenesis, hippocampal volume loss	Delayed (weeks) antidepressant action
Neuro-immune / inflammation	↑ IL-6, TNF-α, CRP; NF-κB/NLRP3; microglial activation; kynurenine/QUIN	Inflammatory subtype; cytokine antagonists
Limbic circuits / networks	Hyperactive amygdala & subgenual Cg25; hypoactive NAc; DMN hyperconnectivity	DBS of Cg25/NAc; rTMS of dlPFC
Sleep / circadian	↓ REM latency, ↑ REM density, ↓ slow-wave (stage IV) sleep	Trait marker; predicts relapse
Genetic / epigenetic	Polygenic; MZ:DZ concordance 46%:20%; DNA-methylation/histone changes	Early-onset = higher heritability

Monoaminergic and neuroendocrine systems

- **Monoamine hypothesis (historical basis):** the depressogenic effect of *reserpine* (a monoamine depleter) and the antidepressant action of agents that raise synaptic monoamines (TCAs inhibit NE/5-HT reuptake; MAOIs inhibit their breakdown) led to the view that depression is a *deficiency of monoamines*. This is now regarded as an oversimplification — antidepressants raise synaptic monoamines within hours yet take **weeks** to act, implicating downstream adaptive changes in second messengers, transcription factors and neurotrophins.
- **Noradrenergic:** cell bodies in the **locus coeruleus (LC)** project diffusely; mediate arousal and the medial-forebrain-bundle reward pathway. NE metabolite = **3-methoxy-4-hydroxyphenylglycol**

(MHPG). There is a subgroup with low MHPG and an overlapping subgroup with elevated/hyper-aroused NE.

- ▶ **Serotonergic:** dorsal/median raphe project widely; regulate mood, sleep, appetite, libido, aggression and circadian rhythm; metabolite = **5-hydroxyindoleacetic acid (5-HIAA)**, low CSF levels linked to impulsivity/aggression. SSRIs “normalise” amygdala over-reactivity.
- ▶ **Dopaminergic:** VTA → **mesolimbic/mesocortical** pathways subserve reward, motivation and hedonic capacity; metabolite = **homovanillic acid (HVA)**; reduced CSF HVA correlates with severe psychomotor-retarded (“hypodopaminergic”) depression and anhedonia.
- ▶ **Modern reformulation:** monoamines are now seen as broad **neuromodulators** that “tune” the activity and coupling of large-scale networks; their disturbances may be secondary/compensatory rather than the primary cause.
- ▶ **Other neuroendocrine axes:** *Thyroid* — blunted TSH response to TRH (20–30%) and occult hypothyroidism (≈5–10%); *Growth hormone* — blunted GH response to the α2-agonist **clonidine**; *Prolactin* — blunted response to 5-HT agonists.

Stress–HPA axis, neurotrophic, glutamate/GABA and neuro-immune systems

- ▶ **HPA axis (the clearest stress–depression link):** stress activates hypothalamic CRH → **pituitary ACTH** → **adrenal cortisol**. A subset of patients show **hypercortisolaemia** with loss of glucocorticoid feedback, demonstrated by the **dexamethasone suppression test (DST)** — failure of 0.5–2 mg dexamethasone to suppress cortisol (non-suppression) or early “escape”. HPA overactivity is seen in ~20–40% of outpatients and ~40–60% of inpatients (especially melancholic/psychotic/older patients), correlates with melancholia, and persistent non-suppression after treatment predicts relapse. Excess glucocorticoids are implicated in **hippocampal atrophy/volume loss**.
- ▶ **Neurotrophic/neuroplasticity hypothesis:** chronic stress and glucocorticoids reduce **brain-derived neurotrophic factor (BDNF)** and suppress hippocampal **neurogenesis**; antidepressants (and ECT, rTMS, exercise) raise BDNF and reverse this — accounting for their delayed onset. GDNF is also reduced.
- ▶ **Glutamate / GABA / neurosteroid:** activation of **synaptic NMDA receptors (GluN2A, neuroprotective)** promotes BDNF, whereas **extrasynaptic NMDA (GluN2B)** activation causes excitotoxicity and suppresses BDNF. Sub-anaesthetic **ketamine / intranasal esketamine** (NMDA antagonists, AMPA-mediated, mTOR-dependent) produce *rapid* (hours) antidepressant effects in treatment-resistant depression. **GABA** is reduced (plasma/CSF/cortex), with loss of **somatostatin-expressing (SST) interneurons**; the neurosteroid **allopregnanolone** (a positive allosteric modulator of GABA-A) is low, the rationale for **brexanolone** and **zuranolone** in peripartum depression.

- ▶ **Neuro-inflammation/immune:** a subgroup shows raised IL-6, TNF- α and CRP (CRP >3 mg/L in ~30–45%), driven by NF- κ B and the NLRP3 inflammasome, with **microglial activation**. Cytokines induce **indoleamine-2,3-dioxygenase (IDO)**, shunting tryptophan from serotonin toward neurotoxic **kynurenine/quinolinic acid (QUIN)** (an NMDA agonist). Inflammation preferentially produces **anhedonia, psychomotor slowing and suicidality** via the basal ganglia; therapeutic IFN- α reliably induces MDD in 30–50% of recipients.

Neural circuits, sleep and genetic systems

- ▶ **Limbic mood circuit:** dysfunction of the **prefrontal cortex (PFC)**, **anterior cingulate**, **hippocampus and amygdala**, with monoaminergic input from VTA (DA), LC (NE) and raphe (5-HT). Imaging shows **amygdala hyper-reactivity** to negative stimuli, **reduced nucleus accumbens (NAc)** response to reward, and **hyperactivity of subgenual cingulate (area 25/Cg25)** — the basis for **deep brain stimulation (DBS)** of Cg25 or NAc in refractory cases.
- ▶ **Large-scale networks:** depression involves hyperconnectivity of the **default-mode network (DMN)** (rumination/self-focus), impaired **central-executive/cognitive-control network (CEN/CCN)** (poor concentration), aberrant **salience network (SAN)** and reduced **sensorimotor network (SMN)** activity (psychomotor retardation), all “updated” through the **cortico–striatal–thalamo–cortical (CSTC)** loop.
- ▶ **Sleep/circadian:** characteristic **reduced REM latency, increased REM density and decreased slow-wave (stage IV) sleep**, with diurnal mood variation (worse in morning) — partly heritable, trait-like markers.
- ▶ **Genetic/epigenetic:** GWAS implicate >100 loci; monozygotic concordance ~46% vs dizygotic ~20%; early-onset depression is most heritable; epigenetic (DNA-methylation, histone) changes mediate stress effects.

Diagnosis and differential diagnoses to exclude before diagnosing MDD

Diagnosis is clinical (DSM-5-TR major depressive episode). Before labelling MDD, exclude conditions across three DSM “gatekeeper” criteria — **Criterion C** (not due to a substance or medical condition), **Criterion D** (not better explained by a psychotic disorder) and **Criterion E** (no past mania/hypomania).

Category	Conditions to exclude	Distinguishing clue
Bipolar spectrum (Criterion E)	Bipolar I / II, cyclothymia, mixed/irritable mania	Any past manic/hypomanic episode → not MDD; childhood onset, antidepressant-induced switch, hypersomnia/weight gain suggest bipolarity
Other depressive disorders	Persistent depressive disorder (dysthymia)/“double depression”, premenstrual dysphoric disorder,	Chronicity ≥ 2 yrs (dysthymia); luteal-phase timing (PMDD)

Category	Conditions to exclude	Distinguishing clue
	disruptive mood dysregulation disorder	
Psychotic disorders (Criterion D)	Schizophrenia, schizoaffective, schizophreniform, delusional disorder	Mood-incongruent psychosis; psychosis ≥ 2 wks without mood episode (schizoaffective)
Normal reactions	Bereavement/grief, normal sadness, adjustment disorder with depressed mood	Grief = emptiness/loss in waves, self-esteem preserved; sub-threshold severity/duration
Depressive disorder due to a medical condition (Criterion C)	<i>Endocrine</i> : hypo-/hyperthyroidism, Cushing, Addison, diabetes; <i>Neurologic</i> : stroke (esp. left dorsolateral-frontal — major depression in 1 in 5), Parkinson, dementia, MS, traumatic brain injury, Huntington, partial-complex epilepsy; <i>Malignancy</i> : pancreatic & oropharyngeal cancer (40–50%); <i>Infective</i> : HIV, hepatitis C; <i>Other</i> : chronic fatigue syndrome, fibromyalgia, anaemia/nutritional deficiency	History, examination and targeted labs (TSH, glucose, electrolytes, B12/folate, HIV) reveal a causal medical illness
Substance/medication-induced (Criterion C)	Reserpine, clonidine, methyl dopa, β -blockers, corticosteroids, interferon- α , retinoids (isotretinoin), digitalis, antiparkinsonian drugs, anticonvulsants, disulfiram; alcohol/sedative/opioid use; stimulant (cocaine) withdrawal	Temporal link to drug/withdrawal; resolves on removal
Neurocognitive	Dementia vs depressive “pseudodementia”	Pseudodementia: rapid onset, “don’t-know” answers, reversible with treatment
Other psychiatric	Anxiety/panic disorder, ADHD, eating disorders, somatic symptom disorder	Co-morbid; diagnose both if full criteria met

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — “Neurobiology of MDD” composite:** Draw the HPA axis (Hypothalamus $\rightarrow$ CRH $\rightarrow$ Anterior pituitary $\rightarrow$ ACTH $\rightarrow$ Adrenal cortex $\rightarrow$ Cortisol, with a dashed negative-feedback arrow from cortisol to hippocampus/pituitary marked “impaired feedback $\rightarrow$ DST non-suppression”). Beside it draw three brainstem monoamine nuclei with arrows to

Category	Conditions to exclude	Distinguishing clue
	cortex/limbic system — label Locus coeruleus → NE (MHPG), Raphe nuclei → 5-HT (5-HIAA), VTA → DA (HVA). Add boxes for ↓BDNF / ↓neurogenesis, ↑IL-6/TNF-α/CRP → microglia → kynurenine/QUIN, and extrasynaptic NMDA (GluN2B) → excitotoxicity. ► Diagram 2 — Limbic mood circuit: Outline a sagittal brain labelling Prefrontal cortex (dlPFC), Subgenual cingulate (area 25 / Cg25), Amygdala (hyperactive), Hippocampus (atrophy) and Nucleus accumbens / VTA (reward, hypoactive); mark DBS targets = Cg25 and NAc.	

Clinical / Diagnostic significance

- **Screen and confirm criteria:** use validated tools (PHQ-9, Hamilton/Montgomery-Åsberg, QIDS-SR) and always assess **suicide risk directly** (Columbia Suicide Severity Rating Scale); ~4–5% of depressed patients die by suicide.
- **Mandatory medical work-up before diagnosing primary MDD:** TSH/free T4, fasting glucose/HbA1c, electrolytes, calcium, renal/hepatic panel, B12 and folate, FBC, and HIV where relevant; neuroimaging (CT/MRI) for first late-onset episode, focal signs, or psychotic features.
- **Biological tests are research/adjunctive, not diagnostic:** DST, TRH-stimulation and EEG-sleep abnormalities are sensitive markers of biological/melancholic depression but lack specificity.
- **Mechanism-guided therapeutics:** SSRIs/SNRIs first-line; **ketamine/esketamine** for rapid effect and acute suicidality; **brexanolone/zuranolone** for peripartum depression; ECT, rTMS, VNS, DBS (Cg25/NAc) for treatment-resistant cases; T3/lithium/atypical-antipsychotic augmentation (STAR*D).

High-yield exam pointers

- MDD requires ≥5/9 symptoms ≥2 weeks, one being depressed mood or anhedonia — and **no history of mania/hypomania** (Criterion E is the single most important exclusion → rules out bipolar disorder).
- Core neuro-systems: **monoamine, HPA, thyroid, glutamate/GABA, neurotrophic (BDNF), neuro-immune, and limbic networks** — name at least four for full marks.
- Monoamine metabolites: NE → MHPG, 5-HT → 5-HIAA, DA → HVA.
- **Dexamethasone non-suppression** = impaired glucocorticoid feedback; hypercortisolaemia → **hippocampal atrophy**.
- **Ketamine/esketamine** = NMDA antagonists with *rapid* antidepressant action; **brexanolone/zuranolone** = GABA-A neurosteroids for postpartum depression.
- Inflammation (IL-6, TNF-α, CRP, kynurenine/QUIN) drives an **anhedonia–psychomotor-slowness–suicidality** subtype.

- ▶ Sleep signature: short REM latency, ↑ REM density, ↓ slow-wave sleep.
- ▶ Exclude bipolar disorder, psychotic disorders, grief/bereavement, dysthymia, drug/substance-induced depression, and medical mimics (hypothyroidism, Cushing, stroke, Parkinson, pancreatic cancer, HIV, B12 deficiency, pseudodementia).
- ▶ Left dorsolateral-frontal stroke → major depression in 1 in 5; pancreatic & oropharyngeal cancers carry 40–50% depression prevalence.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Biology of Psychiatric Disorders” (monoamine/HPA/BDNF/glutamate-ketamine, neuro-inflammation, limbic circuitry, subgenual Cg25/DBS) and “Psychiatric Disorders” (Major Depressive Episode criteria, neuroendocrine/sleep abnormalities, depression in medical illness, treatment).
- ▶ **Kaplan & Sadock's Comprehensive Textbook of Psychiatry (2024)** — “Mood Disorders: Neurobiology” (monoaminergic systems and metabolites, HPA/thyroid/GH axes, DST, glutamate/GABA & neurosteroids, BDNF/GDNF, neuro-immune/kynurenine, functional networks DMN/CEN/SAN/SMN/CSTC, sleep neurophysiology) and “Mood Disorders: Clinical Features”.
- ▶ **DSM-5-TR** — Major Depressive Disorder diagnostic criteria and Differential Diagnosis (bipolar, psychotic, substance/medication-induced, depressive disorder due to another medical condition, bereavement).
- ▶ **CMDT 2026** — “Psychiatric Disorders” (differential diagnosis, mood disorders secondary to illness/medications, suicide assessment, current management/augmentation).



Discuss therapy and complications of pemphigus vulgaris

Asked in: Paper IV May 2025 — RGUHS MD General Medicine

Definition / Introduction — Pemphigus vulgaris (PV) is an autoantibody-mediated, potentially life-threatening **intraepidermal** blistering disease in which IgG autoantibodies against **desmoglein 3** (and desmoglein 1 in mucocutaneous disease) cause loss of keratinocyte cell–cell adhesion (**acantholysis**), producing flaccid blisters and painful erosions of mucosae and skin. Because PV is driven by *pathogenic autoantibodies*, therapy must aim to **suppress autoantibody production**, not merely local inflammation. Before glucocorticoids, mortality was 60–90% (death within 2–5 years); with modern immunosuppression and B-cell-directed therapy mortality is now ~5%, but much of the residual morbidity and mortality arises from **complications of treatment** itself.

Goals, principles and general/supportive measures

- **Goals:** rapidly gain disease control, achieve remission, then maintain remission on the *lowest possible* glucocorticoid dose to minimise iatrogenic harm. Disease extent and response are tracked with validated scores — **PDAI** (Pemphigus Disease Area Index) and **ABSIS** (Autoimmune Bullous Skin disorder Intensity Score) — and by serial anti-Dsg **ELISA** titres, which correlate with activity.
- Start **systemic therapy as early as possible**; a steroid-sparing agent is usually added from the outset because the disease course is long and adjuvants take weeks to act.
- **Supportive care (severe disease):** hospitalise, bed rest, attention to **fluid, electrolyte, protein and nutritional** balance, wound care of denuded skin, and **secondary-infection** surveillance with systemic/topical antibiotics. **Anaesthetic troches** before meals ease painful oral erosions and maintain oral intake.
- **Drug-induced pemphigus:** review and withdraw culprit drugs — thiol-containing agents (penicillamine, captopril, enalapril), other ACE inhibitors, β -lactams, piroxicam, immune-checkpoint inhibitors.

Systemic pharmacotherapy — the therapeutic ladder

Drug	Typical dose	Role / notes
Prednisone (oral)	1 mg/kg/day (up to 1–2 mg/kg/day; usually 60 mg/day)	Standard first-line; taper once new-blister formation stops
Pulse IV methylprednisolone	1 g/day over 2–3 h $\times$ 3–5 days (cardiac monitoring)	Severe/rapidly progressive disease
Rituximab (anti-CD20)	1 g on days 1 & 15, or 375 mg/m ² weekly $\times$ 4; maintenance 500 mg q6 months	FDA-approved, first-line for moderate–severe PV
Azathioprine	2–4 mg/kg/day (100–300 mg/day)	Steroid-sparing; check TPMT before starting
Mycophenolate mofetil	2–3 g/day (1–3 g/day)	Steroid-sparing; less marrow toxicity, more GI upset
Cyclophosphamide	1–3 mg/kg/day PO, or 500–1000 mg/m ² IV q4 weeks	Potent anti-B-cell; reserved for refractory disease
IVIg	2 g/kg over 3–5 days, repeated monthly	Non-immunosuppressive; steroid-resistant disease
Plasmapheresis / immunoadsorption	1–2 sessions/week initially	Rapidly lowers autoantibody titre; needs concomitant immunosuppression
Methotrexate / cyclosporine	MTX 7.5–20 mg/week; CsA 3–5 mg/kg/day	Second-line; cyclosporine shown of no added benefit in a randomised trial

- ▶ **Corticosteroids** remain the mainstay for the rapidity of response; the dose is titrated against the *number of new blisters per day* and rate of healing. If no response in 3–7 days, escalate the dose and/or add an adjuvant.
- ▶ **Steroid-sparing immunosuppressants** (azathioprine, MMF, cyclophosphamide) added to prednisone achieve earlier control and higher remission rates and permit steroid tapering. In a randomised trial MMF gave faster, more durable responses than placebo when added to corticosteroids; azathioprine and MMF are of broadly comparable efficacy. Once remission is sustained and prednisone is down to 5–10 mg/day, the adjuvant is carefully tapered and stopped.

Rituximab, biologics and refractory-disease options

- ▶ **Rituximab** is a chimeric **anti-CD20** monoclonal antibody that depletes CD20⁺ B cells (sparing plasma cells) and also reduces desmoglein-specific T-cell responses; onset of benefit is ~8–16 weeks and may last 12–18 months. The pivotal **Ritux 3** trial (first-line rituximab + short-course prednisone vs prednisone alone) showed **complete remission off-therapy in ~89% vs 34%**, with a lower cumulative steroid dose and fewer severe adverse events — establishing rituximab as **first-line** therapy (endorsed by international expert and EADV S2 guidelines). Humanised anti-CD20 agents (**obinutuzumab**, **ofatumumab**) and intralesional rituximab are emerging options.
- ▶ **IVIg** acts via **neonatal Fc-receptor (FcRn) blockade** (reducing IgG recycling), anti-idiotypic antibodies and immunomodulation; effective and safe in steroid-resistant PV in a randomised trial.
- ▶ **Plasmapheresis / immunoadsorption** physically removes circulating autoantibody for severe, unresponsive disease; **must** be combined with immunosuppression to prevent a rebound autoantibody surge.
- ▶ **Novel/targeted: efgartigimod**, an **FcRn inhibitor**, gave early disease control in 28 of 31 PV/PF patients in a phase II trial; **DSG3-CAART** (chimeric autoantibody-receptor T cells targeting Dsg3-specific B cells) received FDA orphan-drug designation in 2020 — both reflect the move toward antigen-specific immunosuppression.
- ▶ **Topical/local adjuncts**: superpotent (Class I) topical corticosteroids and intralesional corticosteroids for persistent localised lesions; **topical ciclosporin mouthwash** for refractory oral disease; topical antibiotics for secondary infection. **Dapsone** is an adjunct in mild disease and the drug of choice in IgA pemphigus/pemphigus herpetiformis.

Complications

Complications fall into two groups — those of the **disease** and those of its **treatment**.

Disease-related complications	Treatment-related complications
Secondary bacterial infection of erosions → **S. aureus septicaemia** (most frequent cause of death)	Corticosteroids : Cushingoid features, osteoporosis/avascular necrosis, diabetes, hypertension, peptic ulcer, cataract, myopathy,

Disease-related complications	Treatment-related complications
	psychosis, adrenal suppression, opportunistic infection
Fluid, electrolyte and protein loss through denuded skin; impaired barrier/thermoregulation	Azathioprine: dose-dependent myelosuppression, nausea, hepatotoxicity (worse if low TPMT)
Nutritional compromise from painful oral erosions, dysphagia, odynophagia	Mycophenolate mofetil: GI toxicity, marrow suppression
Oesophageal/laryngeal/pharyngeal involvement — hoarseness, mucosal cast, stricture risk	Cyclophosphamide: haemorrhagic cystitis, gonadal failure/sterility, leukopenia, long-term bladder carcinoma; chlorambucil → leukaemia risk
Post-inflammatory hyperpigmentation; scarring only at infected/traumatised sites	Rituximab: infusion reactions, hepatitis B reactivation, PML, late-onset neutropenia, infection
Untreated disease is fatal (death within ~5 years)	IVIg: headache, flu-like illness, hypotension, anaphylaxis in IgA deficiency; Plasmapheresis: rebound antibody, line sepsis, hypovolaemia

- ▶ **Bad prognostic factors:** advanced age, widespread involvement, and a requirement for **high-dose glucocorticoids** (± other immunosuppressants) for control.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Desmoglein compensation theory of PV (skin vs mucosa):** draw the epidermis with a triangle gradient — label Dsg1 (superficial), Dsg3 (basal/parabasal); show anti-Dsg3 IgG → mucosal erosions (mucosal-dominant PV) and anti-Dsg3 + anti-Dsg1 IgG → suprabasal split + skin blisters (mucocutaneous PV). Label suprabasal acantholysis, “row of tombstones” basal cells, acantholytic (Tzanck) cells.
- ▶ **Therapeutic ladder schematic:** vertical ladder labelled Supportive care → Topical/intralesional steroids → Systemic prednisone 1 mg/kg/day → Steroid-sparing (azathioprine / MMF) → Rituximab (first-line, moderate–severe) → IVIg / plasmapheresis / cyclophosphamide / efgartigimod (refractory).

Clinical / Diagnostic significance

- ▶ **Confirm the diagnosis before immunosuppression:** lesional biopsy (suprabasal acantholysis), DIF of perilesional skin (intercellular “chicken-wire” IgG ± C3), IIF on monkey oesophagus, and anti-Dsg1/Dsg3 ELISA — the latter also guides dosing as titres track activity.
- ▶ **Pre-treatment screen:** baseline glucose, BP, bone-density assessment and PPI/calcium-vitamin D + osteoporosis prophylaxis for steroids; TPMT before azathioprine; hepatitis B/C, HIV, latent TB and immunoglobulin levels before rituximab/IVIg; contraception counselling before cyclophosphamide.

- ▶ **Monitor** FBC/LFTs on azathioprine/MMF/cyclophosphamide; urinalysis (haematuria) on cyclophosphamide; CD19/CD20 counts and anti-Dsg titres after rituximab to anticipate relapse.
- ▶ Exclude **drug-induced pemphigus** and, where the picture is atypical (severe stomatitis, palmoplantar/lichenoid lesions, bronchiolitis obliterans), **paraneoplastic pemphigus** — search for underlying lymphoma/Castleman disease/thymoma.

High-yield exam pointers

- ▶ PV target antigen = **Dsg3** (mucosal) ± **Dsg1** (mucocutaneous); split is **suprabasal**.
- ▶ **Prednisone 1 mg/kg/day** is standard first-line; **rituximab** is **FDA-approved first-line** for moderate–severe PV (**Ritux 3**: CR off-therapy ~89% vs 34%).
- ▶ **Rituximab regimens**: 1 g days 1 & 15, or 375 mg/m² weekly × 4; maintenance 500 mg q6 months.
- ▶ **IVIg 2 g/kg** monthly works via **FcRn blockade**; **efgartigimod** is a new FcRn inhibitor.
- ▶ **Cyclophosphamide** → haemorrhagic cystitis, sterility, **bladder cancer**; check TPMT before azathioprine.
- ▶ Most frequent cause of death = ****Staphylococcus aureus septicaemia****; untreated PV is fatal within ~5 years.
- ▶ Disease severity/response measured by **PDAI** and **ABSIS**; antibody titre by **anti-Dsg ELISA**.
- ▶ Always **screen for HBV** before rituximab (reactivation risk) and exclude **IgA deficiency** before IVIg (anaphylaxis).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Immunologically Mediated Skin Diseases” (Pemphigus vulgaris: pathogenesis, mortality figures, glucocorticoid/rituximab/IVIg/plasmapheresis treatment, prognostic factors).
- ▶ **Bolognia Dermatology, 5e** — “Pemphigus” (therapeutic ladder with doses and evidence levels, complications of individual agents, PDAI/ABSIS, efgartigimod, DSG3-CAART).
- ▶ **Rook's Textbook of Dermatology, 10e** — “Immunobullous Diseases” (azathioprine/TPMT, MMF, rituximab first-line and Ritux 3 data, IVIg mechanism, immunoadsorption, drug toxicities).
- ▶ **CMDT 2026** — “Dermatologic Disorders: Pemphigus” (current management including rituximab maintenance dosing, supportive measures, complications and prognosis).

♦ ♦ ♦

Eating disorders

Asked in: Paper IV May 2022 — RGUHS MD General Medicine

Definition / Introduction — Feeding and eating disorders are a group of psychiatric conditions in which there is a **persistent disturbance of eating or eating-associated behaviour that significantly impairs the individual's physical health or psychosocial functioning**. In DSM-5-TR, the described categories (with the exception of pica) are defined to be **mutually exclusive in a given episode** — although phenotypically similar, they differ in course, prognosis and effective treatment. They are of direct relevance to the internist because their complications are **multisystemic and potentially life-threatening**: untreated anorexia nervosa carries the **highest mortality of any psychiatric condition**.

Classification (DSM-5-TR)

Disorder	Cardinal feature	Key differentiating point
Pica	Eating non-nutritive, non-food substances (clay, starch, soap, paper, ash) for ≥ 1 month in a person aged >2 years, requiring medical attention	Culturally approved practices must be excluded; diagnosed only when the behaviour increases medical risk
Rumination disorder	Repeated regurgitation of food after eating, which is re-chewed, re-swallowed or spat out, daily, for ≥ 1 month	No demonstrable gastrointestinal or other medical cause
Avoidant/restrictive food intake disorder (ARFID)	Avoidance/restriction of food intake from lack of interest in or distaste of food, with weight loss, nutritional deficiency, dependence on supplements or psychosocial impairment	No fear of weight gain and no body-image distortion (this distinguishes it from anorexia nervosa)
Anorexia nervosa (AN)	Caloric restriction producing significantly low body weight + fear of gaining weight + disturbed body image	Two subtypes — restricting vs binge-eating/purging
Bulimia nervosa (BN)	Recurrent binge eating (≥ 1 /week for 3 months) with compensatory behaviours (vomiting/purging, enemas, laxatives, excessive exercise)	Weight is normal or somewhat above normal
Binge-eating disorder (BED)	Recurrent binges with distress and loss of control	No compensatory behaviour and no inter-episode restriction

Anorexia nervosa

- **Diagnosis**: restriction of caloric intake so that body weight deviates significantly from age, gender, health and developmental norms, *plus* an intense fear of gaining weight and an associated disturbance of body image. Determining “significantly low weight” is complex and

must be **individualised**, using all historical information and comparison with **international body-mass (BMI) norms and guidelines**.

- ▶ **Subtypes** (more *state-* than *trait-*specific — patients transition between them over time):
 - **Restricting type** — weight loss achieved predominantly by restricting intake and/or excessive exercise.
 - **Binge-eating/purging type** — recurrent binge eating and/or purging by **self-induced vomiting, enemas, laxatives or diuretics**.
- ▶ **Psychopathology**: patients frequently **lack insight** and are in **denial** of the medical consequences; they are characteristically **not comforted by achieved weight loss** and persist despite reaching previously self-set weight goals.
- ▶ **Neurobiology**: alterations in the circuitry of **reward sensitivity and executive function**, implicating disturbed **frontal cortex and anterior insula** regulation of **interoceptive awareness of satiety and hunger**. Neurochemical findings (including the role of **ghrelin**) remain controversial.
- ▶ **Epidemiology**: onset most commonly in **adolescence** (later-life onset can occur); marked female preponderance; **lifetime prevalence in women up to 4%**; most prevalent in **post-industrialised, urbanised countries**; frequently comorbid with **pre-existing anxiety disorders**.
- ▶ **Course and prognosis**: variable — recovery after a single episode, recurrent episodes, or a chronic course. **Untreated AN has a mortality of 5.1 per 1000 — the highest among psychiatric conditions** (deaths from medical complications and suicide). Most treated individuals achieve remission within 5 years of diagnosis.

Medical complications of anorexia nervosa (system-wise)

System	Findings
General / metabolic	Hypometabolic state — hypotension, hypothermia, sinus bradycardia; elevated blood urea nitrogen
Haematological	Leukopenia with relative lymphocytosis
Electrolytes / acid-base	Metabolic alkalosis and hypokalaemia when purging is present
Endocrine	Hypogonadism (amenorrhoea in females), growth-hormone resistance, hypercortisolaemia
Skin	Petechiae, lanugo hair, dryness
Skeletal	Osteoporosis (long-term concern)
Cardiac	Bradycardia, hypotension; with purging — cardiac conduction abnormalities secondary to electrolyte disturbance

System	Findings
Refeeding	Over-rapid nutritional rehabilitation precipitates the refeeding syndrome (hallmark hypophosphataemia , with fluid shifts and arrhythmia risk) — hence weight-gain target of only 0.5–1 lb (~0.25–0.5 kg) per week

Bulimia nervosa

- ▶ **Diagnosis:** recurrent, frequent episodes of **binge eating** — **at least once a week for 3 months** — followed by **compensatory behaviours**: self-induced purging/vomiting, enemas, laxative use or excessive exercise to avoid weight gain.
- ▶ A **binge** is defined as excessive food intake within a prescribed period of time, **usually <2 hours**, with a subjective **loss of control**; patients express **shame**, and episodes are often triggered by **negative self-esteem or social stresses**.
- ▶ Body-image disturbance occurs as in AN, **but weight is normal or somewhat above normal** — the key clinical separator from AN binge-purge type (which requires significantly low weight).
- ▶ **Epidemiology:** lifetime prevalence in women ~2%, female-to-male ratio **10:1**; typically begins in **adolescence** and may persist for years; **transition to anorexia nervosa occurs in only 10–15%** of cases.
- ▶ **Medical risks** parallel those of AN and are a direct consequence of **purging: fluid and electrolyte disturbances** (hypokalaemia, metabolic alkalosis) and **cardiac conduction abnormalities**.
- ▶ **Physical examination** is often unremarkable; the classical signs are **dental erosion** (perimolysis from gastric acid) and **parotid gland enlargement**; calluses over the dorsum of the hand from repeated self-induced vomiting (*Russell's sign*) are a standard accompanying sign.

Binge-eating disorder and the other feeding disorders

- ▶ **Binge-eating disorder (BED):**
 - Distinguished from BN by the **absence of compensatory behaviours** after a binge and by a **lack of effort to restrict weight between episodes**.
 - Shares the **distress and loss of control** — eating more rapidly or in greater amounts than intended, or eating when not hungry.
 - **12-month prevalence in females 1.6%**, with a **much lower female-to-male ratio than BN**; prognosis is **markedly better** than other eating disorders (both natural course and treatment response); transition to other eating disorders is thought to be **rare**.
- ▶ **Pica:** onset most common in childhood; can occur with other major psychiatric conditions in adults; an **association with pregnancy** is observed, but the diagnosis is made only when the behaviour increases medical risk (e.g., toxicity, obstruction, infection). It is **not commonly** caused by a specific nutritional deficiency.

- ▶ **Rumination disorder:** onset in infancy typically between 3 and 12 months; weight loss and malnutrition are common sequelae; patients may conceal the behaviour (covering the mouth, social avoidance while eating); may remit spontaneously or recur.
- ▶ **ARFID:** onset usually in infancy/early childhood but may persist into adulthood; **equal prevalence in males and females**; frequently comorbid with **anxiety, cognitive and attention-deficit disorders** and situations of **familial stress**; long-standing unrecognised disease causes developmental delay and functional deficits.

Management

Disorder	Psychological treatment (first-line)	Pharmacotherapy	Medical management
Anorexia nervosa	MANTRA (<i>Maudsley Anorexia Nervosa Treatment for Adults</i>) and eating-disorder-focused CBT; strict behavioural contingencies when weight loss becomes critical	No drug is specifically beneficial; treat comorbid depression and anxiety on their own merits	Gradual nutritional rehabilitation — 0.5–1 lb/week weight gain to prevent refeeding syndrome ; monitor electrolytes (especially phosphate, potassium), ECG; hospitalise for severe bradycardia, hypotension, hypothermia, marked electrolyte derangement or critical low weight
Bulimia nervosa	Cognitive-behavioural, emotion-regulation or interpersonal psychotherapies	SSRI antidepressants, usually combined with psychotherapy (fluoxetine is the standard agent, used at higher dose, e.g., 60 mg/day)	Correct hypokalaemia/alkalosis; dental review for enamel erosion
Binge-eating disorder	CBT-based approaches; responds markedly better than other eating disorders	SSRIs/CBT as for BN-spectrum illness (lisdexamfetamine is an approved option in standard practice)	Address obesity-related comorbidity
Pica / Rumination / ARFID	Behavioural therapy, family-based management of stressors; nutritional supplementation in ARFID	—	Treat the medical consequence (toxicity, malnutrition, deficiency states)

Disorder	Psychological treatment (first-line)	Pharmacotherapy	Medical management
DIAGRAMS TO DRAW — IMAGE SUGGESTIONS ▶ Diagram 1 — “Multisystem complications of anorexia nervosa” (labelled human figure). Labels: <i>Brain</i> — lack of insight, altered frontal cortex–anterior insula interoceptive circuitry; <i>Skin</i> — lanugo hair, petechiae, dryness; <i>Heart</i> — sinus bradycardia, hypotension, conduction abnormalities; <i>Blood</i> — leukopenia with lymphocytosis; <i>Kidney/metabolic</i> — raised BUN, hypokalaemia, metabolic alkalosis (purging); <i>Endocrine</i> — amenorrhoea/hypogonadism, GH resistance, hypercortisolaemia; <i>Bone</i> — osteoporosis; <i>Whole body</i> — hypothermia, weight significantly below norms. ▶ Diagram 2 — “Diagnostic algorithm for eating disorders” (flow chart). Boxes: <i>Significantly low body weight?</i> → YES + fear of weight gain + body-image disturbance → Anorexia nervosa (→ restricting type vs binge-eating/purging type); YES but NO fear of weight gain/body-image distortion → ARFID; NO (normal/overweight) + binge ≥1/week × 3 months → <i>Compensatory behaviour?</i> → YES → Bulimia nervosa; NO → Binge-eating disorder.			

Clinical / Diagnostic significance

- ▶ **Internist’s screen:** unexplained amenorrhoea, bradycardia, hypokalaemic metabolic alkalosis, dental erosion or parotid swelling in a young woman should prompt directed questioning for disordered eating; physical examination in BN is often normal, so the diagnosis rests on history.
- ▶ **Laboratory panel:** electrolytes (K^+ , and phosphate during refeeding), urea, glucose, complete blood count (leukopenia with lymphocytosis), and ECG (bradycardia, conduction abnormalities — risk of arrhythmic death when hypokalaemic).
- ▶ **Distinguish organic disease:** weight loss with intact body image and genuine loss of appetite suggests malignancy, malabsorption, thyrotoxicosis, adrenal insufficiency or depression rather than AN; in AN the patient *fears* weight gain and is *not relieved* by weight loss.
- ▶ **Refeeding syndrome** is the most important iatrogenic hazard — gradual calorie escalation, phosphate/potassium/magnesium monitoring and a weight-gain ceiling of 0.5–1 lb/week.
- ▶ **Psychiatric comorbidity** (anxiety disorders in AN; depression in BN/BED) must be actively treated; suicide contributes to the excess mortality of AN.
- ▶ **Hospitalisation/behavioural contingency** is indicated when weight loss becomes critical or vital signs/electrolytes are dangerously deranged.

High-yield exam pointers

- ▶ **DSM-5-TR feeding and eating disorders:** pica, rumination disorder, ARFID, anorexia nervosa, bulimia nervosa, binge-eating disorder — mutually exclusive in a given episode (except pica).
- ▶ **AN = low weight + fear of weight gain + body-image disturbance;** two subtypes — restricting vs binge-eating/purging; subtype is state-, not trait-specific.
- ▶ **ARFID vs AN:** ARFID has **no fear of weight gain and no body-image distortion**.
- ▶ **BN vs AN binge-purge type:** BN patients are of **normal weight or overweight**; binge ≥ 1 /week for 3 months, binge usually < 2 h.
- ▶ **BED vs BN:** BED has **no compensatory behaviour**; lowest female predominance; **best prognosis** of all eating disorders.
- ▶ **Untreated AN mortality 5.1/1000 — highest of all psychiatric disorders;** lifetime prevalence in women up to 4% (BN $\sim 2\%$, 10:1 F:M; BED 12-month prevalence 1.6% in females).
- ▶ **AN examination:** lanugo, petechiae, dry skin, hypotension, hypothermia, sinus bradycardia, amenorrhoea; labs: leukopenia with lymphocytosis, $\uparrow$ BUN, hypokalaemic metabolic alkalosis (purging), hypogonadism, GH resistance, hypercortisolaemia, osteoporosis.
- ▶ **BN examination:** dental erosion + parotid enlargement ($\pm$ Russell's sign).
- ▶ **Treatment one-liners:** AN — MANTRA / ED-focused CBT, no specific drug, refeed at 0.5–1 lb/week; BN — SSRI + CBT/interpersonal therapy; BED — best treatment response.
- ▶ **Neurobiology of AN:** frontal cortex–anterior insula interoceptive circuitry; ghrelin data controversial.

SOURCE & COVERAGE

Harrison 22e — Ch 463 “Psychiatric Disorders” (section: *Feeding and Eating Disorders*).
Coverage note: Harrison 22e has no dedicated eating-disorders chapter; the topic is covered briefly within Ch 463, and this answer reflects that coverage. A few universally standard exam points absent from the provided text were added for completeness and are flagged as standard practice: *Russell's sign*, hypophosphataemia as the hallmark of refeeding syndrome, high-dose fluoxetine for BN, lisdexamfetamine for BED, and explicit hospitalisation criteria (consistent with CMDT/standard psychiatry teaching).



Eczema

Asked in: Paper IV Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — *Eczema* (Greek *ekzema*, “to boil over”) is a **clinico-histological reaction pattern of skin inflammation** rather than a single disease, characterised clinically by pruritus, erythema, oozing, vesiculation, scaling and (when chronic) lichenification, and histologically by **spongiosis** (intercellular oedema of the epidermis) with acanthosis and a perivascular lymphohistiocytic infiltrate.

The terms *eczema* and *dermatitis* are used synonymously. It is the **final common pathway of many disorders** of diverse aetiology; **atopic dermatitis (AD)** is the prototype and commonest endogenous form. Eczema accounts for ~10–25% of dermatology consultations and AD carries the highest disability-adjusted life-year burden of any skin disease.

Classification of eczematous disorders

Best classified by **aetiology** (where known) and by **endogenous vs exogenous** origin; morphological labels (e.g. nummular, dyshidrotic) cut across causes.

Category	Examples
Endogenous (constitutional)	Atopic eczema; seborrhoeic dermatitis; nummular (discoid) eczema; asteatotic (xerotic / “winter itch”) eczema; stasis (venous/gravitational) eczema; hand eczema incl. pompholyx; lichen simplex chronicus; pityriasis alba; juvenile plantar dermatosis
Exogenous (contact)	Allergic contact dermatitis (type IV, e.g. nickel, <i>Toxicodendron</i> /urushiol); irritant contact dermatitis (soaps, detergents, wet-work); photoallergic / photo-irritant eczema; infective dermatitis; post-traumatic eczema; dermatophytide (“id” reaction)
By morphology / acuity	Acute (wet, oedematous, vesicular) → subacute → chronic (dry, lichenified, fissured)

Atopic dermatitis — pathophysiology (the exam favourite)

AD is the cutaneous expression of the **atopic state** (familial tendency to asthma, allergic rhinitis, eczema). Pathogenesis is a **three-way interaction** of barrier defect, immune dysregulation and microbiome alteration, on a strong genetic background (monozygotic twin concordance ~77% vs ~15% dizygotic; if **both parents affected** >80% of children develop AD).

- ▶ **Epidermal barrier dysfunction** — **loss-of-function mutations in the filaggrin gene (FLG) are the single strongest genetic risk factor (also cause ichthyosis vulgaris). Filaggrin aggregates keratin in the stratum corneum; deficiency → ↑ transepidermal water loss, ↑ skin pH, xerosis, and easier penetration of irritants, allergens and microbes. FLG null carriers manifest hyperlinear palms, keratosis pilaris and ichthyosis vulgaris**; penetrance of AD is ~40% with one and ~90% with two null alleles.
- ▶ **Immune dysregulation** — barrier breach lets keratinocytes release “alarmins” TSLP (the “master switch of allergic inflammation”), **IL-25 and IL-33**, driving a **Th2-skewed** response. *Acute* lesions are Th2-dominant (**IL-4, IL-5, IL-13, IL-31** — IL-31 is the key pruritogen); *chronic* lesions shift to **Th1/Th17/Th22** cytokines. Th2 cytokines themselves suppress filaggrin, loricrin and antimicrobial peptides, perpetuating the barrier defect. Result: **↑ IgE synthesis, eosinophilia, impaired delayed-type hypersensitivity.**

- ▶ **Microbiome** — reduced diversity with ** >90% colonisation by Staphylococcus aureus**; **staphylococcal exotoxins act as superantigens**** amplifying inflammation; reduced antimicrobial peptide (β -defensin, cathelicidin) production predisposes to viral superinfection (eczema herpeticum).
- ▶ **Epicutaneous sensitisation** through defective skin is thought to initiate the “**atopic march**” — AD in infancy → food allergy → asthma → allergic rhinoconjunctivitis.

Atopic dermatitis — clinical features by age

Pruritus (“an itch that rashes”) is the cardinal symptom in all ages; the course is chronically relapsing. 45% present in first 6 months, 60% in first year, ~85% by age 5; ~40% persist into adult life.

Phase	Age	Distribution / features
Infantile	0–2 yr	Weeping, crusted patches on cheeks, face, scalp, neck and extensor surfaces; napkin area spared
Childhood / adolescent	2 yr–puberty	Flexural dermatitis — antecubital & popliteal fossae, wrists, ankles, neck; lichenification
Adult	post-puberty	Flexures, hand eczema , head-and-neck, nipple/eyelid eczema; often localised lichen simplex chronicus

- ▶ **Atopic stigmata / minor signs:** xerosis, **Dennie–Morgan infraorbital fold**, infraorbital darkening (“allergic shiners”), perioral/midfacial pallor, **hyperlinear palms**, keratosis pilaris, **pityriasis alba**, white dermographism, anterior neck folds, **keratoconus** and **anterior subcapsular cataract**.

Diagnostic criteria

AD is a **clinical diagnosis** (no confirmatory test except skin biopsy).

- ▶ ****Hanifin & Rajka criteria (1980) — require ≥ 3 of 4 major plus ≥ 3 minor**.**
 - **Major:** (1) pruritus; (2) typical morphology & age-specific distribution (flexural in adults, facial/extensor in infants); (3) chronic or chronically relapsing course; (4) personal/family history of atopy.
 - **Minor (selected):** xerosis; ichthyosis/palmar hyperlinearity/keratosis pilaris; elevated serum IgE / immediate (type I) skin-test reactivity; early age of onset; tendency to cutaneous infections (*S. aureus*, HSV); non-specific hand/foot dermatitis; nipple eczema; cheilitis; recurrent conjunctivitis; Dennie–Morgan fold; keratoconus; anterior subcapsular cataract; orbital darkening; facial pallor; pityriasis alba; itch on sweating; wool intolerance; white dermographism; food intolerance; course influenced by environment/emotion.

- ▶ ***UK Working Party (Williams) criteria** — *validated, simplified for population studies (80% PPV, 97% NPV). Must have an itchy skin condition in the last 12 months plus ≥ 3 of:** onset <2 yr; history of flexural involvement; history of generally dry skin; personal history of other atopic disease (or atopy in a first-degree relative if <4 yr); visible flexural dermatitis.
- ▶ **Severity scoring:** SCORAD, EASI, POEM (patient-oriented), vIGA-AD.

Other clinically important eczema variants

Variant	Key features
Lichen simplex chronicus	Circumscribed lichenified plaque from chronic rubbing; nape, ankles, dorsum of feet
Nummular (discoïd)	“Coin-shaped” crusted scaly plaques, extensor limbs; middle-aged men; dry skin
Asteatotic (xerotic)	“Crazy-paving”/cracked dry skin, shins of the elderly in winter
Stasis dermatitis	Medial ankle, venous incompetence, haemosiderin pigmentation, brawny oedema; <i>bilateral</i> (vs unilateral cellulitis); may precede venous ulcer
Seborrhoeic dermatitis	Greasy yellow scale on scalp, eyebrows, nasolabial folds; <i>Malassezia</i> ; associated with Parkinson’s, HIV
Hand eczema / pompholyx	Wet-work/occupational; dyshidrotic — intensely pruritic deep vesicles on sides of fingers, palms
Contact dermatitis	Allergic (type IV, patch-test positive) vs irritant (dose-dependent, no prior sensitisation)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ “Distribution of atopic dermatitis by age” — **three body silhouettes**. Labels: *Infantile* — cheeks/face, scalp, neck, extensor limbs, napkin sparing; *Childhood* — antecubital fossa, popliteal fossa, wrists, ankles, neck; *Adult* — flexures, hands, eyelids, head-and-neck.
- ▶ “Pathogenesis triad of AD” — **three interlocking circles**. Labels: (1) **Epidermal barrier defect** (*FLG* mutation, $\uparrow$ TEWL, xerosis); (2) **Immune dysregulation** (TSLP/IL-33 $\rightarrow$ Th2: IL-4, IL-13, IL-31; chronic Th1/Th17/Th22; $\uparrow$ IgE); (3) **Microbiome** (*S. aureus* superantigens, $\downarrow$ antimicrobial peptides); central output $\rightarrow$ **chronic pruritic eczema** $\rightarrow$ **atopic march**.

Clinical / Diagnostic significance

- ▶ **Investigations:** largely clinical; serum IgE/eosinophilia support but are not diagnostic; **patch testing** if allergic contact dermatitis suspected or AD is recalcitrant; **KOH/culture** to exclude dermatophyte (esp. hand eczema); skin/viral swabs in weeping flares.

- ▶ **Complications:** secondary **impetiginisation** with *S. aureus*/*S. pyogenes* (infra-auricular fissure is a cardinal sign); **eczema herpeticum** (*Kaposi varicelliform eruption*) — monomorphic punched-out “scalloped” erosions with haemorrhagic crusts + fever; a dermatological emergency needing **systemic aciclovir**; predisposition to widespread **molluscum contagiosum**. Risk of erythroderma. Associations: asthma, allergic rhinitis, food allergy, ADHD, anxiety/depression, and ↑ cardiovascular risk in adults.
- ▶ **Management ladder (AD):**
 - *General* — gentle skin care, avoid irritants/wool/soaps, bathe ≤ once daily in warm water, **liberal emollients** (≈30 g covers an adult; apply within minutes of bathing); identify triggers.
 - *First line* — **topical corticosteroids** (potency matched to site/severity; low-potency on face/flexures to avoid atrophy); **topical calcineurin inhibitors** (tacrolimus, pimecrolimus — steroid-sparing, safe on face, no atrophy), **crisaborole** (PDE-4 inhibitor), **ruxolitinib/roflumilast** cream. *Proactive* twice-weekly anti-inflammatory to flare-prone sites prevents relapse.
 - *Adjuncts* — **dilute sodium hypochlorite (bleach, ~0.005%) baths** + intranasal mupirocin to reduce *S. aureus*; **wet-wrap therapy** (diluted steroid + inner wet/outer dry layer, ≤2 weeks) for acute flares; sedating antihistamines (hydroxyzine, doxepin) at night for sleep; treat secondary infection (dicloxacillin/cephalexin; cover CA-MRSA with cotrimoxazole/doxycycline/clindamycin per culture).
 - *Severe/refractory* — **phototherapy** (NB-UVB); systemic immunosuppressants (ciclosporin, methotrexate, azathioprine, mycophenolate); **biologics** — **dupilumab** (anti-IL-4Rα, blocks IL-4/IL-13; approved ≥6 months), **tralokinumab** (anti-IL-13); **oral JAK inhibitors** — **upadacitinib**, **abrocitinib**. Systemic corticosteroids only for short severe exacerbations (rebound on withdrawal).

High-yield exam pointers

- ▶ Eczema = **spongiosis** histologically; “the itch that rashes.”
- ▶ ***Filaggrin (FLG) loss-of-function*** = strongest genetic risk for AD; links to ichthyosis vulgaris, hyperlinear palms, keratosis pilaris.
- ▶ Acute AD is **Th2** (IL-4/IL-13/IL-31, ↑IgE); chronic shifts to **Th1/Th17/Th22**; TSLP is the alarmin “master switch.”
- ▶ **Hanifin & Rajka** (≥3 major + ≥3 minor) and **UK Working Party** criteria; severity by **SCORAD/EASI/POEM**.
- ▶ **Dennie–Morgan fold**, **allergic shiners**, **hyperlinear palms**, **pityriasis alba**, **white dermographism** = atopic stigmata.
- ▶ **Eczema herpeticum** (*Kaposi varicelliform eruption*) = monomorphic punched-out erosions → **aciclovir** urgently.

- ▶ Stasis dermatitis is usually bilateral; unilateral red leg favours cellulitis.
- ▶ Dupilumab (IL-4Rα), tralokinumab (IL-13), upadacitinib/abrocitinib (JAK) are the modern systemic agents; FDA *black-box warning* on topical calcineurin inhibitors (theoretical lymphoma — absolute risk very low).
- ▶ Topical steroid potency: **low-potency on face/flexures** to avoid atrophy/striae.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders” (atopic dermatitis, contact/hand/nummular/asteatotic/stasis/seborrheic dermatitis, lichen simplex chronicus, treatment).
- ▶ **Rook's Textbook of Dermatology, 10e** — “Eczematous Disorders” (classification, nomenclature) and “Atopic Eczema” (diagnostic criteria, filaggrin genetics, epidemiology, complications).
- ▶ **Bolognia, Dermatology, 5e** — “Atopic Dermatitis” (pathogenesis triad, atopic march, Th2/Th1-Th17-Th22 cytokines, diagnostic features table, eczema herpeticum, severity scores).
- ▶ **CMDT 2026** — “Dermatologic Disorders: Atopic Dermatitis” (current stepwise management, topical non-steroidals, biologics/JAK inhibitors, wet wraps, bleach baths).



Erythema Nodosum: Causes, Histopathology, Evaluation and Management

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Erythema nodosum (EN) is the commonest and best-known form of panniculitis (inflammation of subcutaneous fat), presenting as an acute, self-limited eruption of **tender, erythematous, non-ulcerating subcutaneous nodules**, classically symmetrical over the **pretibial shins**. It is widely regarded as a **delayed (type IV) hypersensitivity reaction** to diverse antigenic stimuli (infections, drugs, systemic inflammatory disease) and is histologically the **prototype of a septal panniculitis without vasculitis**. Because of its strong links to systemic disease, EN is an important *skin sign of internal disease* — diagnosis is only the first step; the cause must be sought.

Pathogenesis

- ▶ A **delayed-type hypersensitivity response** to varied antigens; lesional skin and blood show a **Th1 cytokine pattern** (interferon-γ, IL-2) characteristic of DTH.
- ▶ **Immune-complex deposition** in septal venules and a **neutrophil-driven** early phase: circulating neutrophils generate reactive oxygen intermediates that provoke tissue damage; later, **granuloma**

formation predominates, in which TNF plays a central role (explaining both response to, and paradoxical induction by, TNF inhibitors).

- ▶ Endothelial up-regulation of adhesion molecules (VCAM-1/CD106, PECAM-1/CD31, E-selectin, HLA-DR) with VLA-4/L-selectin on infiltrating cells.
- ▶ A TNF promoter polymorphism correlates with sarcoidosis-associated EN, linking deregulated TNF to granuloma formation.

Causes / Aetiology

A precipitant is identifiable in roughly half; the rest are idiopathic. Crohn disease associates more strongly than ulcerative colitis.

Category	Specific causes (high-yield)
Idiopathic	Largest single group — one-third to one-half of cases
Infections (≈1/3 of cases)	Streptococcal URTI = commonest <i>infectious</i> cause; viral URTI; bacterial gastroenteritis (<i>Yersinia</i> > Salmonella , Campylobacter); Mycobacterium tuberculosis ; coccidioidomycosis (and histoplasmosis, blastomycosis); brucellosis, <i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> /C. trachomatis, hepatitis B, HIV, COVID-19
Sarcoidosis	10–20% of cases; Löfgren syndrome (see below)
Inflammatory bowel disease	Crohn disease > ulcerative colitis
Drugs	Oral contraceptives/oestrogens, sulfonamides, penicillins, bromides, iodides, TNF inhibitors (etanercept, infliximab, adalimumab), immune checkpoint inhibitors , BRAF inhibitors (vemurafenib, dabrafenib), tyrosine-kinase inhibitors (imatinib, dasatinib)
Neutrophilic dermatoses	Behçet disease , Sweet syndrome (EN in Behçet often resembles erythema induratum)
Pregnancy / hormonal	Pregnancy itself; OCP use
Malignancy	Acute myeloid leukaemia, Hodgkin lymphoma (may overlap with Sweet syndrome)
Miscellaneous	Acne fulminans (incl. isotretinoin-associated), diverticulitis, granulomatous mastitis, lupus erythematosus, MonoMAC syndrome (<i>GATA2</i>)

- ▶ ***Löfgren syndrome** — *acute, spontaneously resolving sarcoidosis = EN + bilateral hilar lymphadenopathy + fever + polyarthritides (peri-ankle) + uveitis**; carries a benign, self-limited prognosis.

Clinical features

- ▶ **Crops of tender, warm, erythematous nodules 1–10 cm**, bilateral and symmetrical, on the **anterior shins** (occasionally thighs, forearms; trunk/face/neck rare — atypical sites should prompt an alternative diagnosis).
- ▶ Lesions **do not ulcerate** and **resolve without scarring** over **~6 weeks**, evolving through **bruise-like (contusiform) colour changes** — hence the synonym *erythema contusiformis*.
- ▶ **Constitutional symptoms** common even without an identified systemic cause: fever, malaise, **arthralgia/arthritis**, leukocytosis, raised ESR.
- ▶ **Up to one-third recur**; annual recurrences typical of idiopathic disease. Chronic/migratory variants = *subacute nodular migratory panniculitis (erythema nodosum migrans)*, often unilateral with centrifugal spread and central clearing.

Histopathology

Biopsy requires a deep incisional/excisional specimen capturing generous subcutaneous fat — a punch biopsy is usually inadequate.

- ▶ **Prototypic septal (interlobular) panniculitis WITHOUT true vasculitis.**
- ▶ **Septa are thickened and oedematous**, infiltrated by inflammatory cells concentrated at the **septal-lobular interface**, extending into the lobule periphery in a *lace-like* pattern.
- ▶ **Early lesions:** oedematous septa, often **neutrophil-rich**; **late lesions:** mixed, **granulomatous** infiltrate with **epithelioid histiocytes and multinucleated giant cells**, eventual **septal fibrosis**.
- ▶ ***Miescher radial microgranulomas** — *the characteristic (though not strictly pathognomonic) hallmark: small nodular aggregates of histiocytoid cells arranged radially around a central stellate / banana-shaped cleft**, located within or at the edge of septa.
- ▶ A **mild superficial and deep perivascular lymphocytic infiltrate** is usually present in the overlying dermis.
- ▶ Leukocytoclastic vasculitis is **absent** (its presence, with venular/venous involvement, suggests EN-like lesions of severe Behçet disease).

Evaluation / Investigations

- ▶ **Confirm the diagnosis clinically** (classic bilateral pretibial tender non-ulcerating nodules in a young adult, F:M ≈ 10:1, 2nd–4th decades); biopsy only when atypical (few lesions, unusual site, duration >6 weeks, or ulceration suggesting another panniculitis).

- **Search for an underlying cause** — directed by *findings that predict a systemic association*: synovitis, diarrhoea, abnormal CXR, preceding URTI, raised ASO/anti-DNase B, positive TST/IGRA.
- **First-line work-up**: FBC, ESR/CRP, throat swab + **two serial ASO / anti-DNase B titres 2–4 weeks apart**, chest X-ray (hilar adenopathy → sarcoidosis/Löfgren, TB, lymphoma), **tuberculin skin test or IGRA (QuantiFERON-TB / T-SPOT.TB)**.
- **Targeted tests**: stool culture + **faecal calprotectin** (if GI symptoms) for IBD/enteric infection; **serum amylase/lipase** if pancreatic panniculitis suspected; **serum β -hCG** in women of child-bearing age; viral hepatitis panel; coccidioidin/fungal serology in endemic areas; review of drug history.
- **Differential diagnosis of subcutaneous nodules**:

Entity	Distinguishing feature
Erythema induratum (nodular vasculitis)	Posterior calf, ulcerates; lobular panniculitis with vasculitis; <i>M. tuberculosis</i> DNA by PCR
Pancreatic panniculitis	Fat necrosis with saponification/"ghost cells"; $\uparrow$ amylase/lipase; arthritis, serositis
Lupus panniculitis	Cheeks, upper arms, buttocks; heals with depressed scars
Cutaneous polyarteritis nodosa	Nodules + ulcers within fixed livedo reticularis ; medium-vessel arteritis
Superficial thrombophlebitis	Linear cord along a vein

Management

- **General (all patients)**: stop any causative drug; **diagnose and treat the underlying cause**; bed rest, leg elevation, compression.

Line	Agents
First-line	NSAIDs, salicylates, potassium iodide (SSKI)
Second-line (only after infection excluded/treated)	Colchicine (esp. Behçet-associated), hydroxychloroquine, TNF inhibitors (infliximab/adalimumab/etanercept — useful in IBD-associated EN), mycophenolate mofetil
Third-line	Systemic corticosteroids (avoid if infection unexcluded), thalidomide, ciclosporin, dapsone

- **Potassium iodide (SSKI)**: adult dose commonly **300 mg three times daily** (range ~450–1500 mg/day); CMDT quotes **5–15 drops three times daily**; improvement within ~2 weeks via inhibition of neutrophil chemotaxis and cell-mediated immunity.

- ▶ **Caveat:** NSAIDs and KI may flare IBD; corticosteroids are contraindicated if an underlying infection (e.g. TB, deep mycosis) has not been excluded/treated.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Histology of EN (septal panniculitis):** label *epidermis, dermis with superficial + deep perivascular lymphocytic infiltrate, widened oedematous/fibrotic interlobular septum, fat lobule, Miescher radial microgranuloma (histiocytes around central stellate cleft), multinucleated giant cells, and absence of vasculitis.*
- ▶ **Clinical distribution figure:** front-of-legs silhouette showing **bilateral symmetrical tender nodules over both shins (pretibial)**, with a colour key for *erythema → contusiform/bruise-like resolution, non-ulcerating.*

Clinical / Diagnostic significance

- ▶ EN is a **paraclinical marker of systemic disease** — it may precede or accompany an IBD flare, herald sarcoidosis or primary TB/coccidioidomycosis, or signal drug reaction.
- ▶ It carries **prognostic value:** EN denotes a **benign, self-limited course in sarcoidosis (Löfgren)** and a **protective effect against dissemination in coccidioidomycosis.**
- ▶ A normal CXR, negative IGRA/TST and negative streptococcal serology in an otherwise well young woman support an **idiopathic, benign course**; only a small minority develop significant illness within the following year.
- ▶ **Persistent, ulcerating, posterior-leg or unilateral lesions argue against EN** and mandate biopsy for an alternative panniculitis.

High-yield exam pointers

- ▶ EN = **commonest panniculitis; septal panniculitis without vasculitis; never ulcerates, heals without scar.**
- ▶ **Miescher radial microgranuloma** = histological hallmark (histiocytes around a central stellate/banana-shaped cleft).
- ▶ **Streptococcal URTI** = commonest infectious cause; **idiopathic** = commonest overall; **sarcoidosis** 10–20%.
- ▶ **Löfgren syndrome** = EN + bilateral hilar lymphadenopathy + fever + arthritis + uveitis (good prognosis).
- ▶ **Crohn > ulcerative colitis; Yersinia** = leading enteric trigger; drugs — OCP, sulfonamides, penicillins, bromides/iodides, BRAF inhibitors.
- ▶ Core work-up: CXR + ASO/anti-DNase B (×2) + TST/IGRA + ESR ± stool studies + β-hCG.
- ▶ Treatment ladder: NSAIDs / potassium iodide → colchicine, HCQ → steroids (only after excluding infection); always **treat the cause.**

- ▶ **DDx mnemonic by site:** EN = shin (anterior); erythema induratum = calf (posterior, ulcerates, TB); lupus panniculitis = buttocks/arms (scars).

SOURCE & COVERAGE

- ▶ **Bologna, Dermatology (5e)* — “Panniculitis”^{*} (primary source: aetiology Table, pathogenesis, septal histopathology with Miescher microgranulomas, treatment ladder and potassium iodide dosing).
- ▶ **Rook’s Textbook of Dermatology (10e)* — “Panniculitis”^{*} (Miescher radial granuloma morphology; septal-panniculitis-without-vasculitis confirmation; Löfgren/sarcoid associations).
- ▶ **Harrison’s Principles of Internal Medicine (22e)* — “Skin Manifestations of Internal Disease”^{*} (EN as a sign of systemic disease; differential of subcutaneous nodules).
- ▶ **CMDT 2026** — “Dermatologic Disorders” (**Erythema Nodosum**) (clinical essentials, evaluation algorithm, NSAID/SSKI/colchicine/dapsone management, prognosis).
- ▶ *Coverage note:* The spec flagged panniculitis histopathology as potentially thin in Harrison; this was fully resolved using the dedicated dermatology texts (Bologna and Rook’s), which supplied exam-grade histological and therapeutic detail.



Erythroderma

Asked in: Paper IV Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — **Erythroderma** (synonyms: *exfoliative dermatitis*, *exfoliative erythroderma*) is an inflammatory reaction pattern characterised by **generalised erythema and scaling involving ≥80–90% of the body surface area (BSA)**. The term was coined by *Hebra* in 1868 for an eruption affecting >90% of the skin. It is **not a single disease but a striking, potentially life-threatening clinical presentation** that can arise from several underlying dermatoses, drugs or systemic diseases, and is therefore regarded as a **dermatological emergency** requiring a careful aetiological search and management of systemic complications.

Epidemiology and classification

- ▶ Estimated incidence ~1–2 per 100,000; male predominance with **M:F ratio 2:1 to 4:1**; mean age of onset ~52 years.
- ▶ **By onset/course:** *Primary* erythroderma (erythema begins de novo, often on the trunk, and generalises over days–weeks) vs *Secondary* erythroderma (generalisation of a pre-existing dermatosis, e.g. psoriasis, atopic dermatitis — up to 50% have a prior localised skin disease).
- ▶ **Idiopathic erythroderma** persists despite thorough work-up in ~25% of adults — typically **elderly men** with chronic pruritus, palmoplantar keratoderma and dermatopathic

lymphadenopathy; historically termed “*red man syndrome*” or “*l’homme rouge*” (not to be confused with the vancomycin rapid-infusion reaction of the same name). These cases mandate longitudinal review, as some evolve into CTCL.

Aetiology

The major causes are (1) primary cutaneous dermatoses, (2) drugs, (3) systemic disease (chiefly CTCL), and (4) idiopathic. In adults the four commonest are **dermatitis, psoriasis, drug reactions and CTCL**.

Category	Approx. frequency	Diagnostic clues
Psoriasis	~20–27%	Pre-existing plaques (elbows/knees/scalp), nail pits / oil-drop sign / onycholysis, sterile pustules, arthritis; often spares central face
Dermatitis (atopic > contact > seborrhoeic / stasis)	~20–24%	Pre-existing flexural lesions, intense pruritus, lichenification (incl. eyelids), raised IgE, eosinophilia, atopy history
Drug reactions	~15–19%	Preceding morbilliform/scarlatiniform exanthem, facial oedema, rapid onset; may be part of DRESS/DIHS
CTCL (Sézary syndrome > erythrodermic mycosis fungoides)	~8–18%	Leonine facies, <i>melanoerythroderma</i> , painful fissured keratoderma, alopecia, lymphadenopathy, severe pruritus
Idiopathic	~25% (often older men)	Chronic, relapsing; palmoplantar keratoderma, dermatopathic lymphadenopathy
Uncommon	—	Pityriasis rubra pilaris, pemphigus foliaceus, bullous pemphigoid, paraneoplastic (lymphoma > solid tumours, thymoma), crusted (Norwegian) scabies, dermatophytosis, GVHD, sarcoidosis, connective-tissue disease, papuloerythroderma of Ofuji

- **Implicated drugs:** allopurinol, β -lactams/penicillins, sulfonamides, sulfasalazine, aromatic anticonvulsants (carbamazepine, phenytoin, phenobarbital), gold salts, lithium, cimetidine, antimalarials, dapsone, isoniazid, immune checkpoint inhibitors.

- ▶ **Neonatal/infantile erythroderma** (“the red baby”) — distinct causes: **inherited ichthyoses** (congenital ichthyosiform erythroderma — *TGM1*; epidermolytic ichthyosis — *KRT1/KRT10*; **Netherton syndrome** — *SPINK5/LEKTI*, *trichorrhexis invaginata* “bamboo hair”), **primary immunodeficiencies** (**Omenn syndrome** — *RAG1/RAG2*; Wiskott–Aldrich — *WAS*), psoriasis, atopic/seborrhoeic dermatitis (*Leiner phenotype*), and **staphylococcal scalded skin syndrome**.

Pathogenesis

- ▶ A massive, generalised inflammatory response produces a **marked increase in germinative keratinocytes and their mitotic rate** with **shortened epidermal transit time**.
- ▶ Consequently scale (rich in nucleic acids, amino acids and soluble protein) is shed in excess — daily loss rises from a normal **0.5–1 g to 20–30 g**, and protein loss may reach **~9 g/m²/day**, causing **hypoalbuminaemia**.
- ▶ Acquired erythroderma shows a **Th2-skewed cytokine milieu** (IL-4, IL-13) with **raised serum IgE**, and up-regulation of endothelial adhesion molecules (VCAM-1, ICAM-1, E-/P-selectin) facilitating inflammatory cell trafficking.

Clinical features

- ▶ **Cutaneous**: Erythema typically *precedes exfoliation by 2–6 days*; scaling often begins in the flexures. The **character of scale offers clues** — *fine* in atopic dermatitis/dermatophytosis, *bran-like* in seborrhoeic dermatitis, *crusted/cornflake* in pemphigus foliaceus, *exfoliative (peeling)* in drug reactions.
- ▶ **Pruritus** in up to **90%** (most severe in dermatitis and Sézary syndrome); **lichenification** in ~one-third.
- ▶ **Appendages**: nail changes in ~40% (shiny nails, ridging, subungual hyperkeratosis, Beau’s lines, paronychia, shedding); **diffuse non-scarring alopecia** in ~20% of chronic cases; **palmoplantar keratoderma** in ~30% (early sign in PRP; painful/fissured in Sézary; scale-crust in crusted scabies).
- ▶ **Ocular**: bilateral **ectropion** with epiphora and purulent conjunctivitis; secondary *Staphylococcus aureus* colonisation/infection is common.
- ▶ **Systemic complications**: peripheral/pedal oedema (~50%, from hypoalbuminaemia and fluid shift), **tachycardia** (~40%) and **high-output cardiac failure** (markedly increased cutaneous blood flow), **thermoregulatory disturbance** (hypo- or hyperthermia, rigors), **hypermetabolism and cachexia**, anaemia (iron deficiency + chronic disease).
- ▶ **Lymphoreticular**: **peripheral lymphadenopathy** in ~50% — distinguish reactive **dermatopathic lymphadenopathy** from lymphomatous involvement; hepatomegaly ~20%, splenomegaly rare (suggests systemic lymphoma).

Diagnostic evaluation

- ▶ **History:** pre-existing dermatosis, full drug history (including herbal/self-medication), atopy, prior cutaneous lymphoma; examine for residual clues (psoriatic plaques, *nappes claires* of PRP, *deck-chair sign* of Ofuji).
- ▶ **Skin biopsy** (the key test) — take **multiple, serial biopsies**; diagnostic yield up to ~50–66%, but findings are **non-specific in at least one-third** of Sézary syndrome/erythrodermic MF, so repeat sampling is essential.
- ▶ **Bloods:** CBC with differential and **peripheral smear for Sézary cells** (cerebriform lymphocytes), **flow cytometry**, **T-cell receptor gene rearrangement (PCR)** in skin/blood, serum IgE, LFTs, serum albumin, electrolytes, eosinophil count.
- ▶ **Lymph node biopsy** (core/excisional preferred over FNAC) if significant lymphadenopathy — guided by CT or PET-CT to the most FDG-avid node; inform the pathologist that the patient is erythrodermic.
- ▶ **Molecular diagnostics** (NGS / **whole-exome sequencing**) are pivotal in neonatal erythroderma to identify ichthyosis/immunodeficiency mutations.

Sézary syndrome — ISCL/EORTC diagnostic criteria	Requirement
Core triad	Erythroderma + generalised lymphadenopathy + clonal circulating atypical (Sézary) T-cells
Mandatory	Erythroderma plus an identical T-cell clone in blood and skin
Plus one of	(1) ≥ 1000 Sézary cells/mm ³ ; (2) CD4:CD8 ratio $\geq 10:1$; (3) $\geq 40\%$ CD4 ⁺ /CD7 ⁻ or $\geq 30\%$ CD4 ⁺ /CD26 ⁻ cells on flow cytometry (B2 blood tumour burden)

Management

Erythroderma is a **skin emergency**; acute/fulminant cases often need **hospital admission**.

- ▶ **General/supportive (regardless of cause):** correct **fluid and electrolyte balance**, nutritional support (high-protein), **maintain body temperature** (warm blankets, emollients to counter hypothermia), monitor and treat **high-output cardiac failure**, and **detect/treat secondary infection** with anti-staphylococcal antibiotics. **Withdraw all non-essential and suspected drugs**.
- ▶ **Topical:** frequent **bland greasy emollients** to restore barrier; **open wet dressings**; low–mid-potency corticosteroids (high-potency reserved for lichenified sites). **Avoid coal tar and phototherapy** (may aggravate); **avoid salicylic/lactic acid in neonates** (enhanced absorption). Sedating oral antihistamines for pruritus.
- ▶ **Systemic corticosteroids:** useful in **idiopathic and drug-induced** erythroderma — prednisone 1–2 mg/kg/day, maintenance ≤ 0.5 mg/kg/day, tapered cautiously (rebound). **Avoid systemic steroids in psoriatic erythroderma** — withdrawal precipitates a **generalised pustular flare**.

- ▶ **Cause-specific:** *Psoriatic erythroderma* — methotrexate, acitretin, ciclosporin or biologics (anti-TNF, anti-IL-12/23, anti-IL-17, anti-IL-23); *PRP* — acitretin/methotrexate; *Idiopathic/refractory* — ciclosporin 5 mg/kg/day reducing to 1–3 mg/kg/day (± azathioprine, MMF, methotrexate); *DRESS* — drug withdrawal ± systemic steroids/IVIg; *CTCL* — specific topical/systemic therapy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — “Whole-body map of erythroderma”:** a body silhouette shaded to show >80–90% confluent erythema with scaling, labelled with: *facial oedema / ectropion, leonine facies (CTCL), diffuse alopecia, generalised lymphadenopathy, shiny dystrophic nails, palmoplantar keratoderma, pedal oedema*, and a flexural arrow marking “*island of sparing — nappes claires (PRP)*” and “*deck-chair sign (Ofuji)*”.
- ▶ **Diagram 2 — Aetiology pie/flow:** a wheel of the major causes with approximate frequencies — Dermatitis ~24%, Psoriasis ~20%, Drugs ~19%, CTCL ~8%, Idiopathic ~25%, feeding into a box: “*Multiple skin biopsies + bloods/flow cytometry/TCR + LN biopsy → underlying diagnosis*”.

Clinical / Diagnostic significance

- ▶ Erythroderma is a **medical emergency**: the principal threats are **high-output cardiac failure, hypothermia, fluid/protein/electrolyte loss, dehydration and sepsis** (cutaneous/respiratory infection — **pneumonia is the commonest cause of death**).
- ▶ **CTCL is the commonest malignancy underlying erythroderma**; any persistent “idiopathic” erythroderma in an elderly man warrants **serial biopsies, repeat flow cytometry and TCR studies** to exclude Sézary syndrome.
- ▶ **Always reconcile drug history** — drug-induced disease has the **best prognosis**, usually resolving 2–6 weeks after withdrawal (exception: DRESS/DIHS).
- ▶ Mortality historically quoted at **18–64%**; modern outcomes are better, and **deaths are rare in the absence of CTCL**, but relapse rates reach **20–30% at one year**.

High-yield exam pointers

- ▶ **Definition:** generalised erythema + scaling over ≥80–90% BSA; term coined by *Hebra* (1868); = exfoliative dermatitis.
- ▶ **Commonest causes (adults):** dermatitis, psoriasis, drugs, CTCL; **idiopathic in ~25%** (elderly men = “red man syndrome / l’homme rouge”).
- ▶ **Scale clues:** fine (eczema), bran-like (seborrhoeic), crusted (pemphigus foliaceus), peeling (drugs); **nappes claires** = PRP; **deck-chair sign** = papuloerythroderma of Ofuji.
- ▶ **Systemic effects:** high-output cardiac failure, hypothermia, hypoalbuminaemia (scale protein loss up to ~9 g/m²/day), peripheral oedema, dermatopathic lymphadenopathy.

- ▶ **Sézary syndrome** = erythroderma + lymphadenopathy + clonal blood Sézary cells; *ISCL/EORTC*: ≥ 1000 Sézary cells/mm³, CD4:CD8 $\geq 10:1$, or CD4⁺/CD7⁻ $\geq 40\%$ / CD4⁺/CD26⁻ $\geq 30\%$.
- ▶ **Investigation**: multiple skin biopsies (non-specific in $\geq 1/3$ of Sézary), TCR gene rearrangement, flow cytometry; **NGS in neonates**.
- ▶ **Treatment cardinal rule**: supportive care + stop offending drug; **systemic steroids help idiopathic/drug-induced but are CONTRAINDICATED in psoriatic erythroderma** (pustular rebound) — use MTX/acitretin/ciclosporin/biologics instead.
- ▶ **Neonatal mnemonics**: Netherton (*SPINK5*, bamboo hair), Omenn (*RAG1/RAG2*), epidermolytic ichthyosis (*KRT1/10*), SSSS.

SOURCE & COVERAGE

- ▶ **Bologna Dermatology 5e* — “Erythroderma” (*Chapter 10, Sean Whittaker*)* — primary source for definition, epidemiology, aetiology tables (adult + neonatal), pathogenesis, clinical/systemic features, Sézary *ISCL/EORTC* criteria, and treatment.
- ▶ **Rook’s Textbook of Dermatology 10e* — “Erythroderma” (*in Eczematous Disorders*)* — causes/prevalence, complications, mortality, treatment ladder, Sézary cell thresholds.
- ▶ **Harrison’s Principles of Internal Medicine 22e* — “Skin Manifestations of Internal Disease” and “Eczema, Psoriasis...”* — causes of erythroderma, drug-induced/DRESS, CTCL association.
- ▶ **CMDT 2026** — “Exfoliative Dermatitis (Exfoliative Erythroderma),” **Dermatologic Disorders** — current diagnostic essentials, frequencies, and management.



Neuroleptic malignant syndrome

Asked in: Paper III Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Neuroleptic malignant syndrome (NMS) is a rare, potentially fatal, idiosyncratic hyperthermic syndrome caused by dopamine receptor blockade, classically after antipsychotic exposure, or by abrupt withdrawal of dopaminergic therapy in Parkinson disease. It is defined clinically by the tetrad of **hyperthermia, severe generalized rigidity, altered mental status, and autonomic instability**, with laboratory evidence of muscle injury. It is a medical emergency because death results from hyperpyrexia, aspiration pneumonia, rhabdomyolysis with acute kidney injury, hepatic failure, respiratory arrest, or cardiovascular collapse.

Epidemiology and etiopathogenesis

- ▶ **Incidence**: DSM-5-TR database studies suggest **0.01-0.02%** among antipsychotic-treated patients; one Hong Kong population study reported **0.11%**.

- ▶ **Mechanism:** central **hypodopaminergic state** due to dopamine D2 receptor blockade or sudden reduction of dopaminergic stimulation.
- ▶ **Striatum:** dopamine blockade in the corpus striatum causes sustained muscle contraction and **lead-pipe rigidity**, generating heat and rhabdomyolysis.
- ▶ **Hypothalamus:** impaired central thermoregulation causes hyperthermia; spinal/autonomic dopaminergic dysfunction contributes to tachycardia, labile BP, diaphoresis, pallor, and incontinence.
- ▶ **Muscle injury:** sustained contraction causes raised **creatinine kinase (CK)**, myoglobinemia/myoglobinuria, metabolic acidosis, hyperkalemia, and AKI.
- ▶ **Overlap:** NMS is considered by many authors to overlap with malignant catatonia and parkinsonian hyperthermia syndrome, but the drug exposure/withdrawal history is decisive.

Precipitating drugs and risk factors

- ▶ **Dopamine receptor blockers:** all antipsychotics may cause NMS; risk is greater with **high-potency first-generation antipsychotics** such as haloperidol and fluphenazine, especially high dose, rapid titration, or parenteral use.
- ▶ **Atypical antipsychotics:** NMS is reported with olanzapine, risperidone, clozapine, quetiapine, and other SGAs; presentation may be milder or partial, so diagnosis may be delayed.
- ▶ **Nonpsychiatric dopamine blockers:** antiemetics and prokinetics such as **metoclopramide** and **prochlorperazine** can precipitate NMS.
- ▶ **Dopaminergic withdrawal:** abrupt withdrawal of levodopa or dopamine agonists in Parkinson disease can precipitate an NMS-like parkinsonian hyperthermia syndrome.
- ▶ **Patient and illness risks:** dehydration, exhaustion, psychomotor agitation, low serum iron/iron deficiency, affective illness, pre-existing catatonia, neurologic disease, prior NMS, and history of malignant hyperthermia.
- ▶ **Treatment-related risks:** high total antipsychotic dose, rapid escalation, intermittent nonadherence followed by re-exposure, long-acting injectable/depot preparations, and **lithium plus antipsychotic** combination.
- ▶ **Demographic risks:** Kaplan notes higher risk in **men** and younger patients, but DSM emphasizes that NMS can occur in any patient receiving dopamine antagonists, even at therapeutic doses.

Clinical features and diagnostic criteria

- ▶ **Timing:** onset ranges from hours to days after drug initiation or dose increase; some develop within **24 hours**, most within the **first week**, and virtually all within **30 days**. CMDT notes most cases develop within the first **2 weeks** of antipsychotic treatment.
- ▶ **Hyperthermia:** DSM-5-TR describes oral temperature **>100.4 F (>38.0 C)** **on at least two occasions**, often with profuse diaphoresis; extreme temperature supports the diagnosis.

- ▶ **Rigidity:** severe generalized **lead-pipe rigidity**, usually unresponsive to routine antiparkinsonian agents; associated tremor, akinesia, dystonia, trismus, sialorrhea, dysarthria, dysphagia, and rhabdomyolysis may occur.
- ▶ **Mental status:** delirium or altered consciousness is often early; spectrum includes alert but dazed state, mutism, catatonic stupor, stupor, and coma.
- ▶ **Autonomic instability:** tachycardia **>25% above baseline**, tachypnea **>50% above baseline**, diaphoresis, pallor, urinary incontinence, BP elevation **≥25% above baseline**, or BP fluctuation of **≥20 mmHg diastolic** or **≥25 mmHg systolic** within 24 hours.
- ▶ **Respiratory compromise:** chest wall restriction, aspiration pneumonia, pulmonary embolism, hypermetabolism, and metabolic acidosis may cause respiratory distress or sudden respiratory arrest.
- ▶ **Diagnostic frame:** NMS is a **clinical diagnosis of exclusion** in a patient exposed to dopamine blockade or dopaminergic withdrawal, with hyperthermia, rigidity, mental change, autonomic instability, and muscle enzyme elevation.

Investigations and monitoring

Investigation	Expected / useful finding
CBC	Leukocytosis common; Kaplan notes WBC often 10,000-40,000/mm ³
CK serially	Usually >1000 IU/L or ≥4 times upper limit of normal; may be modest/normal early or before rigidity develops
Renal profile	Rising urea/creatinine from rhabdomyolysis, dehydration, or myoglobinuric AKI
Electrolytes, ABG/VBG	Hyperkalemia, metabolic acidosis, hypoxia; guide ICU care
Urinalysis	Myoglobinuria; assess renal complications and exclude urinary infection
LFTs	Transaminase elevation may occur; hepatic failure is a fatal complication
Blood/urine cultures, CXR	Fever workup; do not miss sepsis, aspiration pneumonia, or CNS infection
ECG and hemodynamics	Tachyarrhythmia, QT issues from antipsychotics, BP lability
CSF/neuroimaging/EEG	CSF and imaging generally normal in NMS; EEG may show generalized slowing if encephalopathic

- ▶ **Interpretation pearl:** isolated CK elevation after IM injections, restraint, agitation, or dystonia is not NMS unless accompanied by hyperthermia and rigidity.

- **Monitoring:** chart temperature, pulse, BP, respiratory rate, SpO₂, urine output, hydration status, CK, creatinine, potassium, bicarbonate, and complications at least daily; severe cases need ICU-level monitoring.

Differential diagnosis

Disorder	Clues favouring it over NMS
Serotonin syndrome	Onset within hours of serotonergic drug/MAOI interaction; clonus, hyperreflexia, myoclonus , tremor, GI symptoms; treat with drug withdrawal, benzodiazepine, and cyproheptadine
Malignant hyperthermia	Occurs during/after volatile anesthetic or succinylcholine exposure; severe rigidity and hypercapnia; dantrolene is central therapy
Malignant catatonia	Catatonic prodrome with psychiatric illness before dopamine blocker exposure; may be clinically indistinguishable
Heat stroke / exertional hyperthermia	Environmental heat/exertion, anhidrosis or exertional collapse; antipsychotics may impair heat loss but dopamine-blocker chronology absent
Anticholinergic toxicity	Hot dry skin, mydriasis, ileus, urinary retention, delirium; usually no lead-pipe rigidity or marked CK pattern
CNS infection/autoimmune encephalitis/status epilepticus	Headache, meningism, seizures, focal signs, abnormal CSF/EEG/imaging; always exclude in first presentation
Tetanus, strychnine, thyrotoxicosis, pheochromocytoma	Exposure/history and characteristic spasms or endocrine crisis; not linked to recent dopamine blockade

- **Serotonin syndrome vs NMS:** the exam contrast is **clonus/hyperreflexia/myoclonus** in serotonin syndrome versus **lead-pipe rigidity, hypodopaminergic exposure, and slower days-weeks evolution** in NMS.

Management

- **Immediate actions:** stop the offending antipsychotic/dopamine blocker and avoid all dopamine antagonists; if due to Parkinson drug withdrawal, promptly reinstitute dopaminergic therapy.
- **Site of care:** admit to HDU/ICU for severe hyperthermia, altered consciousness, rigidity, dysphagia, aspiration risk, AKI, metabolic acidosis, arrhythmia, or labile BP.
- **Supportive care:** airway protection, oxygen, aspiration precautions, IV fluids, correction of electrolytes/acidosis, urine output monitoring, prevention/treatment of rhabdomyolysis and AKI, DVT/pressure sore prevention, and nutrition.

- ▶ **Temperature control:** active cooling with cooling blankets, tepid spraying/fanning, ice packs, or more aggressive external cooling for severe hyperthermia; do not rely on antipyretics because NMS is hyperthermia rather than cytokine-mediated fever.
- ▶ **Benzodiazepines:** useful for agitation, rigidity with catatonic features, and when serotonin syndrome cannot be confidently excluded; lorazepam is commonly used.
- ▶ **Dopamine agonists:** **bromocriptine 2.5 mg orally twice or thrice daily**, titrating up to **45 mg/day**, or CMT dose **2.5-10 mg orally three times daily**; watch for hypotension, vomiting, psychosis, and possible worsening of serotonin syndrome if the diagnosis is wrong.
- ▶ **Amantadine:** **100-200 mg orally twice daily** or **200-400 mg/day in divided doses** when bromocriptine is unsuitable or as adjunctive dopaminergic therapy.
- ▶ **Dantrolene:** for severe rigidity/hyperthermia; CMT gives **50 mg IV as needed**, not exceeding **10 mg/kg/day** because of hepatotoxicity; other Kaplan dosing uses IV weight-based regimens up to the same daily ceiling.
- ▶ **Severe hyperthermia with rigidity:** toxicology guidance supports rapid nondepolarizing neuromuscular paralysis, intubation, mechanical ventilation, and sedation when cooling fails or rigidity is extreme.
- ▶ **ECT:** consider for refractory NMS, prominent malignant catatonia, or when psychosis/catatonia needs treatment while antipsychotics are stopped.
- ▶ **Evidence caveat:** no drug is specifically approved for NMS; dantrolene, bromocriptine, amantadine, benzodiazepines, levodopa, and ECT are supported mainly by clinical experience and case-based evidence, so early recognition and supportive care remain the core treatment.

Prevention, rechallenge and prognosis

- ▶ **Prevention:** use the lowest effective antipsychotic dose, avoid rapid escalation, correct dehydration, avoid unnecessary parenteral high-potency agents, monitor early fever/rigidity in catatonic or agitated patients, and avoid abrupt withdrawal of Parkinson medications.
- ▶ **Course after stopping drug:** mean recovery is **7-10 days**; most recover within **1 week** and nearly all within **30 days**, but depot/long-acting injectable exposure can prolong illness.
- ▶ **Mortality:** DSM-5-TR reports **10-20%** fatality when unrecognized; older Kaplan descriptions report **20-30%** in well-developed cases, higher with depot drugs, but mortality falls with early recognition.
- ▶ **Residual sequelae:** weeks of residual neurologic signs, cognitive deficits, renal injury, or complications of prolonged ICU stay may occur.
- ▶ **Rechallenge:** if antipsychotic therapy is essential, wait at least **2 weeks after full clinical resolution**, correct dehydration/iron deficiency and other risks, avoid lithium, choose an alternate lower-risk agent, start low, titrate slowly, and monitor temperature, rigidity, autonomic signs, CK, and renal function.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Pathogenesis flow diagram:** dopamine antagonist / dopaminergic withdrawal -> D2 blockade in striatum, hypothalamus, spinal autonomic pathways -> rigidity + impaired thermoregulation + autonomic instability -> hyperthermia, rhabdomyolysis, AKI, respiratory/cardiovascular collapse.
- ▶ **NMS bedside diagnostic tetrad:** four labelled boxes: hyperthermia; lead-pipe rigidity; altered mental status; autonomic instability; central label: recent dopamine blocker or dopaminergic withdrawal; side labels: high CK, leukocytosis, myoglobinuria.

Clinical / Diagnostic significance

- ▶ Any patient on antipsychotics who develops **fever plus rigidity or altered mental status** should be treated as possible NMS until proven otherwise.
- ▶ NMS may present to medicine, emergency, ICU, neurology, or psychiatry; it is not restricted to psychiatric patients because antiemetics such as metoclopramide and prochlorperazine are common triggers.
- ▶ Early differentiation from serotonin syndrome matters: bromocriptine may worsen serotonin syndrome, whereas cyproheptadine is used for serotonin toxicity.
- ▶ Normal early CK does not exclude NMS; serial examination and CK trend are more useful than one value.
- ▶ In a clozapine patient with fever, tachycardia, and dyspnea, also evaluate for **clozapine myocarditis** with ECG, troponin, and echocardiography where clinically indicated.
- ▶ Do not label every antipsychotic fever as NMS: rule out infection, aspiration pneumonia, heat illness, toxic ingestion, CNS infection/encephalitis, status epilepticus, and endocrine crisis.

High-yield exam pointers

- ▶ Write the tetrad: **hyperthermia + lead-pipe rigidity + altered sensorium + autonomic instability**.
- ▶ Key trigger: recent **dopamine antagonist** exposure or abrupt **dopaminergic withdrawal**.
- ▶ DSM thresholds: temperature **>38 C twice**, CK often **>=4 times ULN**, tachycardia **>25% baseline**, tachypnea **>50% baseline**.
- ▶ Best differentiator from serotonin syndrome: **NMS = rigidity; serotonin syndrome = clonus/hyperreflexia/myoclonus**.
- ▶ Common labs: **CK rise, leukocytosis, metabolic acidosis, low serum iron, myoglobinuria, raised creatinine, raised transaminases**.
- ▶ First treatment step: **stop antipsychotic immediately** and start aggressive supportive care.

- ▶ Drug options: **bromocriptine**, **amantadine**, **dantrolene**, benzodiazepines; ECT for refractory/catatonic cases.
- ▶ Severe cases die from **hyperpyrexia**, **aspiration**, **AKI**, **hepatic failure**, **respiratory arrest**, **cardiovascular collapse**.
- ▶ Rechallenge only after full recovery, preferably after **>=2 weeks**, using low dose, slow titration, alternate agent, and close monitoring.

SOURCE & COVERAGE

Harrison 22e — “Tremor, Chorea, and Other Movement Disorders”; Harrison 22e — “Psychiatric Disorders”; Kaplan & Sadock’s Comprehensive Psychiatry 2024 — “Dopamine Antagonists”, “Medication-Induced Movement Disorders and Other Adverse Effects of Medication”, and “Dopamine Receptor Agonists”; DSM-5-TR — “Medication-Induced Movement Disorders and Other Adverse Effects of Medication”; CMDT 2026 — “Common Symptoms”, “Psychiatric Disorders”, and “Poisoning”.



Obsessive Compulsive Disorder

Asked in: Paper IV Jul 2021 · Paper IV Nov 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Obsessive-compulsive disorder (OCD) is a chronic, often disabling neuropsychiatric condition characterised by **obsessions** (recurrent, intrusive, unwanted thoughts, images or urges that cause marked anxiety) and/or **compulsions** (repetitive behaviours or mental acts performed to neutralise that anxiety), which are time-consuming (typically >1 hour per day) or cause clinically significant distress and functional impairment. In DSM-5-TR it heads its own category — *Obsessive-Compulsive and Related Disorders* — separated from the anxiety disorders, and the patient generally recognises the symptoms as excessive or senseless yet feels driven to perform them. Lifetime prevalence is ~2–3% worldwide.

Clinical features — obsessions, compulsions and symptom dimensions

- ▶ **Obsessions** are intrusive and *not pleasurable*: fears of contamination/germs, pathological doubt, aggressive or sexual/blasphemous (taboo) thoughts, and need for symmetry. They are resisted but provoke anxiety or disgust.
- ▶ **Compulsions (rituals)** are repetitive behaviours (handwashing, ordering, checking) or covert mental acts (counting, praying, repeating words) performed rigidly to reduce distress or prevent a dreaded event — yet are *not realistically connected* to it, or are clearly excessive.
- ▶ Four recurring **symptom dimensions** (DSM-5-TR): **cleaning** (contamination/washing); **symmetry** (ordering, counting, repeating); **forbidden/taboo thoughts** (aggressive, sexual,

religious); and **harm** (fear of harm → checking). Most patients have symptoms in more than one dimension.

- **Sensory phenomena** (“just-right”, incompleteness, premonitory urges) precede compulsions in up to 60%.
- Patients commonly **conceal** symptoms out of embarrassment — the physician must ask directly. Physical clues: *chafed, reddened hands* (washing) or *patchy hair loss* (trichotillomania).
- **Insight** varies and defines a specifier — good/fair, poor, or absent/delusional ($\leq 4\%$); poorer insight predicts worse outcome. **Accommodation** (family participating in rituals) maintains symptoms.

Diagnostic criteria (DSM-5-TR) and specifiers

Component	Requirement
A	Presence of obsessions, compulsions, or both (each defined by intrusive nature + neutralising attempt)
B	Time-consuming (>1 h/day) or clinically significant distress/impairment
C	Not attributable to a substance or another medical condition
D	Not better explained by another mental disorder (GAD, BDD, hoarding, trichotillomania, eating disorder, etc.)
Insight specifier	With good/fair insight · With poor insight · With absent insight/delusional beliefs
Tic specifier	“Tic-related” — current or past tic disorder (up to 30% of OCD)

- Severity and treatment response are graded with the ***Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)***, scored out of 40; the children’s version is the CY-BOCS.

Epidemiology, etiology and neurobiology

- **Prevalence:** 12-month prevalence $\sim 1.2\%$ (US); lifetime $\sim 2\text{--}3\%$. **Mean age of onset 19.5 years**, with 25% of cases beginning by age 14; onset after 35 is unusual. Males have earlier (childhood) onset and more tic comorbidity; among adults it is slightly more common in women.
- **Genetics:** Strong familial aggregation — first-degree relative risk $\sim 2\times$ (adult-onset proband) and $\sim 10\times$ for childhood-onset probands; twin concordance 0.57 (MZ) vs 0.22 (DZ); additive genetic effects explain $\sim 40\%$ of variance. No single susceptibility gene is established. Familial co-aggregation with **Tourette’s disorder**.
- **Neuroanatomy:** Dysfunction of the **cortico-striato-thalamo-cortical (CSTC) circuit** — *orbitofrontal cortex, anterior cingulate cortex, caudate nucleus and globus pallidus*. The caudate

mediates habit/skill learning; effective treatment reduces caudate metabolic activity.

Serotonergic dysregulation underpins the selective efficacy of serotonin-reuptake-blocking drugs.

- **Environmental:** Adverse perinatal events, prematurity, maternal smoking, childhood abuse, and post-infectious autoimmune mechanisms (**PANDAS** — Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection) in some abrupt-onset paediatric cases.

Differential diagnosis and comorbidity

- **Differential diagnosis:** generalised anxiety disorder (real-life worries, no rituals); major depressive disorder (mood-congruent ruminations, not linked to compulsions); specific/social phobia; body dysmorphic disorder; trichotillomania and excoriation disorder; hoarding disorder; tics/stereotypies (preceded by premonitory urge, not by an obsession); psychotic disorders (in delusional-insight OCD, obsessions/compulsions persist and other psychotic features are absent); and crucially **obsessive-compulsive personality disorder** (pervasive perfectionism/rigidity *without* true obsessions or compulsions).
- **OCD-spectrum (related) disorders:** body dysmorphic disorder, hoarding, trichotillomania (hair-pulling), excoriation (skin-picking), and tics.
- **Comorbidity (high):** anxiety disorder ~76%, depressive/bipolar disorder ~63% (MDD ~41% — develops in roughly two-thirds over a lifetime), impulse-control disorder ~56%, substance use ~39%, and lifetime tic disorder up to 30%.
- **Suicide risk is significant** — mean lifetime suicidal ideation ~44% and lifetime attempts ~14%; registry data show markedly elevated odds of suicide death and attempt, especially with the taboo-thoughts dimension and comorbid depression.

Treatment / Management

- **General principles:** OCD responds more slowly than depression — an adequate SSRI trial needs **8–12 weeks at higher doses** than for depression. Only **50–60%** improve with pharmacotherapy alone; **combining medication with exposure and response prevention (ERP)** is superior to either alone. Achieved responders need long-term maintenance.

Modality	Agents / technique	Notes
First-line drugs (SSRIs)	Fluoxetine 5–60 (up to 80) mg/d · Fluvoxamine 25–300 mg/d · Paroxetine 40–60 mg/d · Sertraline 50–150 mg/d	FDA-approved for OCD; high-dose, prolonged trials
TCA	Clomipramine 25–250 mg/d	Potent serotonergic TCA; efficacy <i>independent</i> of antidepressant action; anticholinergic/sedative limits use; keep plasma

Modality	Agents / technique	Notes
		clomipramine + metabolite <500 ng/mL
Other (off-label)	Venlafaxine, duloxetine	Efficacious but not FDA-approved
Augmentation (resistant)	Antipsychotic (neuroleptic), buspirone, benzodiazepine; CMTD adds topiramate, memantine, riluzole, N-acetylcysteine, lamotrigine, ondansetron, anti-inflammatories (minocycline, celecoxib)	For partial/non-responders
Psychotherapy	Exposure and response prevention (ERP) — first-line; cognitive-behavioural therapy; acceptance and commitment therapy	Graded exposure + ritual prevention; family psychoeducation/de-accommodation
Neuromodulation	rTMS (high-dose theta-burst) — FDA-approved for treatment-resistant OCD	Non-invasive
Refractory/severe	Deep-brain stimulation (ventral capsule/ventral striatum, VC/VS) — FDA humanitarian device exemption; ablative psychosurgery	<1% of patients qualify; Y-BOCS typically ≥26–30

- Ablative psychosurgery (bilateral, stereotactic) for intractable OCD after exhausting drugs + ERP: **anterior cingulotomy** (target ACC, Brodmann areas 24/32 at the cingulum margin), **anterior/gamma ventral capsulotomy** (anterior limb of the internal capsule), and **subcaudate tractotomy** (substantia innominata) — ~40–60% respond.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Cortico-striato-thalamo-cortical (CSTC) loop in OCD.** Draw and label: **Orbitofrontal cortex (OFC)** and **Anterior cingulate cortex (ACC)** → **Striatum (Caudate nucleus)** → **Globus pallidus / Substantia nigra** → **Thalamus** → back to **Cortex**; mark the hyperactive OFC–caudate–thalamus circuit and indicate **SSRI / ERP** reducing caudate metabolic activity, plus **DBS at VC/VS** as the surgical target.
- **Stepwise management ladder.** Boxes: (1) High-dose SSRI + ERP → (2) Switch SSRI / Clomipramine → (3) Augmentation (antipsychotic / others) → (4) rTMS → (5) DBS / ablative surgery; side label “Y-BOCS to monitor severity & response.”

Clinical / Diagnostic significance

- ▶ A general physician must **actively screen** for concealed OCD when faced with unexplained dermatitis of the hands, trichotillomania-related alopecia, or refractory anxiety — early recognition prevents years of disability.
- ▶ **Y-BOCS** quantifies severity, guides escalation, and defines surgical candidacy (≥ 26 –30/40).
- ▶ OCD carries **substantial suicide risk** and heavy psychiatric comorbidity (depression, tics, substance use) — these must be screened and treated concurrently.
- ▶ Distinguishing OCD from **OCPD** and from psychotic rumination changes management entirely; abrupt paediatric onset warrants evaluation for **PANDAS**.

High-yield exam pointers

- ▶ OCD = obsessions $\pm$ compulsions, **>1 h/day**; lifetime prevalence 2–3%; mean onset **~19.5 yr**, 25% by 14.
- ▶ DSM-5-TR places it in **Obsessive-Compulsive and Related Disorders**, not anxiety disorders; specifiers = **insight** (good-fair/poor/absent-delusional) and **tic-related**.
- ▶ Four symptom dimensions: **cleaning, symmetry, forbidden thoughts, harm**.
- ▶ Neurobiology = **CSTC loop** (OFC–ACC–caudate–globus pallidus–thalamus) + **serotonin** dysregulation; co-aggregates with **Tourette's**.
- ▶ **SSRIs first-line** (higher doses, 8–12 week trials); **clomipramine** second-line (keep level <500 ng/mL); only **50–60%** respond to drugs alone.
- ▶ **ERP** is the core psychotherapy; **drug + ERP** beats either alone.
- ▶ Refractory ladder: augmentation $\rightarrow$ **rTMS (FDA-approved)** $\rightarrow$ **DBS (VC/VS, HDE)** / ablative psychosurgery (cingulotomy, capsulotomy).
- ▶ Up to **30%** have a comorbid tic disorder; MDD develops in **~two-thirds**; significant **suicide risk**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Psychiatric Disorders” (OCD clinical features, neuroanatomy, drug doses, treatment-resistance and neuromodulation).
- ▶ **DSM-5-TR (American Psychiatric Association)** — “Obsessive-Compulsive Disorder” (diagnostic criteria, specifiers, symptom dimensions, epidemiology, course, risk factors, suicide, comorbidity, differential diagnosis).
- ▶ **Kaplan & Sadock's Comprehensive Psychiatry, 2024** — psychiatric neurosurgery for intractable OCD (Y-BOCS thresholds, anterior cingulotomy, anterior/gamma ventral capsulotomy, subcaudate tractotomy, DBS at VC/VS) and PANDAS.
- ▶ **CMDT 2026** — “Psychiatric Disorders” (current pharmacologic/behavioural management, augmentation agents, rTMS, DBS, prognosis).

Coverage note: Harrison 22e covers OCD only briefly; depth here (DSM-5-TR criteria/specifiers, surgical targets, augmentation regimens) is drawn from the dedicated psychiatric texts and CMDT as directed by the grounding hierarchy.



Personality disorders

Asked in: Paper IV 17 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Personality disorders (PDs) are **characteristic patterns of thinking, feeling and interpersonal behaviour that are relatively inflexible**, deviate markedly from the expectations of the individual's culture, and cause **significant functional impairment or subjective distress**. The behaviours are not secondary to another mental disorder, substance use or a general medical condition — an important distinction, because *personality change may be the first sign of serious neurologic, endocrine or other medical illness* (e.g., frontal-lobe tumour). PDs occur in **10–20% of the general population and in about half of psychiatric in-/out-patients**, where they constitute the prototypical “difficult patient”.

General diagnostic criteria (DSM-5-TR)

- ▶ **Criterion A** — an *enduring pattern* of inner experience and behaviour deviating markedly from cultural expectations, manifest in **two or more of: cognition, affectivity, interpersonal functioning, impulse control**.
- ▶ **Criterion B** — the pattern is **inflexible and pervasive** across a broad range of personal and social situations.
- ▶ **Criterion C** — leads to **clinically significant distress or impairment** (social, occupational or other functioning).
- ▶ **Criterion D** — **stable and of long duration**; onset traceable at least to **adolescence or early adulthood**.
- ▶ **Criteria E and F** — not better explained by another mental disorder, a substance or another medical condition (e.g., head trauma).
- ▶ **Diagnosis before age 18 years** requires the features to be present for **at least 1 year**; the single exception is **antisocial PD, which cannot be diagnosed below 18 years**.
- ▶ Traits are typically **egosyntonic** (perceived as appropriate by the patient) and **alloplastic** (blame is externalised); avoidant and dependent PD are relatively egodystonic. Collateral information and cultural/gender context are essential.

Classification — DSM-5-TR clusters and dimensional models

Cluster	Disorders	Shared descriptor	Temperament correlate (Cloninger)
A — odd, eccentric, aloof	Paranoid, Schizoid, Schizotypal	Emotional distance, restricted affect, social isolation	Low reward dependence (detachment)
B — dramatic, erratic, impulsive	Antisocial, Borderline, Histrionic, Narcissistic	Impulsive, excessively emotional behaviour	High novelty seeking (impulsivity)
C — anxious, fearful	Avoidant, Dependent, Obsessive-compulsive	Enduring anxiety and fear	High harm avoidance (OCPD: high persistence)

- Cluster boundaries are **overlapping and partly artificial**; many patients meet criteria for more than one PD, and comorbid major mental disorder risk is increased. All PDs share **low self-directedness and low cooperativeness**.
- DSM-5-TR also recognises **personality change due to another medical condition** (labile, disinhibited, aggressive, apathetic, paranoid, combined subtypes) and **other specified / unspecified PD** (mixed, passive-aggressive, depressive presentations).
- Alternative DSM-5 model (Section III) — hybrid dimensional–categorical**: **Criterion A** = moderate or greater impairment on the **Level of Personality Functioning Scale** (self = *identity, self-direction*; interpersonal = *empathy, intimacy*; levels 0–4); **Criterion B** = pathological traits in **five domains — Negative Affectivity, Detachment, Antagonism, Disinhibition, Psychoticism** (25 facets). It retains six disorders (antisocial, avoidant, borderline, narcissistic, obsessive-compulsive, schizotypal) plus **PD–trait specified**.
- ICD-11 (WHO, 2019) — abolishes categorical subtypes**: PD is rated first by **severity (mild / moderate / severe)** based on self and interpersonal dysfunction (with a *late-onset* qualifier when no manifestations exist before age 25), then qualified by **five trait domains — negative affectivity, detachment, dissociality, disinhibition, anankastia — plus a “borderline pattern” specifier**.

Aetiology and pathophysiology

- Genetic contribution**: one study of 106,000 subjects identified **nine loci** significantly linked to aspects of neuroticism (Harrison); genetics explains roughly **half of the variance** in temperament traits.
- Cluster A disorders** aggregate in families of probands with **schizophrenia and delusional disorder** (schizotypal PD shows smooth-pursuit eye-movement abnormalities, a putative schizophrenia-vulnerability marker).

- ▶ **Antisocial PD:** adoption studies show genetic + environmental contributions; **conduct disorder before age 10 plus ADHD**, erratic parenting and neglect increase adult risk; familial co-transmission with substance use and somatisation disorder.
- ▶ **Borderline PD:** a *tripartite model* — **childhood trauma** (physical/sexual abuse, neglect, early parental loss), **vulnerable temperament**, **triggering events**; **five times more common among first-degree relatives of probands**.
- ▶ Antisocial–narcissistic–histrionic form a familial “**spectrum**” of increasing severity (manipulation → exploitation → violent/property crime) driven by impulsive-aggressive traits.

Clinical features of the individual disorders

Disorder	Hallmark (key criteria)	Epidemiology / pearls
Paranoid	Pervasive distrust and suspiciousness — bears grudges, doubts loyalty/fidelity, reads hidden demeaning meanings (≥ 4 features)	0.5–4.4%; more in males; may precede delusional disorder; brief reactive psychosis under stress
Schizoid	Social detachment + restricted affect — “loner”, anhedonia, indifferent to praise or criticism, no desire for relationships (≥ 4)	3.1–4.9%; more in males; solitary work may suit them
Schizotypal	Ideas of reference, magical thinking , unusual perceptions, odd speech/affect, social anxiety that does not diminish with familiarity (≥ 5)	3.9–4.6%; transient psychotic episodes; >50% have lifetime major depression; familial link to schizophrenia
Antisocial	Disregard for/violation of others’ rights since age 15 — deceit, impulsivity, aggression, recklessness, irresponsibility, lack of remorse (≥ 3); requires age ≥ 18 + conduct disorder before 15	3% men, 1% women (3:1); flagrant behaviour “burns out” after age 30; <i>psychopathy</i> variant = low anxiety + bold dominance
Borderline	Instability of affect, self-image and relationships + marked impulsivity — frantic avoidance of abandonment, idealisation–devaluation , identity disturbance, self-damaging impulsivity, recurrent suicidal/self-mutilating behaviour , chronic emptiness, intense anger, stress-related paranoid/dissociative symptoms (≥ 5 of 9)	~2% general, 10% of outpatients, 20% of inpatients; 75% female; defence = splitting ; up to 80% of hospitalised patients attempt suicide; completed suicide up to 5% (CMDT)

Disorder	Hallmark (key criteria)	Epidemiology / pearls
Histrionic	Excessive emotionality and attention seeking — seductiveness, shallow rapidly shifting emotions, suggestibility, impressionistic speech , theatricality (≥ 5)	~2%; suicidal <i>gestures</i> to coerce caregiving; comorbid somatisation/conversion
Narcissistic	Grandiosity, need for admiration, lack of empathy — entitlement, exploitativeness, chronic envy, arrogance (≥ 5)	<1% general, 2–16% clinical; 50–75% male; fragile self-esteem with rage/depression after criticism
Avoidant	Hypersensitivity to negative evaluation, social inhibition, feelings of inadequacy — but craves relationships (vs schizoid) (≥ 4)	0.5–2%; overlaps with generalised social phobia
Dependent	Excessive need to be taken care of — clinging, submissive, cannot decide alone, fears separation, urgently seeks replacement relationships (≥ 5)	0.5–0.6%; predisposed by chronic physical illness, separation anxiety
Obsessive-compulsive (anankastic)	Preoccupation with orderliness, perfectionism and control — rules/lists, workaholism, hypermorality, inability to discard objects, stinginess, rigidity (≥ 4)	2–8%; twice as common in males ; <i>no true obsessions/compulsions</i> (unlike OCD); type-A features

Differential diagnosis and assessment

- ▶ Exclude **another medical condition** (frontal-lobe tumour, temporal-lobe epilepsy, head trauma, hyperthyroidism), **substance use** and episodes of another mental disorder; *new personality change in middle/late life mandates organic work-up*.
- ▶ **Cluster A vs psychotic disorders** — PDs lack sustained delusions/hallucinations; schizophrenia preceded by schizotypal/schizoid traits is coded “premorbid”.
- ▶ **Borderline vs mood disorders** — abandonment fears, identity disturbance, emptiness and idealisation–devaluation favour borderline; bipolar/cyclothymia are episodic.
- ▶ Classic differentials: **avoidant vs social phobia**, **OCPD vs OCD**, **antisocial vs adult antisocial behaviour** (no enduring personality pathology).
- ▶ Patients commonly present with **anxiety, depression or psychotic decompensation when coping fails** (CMDT) — the underlying PD is easily missed.

Management

- ▶ **Hospitalisation** only for serious suicidal or homicidal danger; otherwise day-hospital, halfway-house or therapeutic-community settings (CMDT).
- ▶ **Psychotherapy is the mainstay**, proceeding in stages: crisis management and stabilisation → positive perspective/therapeutic alliance → growth in self-awareness and integration (Kaplan).
- ▶ **Dialectical behaviour therapy (DBT)** — individual + group programme blending **mindfulness with a cognitive-behavioural model**, designed for **chronic suicidality / borderline PD**; efficacy shown in several **randomised trials** (Harrison, CMDT).
- ▶ Other modalities: **mentalization-based treatment**, **transference-focused psychotherapy**, **schema-focused therapy**, psychodynamic, CBT and group therapy; the therapist must manage **negative countertransference** and maintain boundaries.
- ▶ **Pharmacotherapy is adjunctive, symptom-domain-targeted** (evidence limited; use temporarily and taper):

Target symptom domain	First-line drugs	Notes
Mood dysregulation / anxiety	SSRIs/SNRIs; lithium, lamotrigine or valproate for emotional lability; MAOIs for atypical depression/rejection hypersensitivity	TCAs risky in overdose and may worsen atypical depression; avoid long-term benzodiazepines (dependence)
Impulsive (affective) aggression	Lithium (multiple double-blind trials), SSRIs (fluoxetine 20–60 mg/day; sertraline 50–200 mg/day), anticonvulsants — carbamazepine 400–800 mg/day, valproate 500–2000 mg/day, lamotrigine 50–200 mg/day	No effective drug for predatory (planned) aggression ; benzodiazepines disinhibit violence
Social–emotional detachment (cluster A)	Low-dose second-generation antipsychotics ; antidepressants if underlying depression	May reduce social withdrawal in “aloof” PDs
Cognitive–perceptual distortions / brief psychosis	Low-dose atypical antipsychotics (e.g., risperidone 0.5–2 mg/day, olanzapine 2.5–10 mg/day, quetiapine) only for symptom duration	Schizotypal patients often improve with antipsychotics

- ▶ Cluster-wise rule of thumb (Harrison): **cluster A** — antidepressants ± low-dose antipsychotics; **cluster B** — anticonvulsant mood stabilisers and MAOIs for mood reactivity, behavioural dyscontrol and rejection hypersensitivity; **cluster C** — drugs used for anxiety disorders (SSRIs).
- ▶ **Neuromodulation** — growing evidence for **transcranial magnetic stimulation** for borderline mood dysregulation and impulsivity (CMDT 2026).

- ▶ **Prognosis** — borderline and antisocial PD attenuate with age (borderline stabilises in the 4th–5th decades); obsessive-compulsive and schizotypal PD persist; **antisocial and narcissistic PD have a guarded prognosis** (limited engagement in therapy).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — DSM-5-TR cluster wheel:** three sectors around a central circle labelled “General criteria: enduring, pervasive, inflexible, early-onset pattern → distress/impairment”. Sector labels: **Cluster A (odd–eccentric): Paranoid, Schizoid, Schizotypal — low reward dependence; Cluster B (dramatic–erratic): Antisocial, Borderline, Histrionic, Narcissistic — high novelty seeking; Cluster C (anxious–fearful): Avoidant, Dependent, Obsessive-compulsive — high harm avoidance.**
- ▶ **Diagram 2 — ICD-11 two-step dimensional model:** horizontal severity arrow labelled *Mild PD* → *Moderate PD* → *Severe PD* (axis caption: “self + interpersonal dysfunction; harm to self/others”); below it five trait-qualifier boxes labelled **Negative affectivity, Detachment, Dissociality, Disinhibition, Anankastia**, plus flags **Borderline-pattern specifier** and “Late onset: no manifestations before age 25”.

Clinical / Diagnostic significance

- ▶ PD patients are demanding, non-adherent and boundary-testing; recognising the pattern prevents counter-therapeutic reactions (firm limits for borderline, non-confrontational clarity for paranoid patients).
- ▶ **Always exclude organic disease** in apparent personality change: frontal-lobe tumour, temporal-lobe epilepsy, head injury, thyroid disease and substance use can all masquerade as PD.
- ▶ **Borderline PD is a medical emergency risk** — recurrent self-harm, overdose risk (avoid TCAs), suicide in up to 5%; document risk assessment and use DBT-based crisis planning.
- ▶ Comorbidity is the rule: depression, anxiety, substance use, eating disorders (bulimia with borderline), somatisation (histrionic) — treat comorbid syndromes actively.
- ▶ PD predicts poorer outcomes of comorbid illness and heavy use of health, welfare and prison resources; OCPD traits correlate with type-A behaviour and myocardial infarction risk.

High-yield exam pointers

- ▶ **Three clusters:** A = odd/eccentric (paranoid, schizoid, schizotypal); B = dramatic/erratic (antisocial, borderline, histrionic, narcissistic); C = anxious/fearful (avoidant, dependent, obsessive-compulsive).
- ▶ General criteria: enduring, pervasive, inflexible pattern from adolescence/early adulthood causing distress/impairment; ≥2 of cognition, affectivity, interpersonal functioning, impulse control.

- ▶ **Antisocial PD:** only PD that cannot be diagnosed <18 years; requires conduct disorder before 15; M:F = 3:1; “burns out” after 30.
- ▶ **Borderline PD:** ≥5 of 9 criteria; splitting; 75% female; suicide up to 5%; **DBT is the best-evidenced treatment.**
- ▶ **Schizotypal vs schizoid:** schizotypal has magical thinking/perceptual distortions; schizoid is merely detached. **Avoidant vs schizoid:** avoidant *wants* relationships but fears rejection.
- ▶ **OCPD ≠ OCD** — no true obsessions/compulsions; egosyntonic; twice as common in males.
- ▶ Pharmacotherapy is symptom-targeted: SSRIs for mood/impulsivity, lithium/anticonvulsants for affective aggression, low-dose atypical antipsychotics for cognitive-perceptual symptoms; **benzodiazepines are generally avoided** (dependence, disinhibition).
- ▶ **ICD-11** has replaced categories with a severity rating (mild/moderate/severe) + five trait qualifiers + borderline-pattern specifier; the **DSM-5** alternative model uses the Level of Personality Functioning Scale + five trait domains.

SOURCE & COVERAGE

Harrison’s Principles of Internal Medicine, 22e — “Psychiatric Disorders” (Personality Disorders section); Kaplan & Sadock’s Comprehensive Textbook of Psychiatry — “Personality Disorders” chapter (Cloninger & Lester) and “The Classification of Mental Disorders in the International Classification of Diseases (ICD-11)”; DSM-5-TR — “Personality Disorders” and “Alternative DSM-5 Model for Personality Disorders”; CMDT 2026 — “Psychiatric Disorders” (Personality Disorders: classification, DBT, pharmacotherapy doses, TMS). *Coverage note:* Harrison 22e itself covers personality disorders only briefly (clusters, genetics, one treatment paragraph); the criteria-level detail, epidemiology and dimensional models above are drawn from Kaplan & Sadock and DSM-5-TR, with current management from CMDT 2026.



Post-traumatic stress disorder

Asked in: Paper IV Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Post-traumatic stress disorder (PTSD) is a chronic, often recurrent trauma- and stressor-related disorder that develops after exposure to an extreme traumatic event such as the threat of personal death or injury or the death of a loved one. It is characterised by intrusive re-experiencing of the trauma, persistent avoidance of reminders, negative alterations in cognition and mood, and heightened arousal, persisting for more than 1 month and causing significant distress or functional impairment. It lies on a continuum with **acute stress disorder** (a self-limited reaction occurring shortly after the trauma); when the reaction is delayed or recurrent it is termed PTSD.

Between **5 and 10%** of the population will satisfy criteria for PTSD at some point in life, with women affected more often than men.

Etiology, risk factors and epidemiology

- ▶ **Inciting event:** exposure to actual or threatened death, serious injury or sexual violence — directly experienced, witnessed, learned to have happened to a close relative/friend, or through repeated/extreme exposure to aversive details (e.g., first responders, police investigating child abuse).
- ▶ **Lifetime prevalence:** 5–10% of Americans; **women > men**.
- ▶ **Risk factors:** a past psychiatric history; personality traits of **high neuroticism and extroversion**; presence of peritraumatic dissociative symptoms and development of an acute stress disorder at the time of trauma (strongly predict later PTSD).
- ▶ **Genetics:** twin studies show a **substantial genetic influence** on all PTSD symptoms, with comparatively less evidence for an environmental effect.
- ▶ **Comorbidity:** patients are at high risk of other disorders related to **anxiety, mood, and substance abuse** (especially alcohol).

Clinical features

- ▶ **Re-experiencing / intrusion:** the trauma is typically re-experienced through intrusive thoughts, distressing dreams, or **flashbacks**, particularly when cues of the original event are present.
- ▶ **Avoidance:** patients actively avoid stimuli that precipitate recollections of the trauma.
- ▶ **Hyperarousal:** a resulting increase in **vigilance, arousal and exaggerated startle response**.
- ▶ **Emotional numbing / dissociation:** associated **detachment and loss of emotional responsivity**; the patient may feel *depersonalised* and may be unable to recall specific aspects of the trauma.
- ▶ **Temporal pattern:** reaction may be acute (acute stress disorder) or delayed and recurrent (PTSD).
- ▶ **Screening:** a validated four-item screen, the **PC-PTSD** (Primary Care PTSD screen), is available for case-finding in primary care.

DSM-5-TR diagnostic criteria (Table 463-6) — symptom clusters

PTSD is diagnosed using the DSM-5-TR. Criteria A–H must be satisfied (criteria for adults and children >6 years summarised below).

Criterion	Requirement	Representative features
A — Stressor	Exposure to actual/threatened death, serious injury or sexual violence	Direct experience; witnessing in person; learning it occurred to a close relative/friend (violent or accidental); repeated/extreme

Criterion	Requirement	Representative features
		exposure to aversive details (work-related)
B — Intrusion (≥ 1)	Re-experiencing	Intrusive distressing memories; recurrent distressing dreams; dissociative flashbacks ; intense distress at cues; marked physiological reactions to cues
C — Avoidance (one or both)	Persistent avoidance	Avoidance of distressing memories/thoughts/feelings; avoidance of external reminders (people, places, conversations, objects, situations)
D — Negative cognition/mood (≥ 2)	Worsening after trauma	Inability to recall an important aspect (dissociative amnesia); exaggerated negative beliefs about self/others/world; distorted self-blame; persistent negative emotional state (fear, horror, anger, guilt, shame); diminished interest; detachment/estrangement; inability to feel positive emotions
E — Arousal/reactivity (≥ 2)	Worsening after trauma	Irritability/angry outbursts; reckless or self-destructive behaviour; hypervigilance ; exaggerated startle; impaired concentration; sleep disturbance
F — Duration	> 1 month (criteria B, C, D and E)	—
G — Distress	Clinically significant distress or impairment	Social, occupational or other important domains
H — Exclusion	Not due to a substance or another medical condition	—

- Specify “With dissociative symptoms”: persistent/recurrent **depersonalisation** (detachment, as an outside observer of oneself) and/or **derealisation** (unreality of surroundings), not attributable to a substance or condition such as complex partial seizures.
- Specify “With delayed expression”: full criteria not met until ≥ 6 months after the event (some symptoms may begin immediately).
- In children ≤ 6 years, modified criteria apply — intrusion may manifest as **trauma-specific reenactment in play**, dreams may lack recognisable content, and avoidance/negative-mood items are combined into a single cluster.

Pathophysiology

- ▶ It is hypothesised that PTSD involves **excessive release of norepinephrine** from the **locus coeruleus** in response to stress, with **increased noradrenergic activity** at **projection sites** in the **hippocampus and amygdala** — theoretically facilitating the **encoding of fear-based memories**.
- ▶ **Greater sympathetic responses** occur to trauma-associated cues, whereas **pituitary-adrenal responses are blunted**.
- ▶ Beyond fear learning, documented changes include altered **threat detection (insula overactivity)**, executive dysfunction, impaired **emotional regulation**, and disturbed **contextual learning**.
- ▶ Candidate **predictive biomarkers**: increased heart rate and serum lactate, decreased coagulation, insulin resistance, and alterations in glycolysis and fatty-acid uptake.

Treatment / Management

General principles: acute stress reactions are usually self-limited; chronic, recurrent PTSD requires a combined drug-plus-behavioural approach. **Benzodiazepines and SSRIs should NOT be given in the early aftermath of trauma**, and routine **debriefing does not prevent PTSD and may exacerbate symptoms**. Attempts to prevent/ameliorate PTSD in the acute period (escitalopram, hydrocortisone, intranasal oxytocin) have proven **equivocal**.

Modality	Agents / methods	Notes
Acute stress reaction	Short-term benzodiazepines + supportive/expressive psychotherapy	Self-limited; benzodiazepines avoided in early post-trauma period for PTSD prevention
First-line drugs (PTSD)	SSRIs — paroxetine and sertraline (FDA-approved for PTSD)	Reduce anxiety, intrusion and avoidance
Other useful drugs	Venlafaxine , fluoxetine , topiramate	Reduce anxiety, intrusion symptoms and avoidance behaviours
For insomnia	Low-dose trazodone , mirtazapine (sedating antidepressants)	Given at night
Emerging adjuncts	MDMA as adjunct to intensive psychotherapy; stellate ganglion block	MDMA demonstrated efficacy as a psychotherapy adjunct
Psychotherapy (most effective)	Trauma-focused cognitive-behavioural therapy ; eye-movement desensitisation and reprocessing (EMDR) ; prolonged exposure therapy (augmented / virtual reality)	Dismantle avoidance via stepwise focusing on the traumatic experience; help master fear of recurrence

Modality	Agents / methods	Notes
DIAGRAMS TO DRAW — IMAGE SUGGESTIONS		
▶ PTSD symptom-cluster wheel / box diagram — a central box labelled “<i>Traumatic event (Criterion A)</i>” with four radiating clusters labelled: (1) Intrusion / re-experiencing (B) — flashbacks, nightmares, intrusive memories; (2) Avoidance (C) — of thoughts and external reminders; (3) Negative cognition & mood (D) — guilt, detachment, negative beliefs, amnesia; (4) Hyperarousal/reactivity (E) — hypervigilance, startle, irritability, insomnia. Annotate “Duration >1 month (F)”. ▶ Neurobiology schematic — label: <i>Locus coeruleus</i> → <i>excess norepinephrine</i>; <i>Amygdala</i> (<i>fear encoding, ↑</i>); <i>Hippocampus</i> (<i>memory</i>); <i>Insula</i> (<i>threat detection, overactive</i>); <i>Prefrontal cortex</i> (<i>impaired emotional regulation</i>); <i>Blunted HPA / pituitary-adrenal axis</i>.		

Clinical / Diagnostic significance

- ▶ **Recognise referral triggers:** PTSD symptoms, like psychosis, mania, severe depression and suicidal/homicidal preoccupation, warrant psychiatric consultation or transfer of care.
- ▶ **Screen in primary care** using the four-item PC-PTSD, especially after trauma, assault, disaster, combat or serious illness.
- ▶ **Differentiate from acute stress disorder** (same symptoms but earlier onset and self-limited; PTSD requires duration >1 month) and from **adjustment, panic, phobic and depressive disorders**.
- ▶ **Co-manage comorbidities** — alcohol/substance misuse, depression and other anxiety disorders are frequent and worsen prognosis.
- ▶ **Avoid harm:** do not start SSRIs/benzodiazepines in the immediate post-trauma window, and avoid single-session debriefing.
- ▶ **Set expectations:** medication relapse rates are high if used alone — combine pharmacotherapy with trauma-focused psychotherapy for durable response.

High-yield exam pointers

- ▶ PTSD = trauma-related disorder with **four symptom clusters (B–E)** persisting **>1 month**; <1 month with prominent dissociation = acute stress disorder.
- ▶ **Lifetime prevalence 5–10%; women > men**; validated PC-PTSD four-item screen.
- ▶ **Risk factors:** prior psychiatric history, high neuroticism/extroversion, peritraumatic dissociation; **strong genetic (twin-study) contribution**.
- ▶ **Core neurobiology:** ↑ norepinephrine from **locus coeruleus**, ↑ noradrenergic drive to **amygdala & hippocampus** → fear-memory encoding; **blunted HPA axis**; insula overactivity.

- ▶ **FDA-approved drugs:** paroxetine and sertraline (SSRIs). Also venlafaxine, fluoxetine, topiramate.
- ▶ **Most effective psychotherapies:** trauma-focused CBT, EMDR, prolonged exposure therapy.
- ▶ **Pitfalls:** do NOT give benzodiazepines/SSRIs in the early aftermath; **debriefing does not prevent PTSD and may worsen it.**
- ▶ **Specifiers:** *with dissociative symptoms* (depersonalisation/derealisation); *with delayed expression* (criteria met ≥ 6 months later).
- ▶ Emerging adjuncts: **MDMA-assisted psychotherapy** and **stellate ganglion block**; trazodone/mirtazapine for insomnia.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 463 "Psychiatric Disorders" (Stress Disorders section, Table 463-6 DSM-5-TR criteria, Etiology/Pathophysiology and Treatment of Stress Disorders). Coverage note: the chapter covers PTSD comprehensively for an MD-level answer; DSM-5-TR criteria are reproduced from Table 463-6. The PC-PTSD acronym expansion ("Primary Care PTSD screen") and the standard cluster-count phrasing are universally accepted additions; all drug names, doses-where-stated, FDA approvals, and neurobiological mechanisms are faithful to the source text.



Psoriasis and its complications

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — Psoriasis is a common, chronic, immune-mediated, genetically determined inflammatory skin disease characterised by sharply demarcated, erythematous plaques surmounted by silvery (*micaceous*) scale, affecting up to ~2% of the world population. It is best understood as a **systemic inflammatory disorder**: the IL-23/IL-17 (Th17) axis drives keratinocyte hyperproliferation in skin while the same inflammation underpins articular, metabolic and cardiovascular *complications* — most importantly **psoriatic arthritis (PsA)** and **metabolic syndrome**. There is a fundamental division into **plaque (non-pustular)** and **pustular** forms.

Epidemiology, aetiopathogenesis and genetics

- ▶ **Bimodal onset (Type I / Type II):** Type I — early onset (peak 16–22 yr), strong family history, **HLA-C*06:02*-associated, more severe*; Type II — late onset (peak 57–62 yr), *sporadic, HLA-C*06:02-unrelated*, generally milder.
- ▶ **Genetics:** lifetime risk 4% / 28% / 65% with neither / one / both parents affected; monozygotic twin concordance gives heritability ~60–90%. Polygenic/multifactorial with >65 susceptibility loci.

- **PSORS1** (chromosome 6p, MHC class I) — the major determinant; consensus risk allele *HLA-C*06:02**.
- **PSORS2 = CARD14** — gain-of-function mutations enhance NF-κB signalling in keratinocytes.
- **IL36RN** loss-of-function (deficiency of IL-36 receptor antagonist) and **AP1S3** — drive **generalised pustular psoriasis**.
- ▶ **Pathogenesis:** plasmacytoid dendritic cells/neutrophils release **NETs** and the cathelicidin peptide **LL37**, which (with self-DNA) triggers IFN-α; myeloid dendritic cells secrete **IL-12 (→Th1)** and **IL-23 (→Th17)**; **IL-17A/IL-17F**, **TNF-α**, **IL-22** drive keratinocyte hyperproliferation and self-amplifying loops via **JAK-STAT** and **NF-κB** — the rationale for all modern targeted therapy.
- ▶ **Triggers / exacerbating factors:** streptococcal pharyngitis (guttate), HIV, **Koebner (isomorphic) phenomenon** (cutaneous trauma, *Heinrich Köbner 1877*), drugs (**lithium**, antimalarials, beta-blockers, **TNF-α inhibitors** [paradoxical], **interferon-α**, **NSAIDs**, **ACE inhibitors**), withdrawal of systemic/potent topical corticosteroids, smoking, alcohol, obesity, psychological stress.

Clinical variants and diagnostic signs

Variant	Key features
Chronic plaque (vulgaris)	Commonest (~80–90%); symmetric well-demarcated plaques on elbows, knees, scalp, sacrum, extensors
Guttate (eruptive)	Shower of 2–10 mm “drop-like” papules in children/young adults, ~2 weeks after group A streptococcal pharyngitis
Inverse (flexural)	Glazed, scale-poor plaques in axillae, groin, submammary, natal cleft, umbilicus; obesity-associated
Erythrodermic	>90% body surface; <i>complication</i> — skin failure (see below)
Pustular	Localised palmoplantar pustulosis, or generalised (von Zumbusch)
Nail	Pitting (~1 mm), subungual “ oil-drop ”/ salmon patch (highly specific), subungual hyperkeratosis, splinter haemorrhages, distal onycholysis
Scalp / seborrheic dermatitis	Often first site; pityriasis amiantacea

- ▶ **Diagnostic signs:** *Auspitz sign* (pinpoint bleeding on scale removal from thin suprapapillary epidermis), *ring/halo of Woronoff* (pale rim around resolving plaque), *Koebner phenomenon*; geographic & fissured tongue associations.

Histopathology

- ▶ **Confluent parakeratosis** with focal orthokeratosis and near-absence of the granular layer.
- ▶ **Regular epidermal hyperplasia** with elongated, clubbed/fused rete ridges and **suprapapillary thinning**.
- ▶ **Munro microabscesses** — neutrophils in the (para)keratotic stratum corneum.
- ▶ **Spongiform pustule of Kogoj** — neutrophils within the stratum spinosum (prominent in pustular forms).
- ▶ Dilated, tortuous papillary capillaries (correlate of the Auspitz sign).

Complications and co-morbidities

Psoriasis (especially severe disease) carries excess morbidity and mortality across most organ systems; **severe disease shortens life expectancy by ~4–6 years**, chiefly from cardiovascular death.

A. Psoriatic arthritis (PsA) — the principal articular complication, a **seronegative spondyloarthritis** occurring in up to ~30–40% of patients; skin precedes joints in ~70%. **Five patterns (Moll & Wright)**: asymmetric mono-/oligoarthritis (classically regarded as commonest), symmetric “rheumatoid-like” polyarthritis (~50% in Harrison), **distal interphalangeal-predominant** (distinguishes from RA), **arthritis mutilans** (rare, deforming “telescoping” digits), and **axial disease/spondylitis** (HLA-B27-linked). Hallmarks: **dactylitis** (“sausage digit”), **enthesitis** (Achilles, plantar fascia), nail disease (~80%). Diagnosis by **CASPAR criteria** (≥ 3 points; sensitivity 99%, specificity 91%):

CASPAR category	Points
Current psoriasis (2) / personal history (1) / family history 1st–2nd degree relative (1)	2 / 1 / 1
Typical psoriatic nail involvement	1
Negative rheumatoid factor	1
Current or past dactylitis	1
Radiographic juxta-articular new bone formation (hands/feet)	1

B. Acute dermatological emergencies (skin failure):

- ▶ **Erythrodermic psoriasis** (1–2% of patients; underlies ~25% of all erythroderma) — sepsis, hypothermia/hyperthermia, hypoalbuminaemia, anaemia, dehydration, high-output cardiac failure.
- ▶ **Generalised pustular psoriasis (von Zumbusch)** — fever, sheets of sterile pustules (“lakes of pus”), leucocytosis; complications: **acute kidney injury**, hypoalbuminaemia with hypocalcaemia, neutrophilic cholangitis / cholestatic jaundice, ARDS (aseptic pneumonitis),

telogen effluvium, amyloidosis; mortality 2–16%. GPP confined to pregnancy = **impetigo herpetiformis** (last trimester; placental insufficiency, stillbirth).

C. Systemic co-morbidities (Box 35.2):

- ▶ **Metabolic syndrome** (prevalence ~34% vs 26%) — obesity (strongest, often predates psoriasis), hypertension, hyperlipidaemia, type 2 diabetes.
- ▶ **Cardiovascular disease** — myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation, venous thromboembolism (risk greatest in young, severe disease/PsA).
- ▶ **Other immune-mediated disease** — Crohn's disease, ulcerative colitis, coeliac disease, **uveitis**.
- ▶ **Hepatobiliary** — **non-alcoholic fatty liver disease (up to 50%)**, alcoholic liver disease.
- ▶ **Malignancy** — non-melanoma skin cancer (esp. post-PUVA), Hodgkin lymphoma.
- ▶ **Psychiatric** — depression, anxiety, increased suicidality; alcohol misuse.
- ▶ **Miscellaneous** — hyperuricaemia/gout, secondary (AA) amyloidosis, IgA nephropathy (rare).

Management

- ▶ **Assess severity** with the **PASI (Psoriasis Area and Severity Index, 0–72)** grading erythema, scaling and induration over four regions, $\pm$ **BSA** and **DLQI**; “candidate for systemic therapy” $\approx$ **BSA $\geq 10\%$** , high-impact sites, or topical failure. Screen at every visit for **PsA, metabolic syndrome and depression**.
- ▶ **Topical (limited disease)**: mid-/high-potency corticosteroids; **vitamin D analogues** (calcipotriene 0.005% [max 100 g/wk], calcitriol 0.003% [max 200 g/wk] — hypercalcaemia risk); tazarotene; coal tar, salicylic acid, dithranol; **calcineurin inhibitors** (tacrolimus/pimecrolimus) for face/flexures; newer **roflumilast (PDE-4)** and **tapinarof (AhR agonist)** creams.
- ▶ **Phototherapy (moderate/widespread)**: **narrowband UVB** (first-line, 3 $\times$ /week) and **PUVA**; avoid with ciclosporin and in the immunosuppressed (skin-cancer risk).
- ▶ **Conventional systemics**: **methotrexate** (≤ 25 mg weekly + folic acid 1–2 mg/day; cumulative 3.5–4 g $\rightarrow$ hepatology); **acitretin** (0.5–0.75 mg/kg/day; teratogen — avoid pregnancy 3 yr; best for pustular); **ciclosporin** (≤ 5 mg/kg/day; rebound on stopping); **apremilast (PDE-4)**; **deucravacitinib (oral TYK2 inhibitor)**.
- ▶ **Biologics**: anti-TNF- α (etanercept, adalimumab, infliximab, certolizumab, golimumab); **anti-IL-12/23 ustekinumab**; **anti-IL-23p19** (guselkumab, risankizumab, tildrakizumab); **anti-IL-17** (secukinumab, ixekizumab, brodalumab, bimekizumab); **anti-IL-36R spesolimab** for GPP. Screen for TB, HIV, hepatitis B/C before starting; TNF inhibitors with caution in CHF.
- ▶ **Avoid systemic (oral) corticosteroids** — withdrawal precipitates life-threatening pustular/erythrodermic flares. Weight loss improves both disease and response.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled cross-section of a psoriatic plaque (histology):** label *parakeratosis*, *Munro microabscess* (*neutrophils in stratum corneum*), *Kogoj spongiform pustule* (*stratum spinosum*), *absent/diminished granular layer*, *acanthosis with elongated regular rete ridges*, *suprapapillary thinning*, *dilated tortuous papillary capillary*, *dermal lymphocytic infiltrate*.
- ▶ **IL-23/IL-17 immunopathogenesis schematic:** label *plasmacytoid DC* → *IFN- α* , *myeloid DC* → *IL-12 (Th1)* and *IL-23 (Th17)*, *Th17* → *IL-17A/IL-17F*, *IL-22*, *TNF- α* , *keratinocyte hyperproliferation* — with arrows showing biologic drug targets (*anti-TNF*, *anti-IL-12/23*, *anti-IL-23*, *anti-IL-17*, *TYK2/JAK*).

Clinical / Diagnostic significance

- ▶ Diagnosis is **clinical**; biopsy reserved for atypical cases. No constant laboratory abnormality; **hs-CRP/ESR** rise in PsA and GPP. KOH/fungal culture distinguishes nail/flexural psoriasis from onychomycosis and candidiasis.
- ▶ **Differential diagnosis:** seborrheic dermatitis, eczema, lichen planus, pityriasis rosea, pityriasis rubra pilaris, secondary syphilis, mycosis fungoides, tinea, discoid lupus; severe/atypical/treatment-resistant psoriasis should prompt **HIV testing**.
- ▶ Recognise **erythrodermic and von Zumbusch GPP as emergencies** needing fluid/electrolyte support, temperature control and rapid systemic therapy (infliximab for severe flares; spesolimab for GPP).
- ▶ Treat psoriasis as a **systemic disease** — proactively screen and manage cardiometabolic risk, PsA (early referral prevents irreversible joint destruction) and mood disorder.

High-yield exam pointers

- ▶ **IL-23/IL-17 (Th17) axis** is central; **HLA-C*06:02 / PSORS1* is the **major genetic determinant**; *CARD14* and *IL36RN*** drive familial/pustular disease.
- ▶ **Auspitz sign**, **Woronoff ring**, **Koebner phenomenon** — classic triad of signs; nail “**oil-drop**” sign is highly specific.
- ▶ Histology: **Munro microabscess** (stratum corneum) vs **Kogoj spongiform pustule** (stratum spinosum); parakeratosis + suprapapillary thinning.
- ▶ **Guttate** follows streptococcal pharyngitis; **inverse** is scale-poor and flexural; **von Zumbusch** is febrile generalised pustular psoriasis.
- ▶ **PsA** = seronegative spondyloarthritis; **5 Moll & Wright patterns**; diagnose by **CASPAR** (≥ 3 points); DIP involvement, dactylitis and enthesitis distinguish from RA.
- ▶ **Complications:** PsA, metabolic syndrome, MI/stroke, NAFLD, lymphoma/NMSC, depression, amyloidosis; severe disease shortens life by ~4–6 years.

- ▶ **Never give systemic steroids** (rebound pustular psoriasis); first-line widespread therapy = **NB-UVB**; **methotrexate** is the workhorse systemic, especially with PsA.
- ▶ Screen for **TB/HIV/hepatitis B & C** before biologics; **TNF inhibitors** can paradoxically induce psoriasis and worsen CHF.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders” (clinical types, FDA-approved systemic and biologic therapy tables, PsA subtypes).
- ▶ **Rook's Textbook of Dermatology, 10e** — “Psoriasis and Related Disorders” (epidemiology, Type I/II, genetics PSORS1/HLA-C*06:02/CARD14/IL36RN, IL-23/IL-17 pathogenesis, histopathology, clinical variants, PASI, Box 35.2 co-morbidities, von Zumbusch GPP, impetigo herpetiformis, PsA with Moll & Wright and CASPAR criteria).
- ▶ **CMDT 2026** — “Dermatologic Disorders: Psoriasis” (current management, drug doses: calcipotriene/calcitriol ceilings, methotrexate, acitretin, etanercept, deucravacitinib, spesolimab).



Psoriasis cutaneous and extra cutaneous manifestations

Asked in: Paper IV Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Psoriasis is one of the commonest dermatologic diseases, affecting up to **2% of the world's population**. It is a chronic, **immune-mediated** disorder clinically characterised by **erythematous, sharply demarcated papules and rounded plaques covered by silvery micaceous scale**, which are variably pruritic. It is now best regarded as a **systemic “psoriatic disease”**: beyond the skin and nails it carries musculoskeletal (psoriatic arthritis), ocular, gastrointestinal, cardiometabolic and psychiatric burden. Skin lesions contain infiltrates of **activated T cells** that elaborate cytokines driving **keratinocyte hyperproliferation**, with a strong genetic predisposition (positive family history in **30–50%**).

Pathogenesis (in brief)

- ▶ T-cell-mediated disorder; activated T cells release proinflammatory cytokines → keratinocyte hyperproliferation → characteristic plaques and scale.
- ▶ The **IL-23/IL-17 axis** is central — explaining why agents targeting IL-23, IL-12/23, IL-17 and TNF-α are highly effective.
- ▶ **Strong genetic component**: 30–50% report a positive family history; the spondyloarthritis literature links psoriatic disease to ***HLA-B27*** (positive in ~20% of all PsA and ~50% of axial PsA).

- ▶ **Koebner (isomorphic) phenomenon** — traumatised skin develops new lesions.
- ▶ **Exacerbating factors:** infections (streptococcal), psychological stress, and drugs — **lithium, beta blockers, antimalarials**; systemic glucocorticoid withdrawal can precipitate pustular flares.

Cutaneous manifestations — morphology

- ▶ **Primary lesion:** sharply demarcated, erythematous plaque with a loosely adherent **silvery (micaceous) scale**; predominantly over **extensor surfaces** — **elbows, knees, gluteal cleft and scalp**, with a tendency to **symmetry**.
- ▶ Course is typically **indolent and chronic**; plaque psoriasis develops slowly and **rarely remits spontaneously**.
- ▶ **Auspitz sign** (pinpoint bleeding on removal of scale, reflecting dermal vascular proliferation) and **Munro microabscesses** on histology are classic features (standard textbook; see Coverage note).
- ▶ **Histology** (Table 60-2): **acanthosis with dermal vascular proliferation**.

Clinical variants of cutaneous psoriasis

Variant	Typical patient / trigger	Distinguishing features
Plaque-type (psoriasis vulgaris)	Commonest variety; adults	Stable, slowly enlarging plaques; elbows, knees, gluteal cleft, scalp; symmetric; indolent
Inverse (flexural) psoriasis	Intertriginous skin	Affects axillae, groin, submammary region, navel ; also scalp, palms, soles; sharply demarcated plaques that may be moist and without scale due to location
Guttate (eruptive) psoriasis	Children and young adults; often after URTI with β -hemolytic streptococci	Acute onset of many small erythematous, scaling papules ; DDX — pityriasis rosea, secondary syphilis
Pustular psoriasis	Localised (palms/soles) or generalised; triggers — local irritants, pregnancy, drugs, infection, systemic glucocorticoid withdrawal	Erythema studded with sterile pustules ; generalised form has fever (39–40°C) for several days , recurrent episodes; may become erythrodermic . Oral retinoids are treatment of choice (non-pregnant). Localised form mimics dyshidrotic eczema

Nail involvement

- ▶ **Fingernail involvement** may be the only clue when the skin presentation is atypical.

- ▶ **Nail matrix disease:** pitting (punctate), leukonychia, crumbling, and red spots in the lunula.
- ▶ **Nail bed disease:** onycholysis, subungual hyperkeratosis, oil-drop (salmon patch) change, and splinter haemorrhages; nail thickening.
- ▶ Nail disease is intimately linked to **DIP-joint** psoriatic arthritis (the nail bed is closely related to the DIP joint).
- ▶ Frequency: ~40% of psoriasis patients *without* arthritis have nail lesions, rising to ~90% in those with PsA — i.e., nail change is a strong marker of arthritis.

Extra-cutaneous manifestations

1. Psoriatic arthritis (PsA) — the major extra-cutaneous manifestation

- ▶ Affects **up to 30%** of psoriasis patients (range 6–42%); incidence ~3 per 100 patient-years, rising with severity of skin disease; onset usually 30–50 years.
- ▶ **Moll & Wright (1973)** definition: inflammatory arthritis (peripheral and/or sacroiliitis/spondylitis) **with cutaneous psoriasis** and **absence of RF**; described **five phenotypes** (below); enthesitis and dactylitis added later.
- ▶ Temporal pattern: **psoriasis precedes arthritis** in ~80%, simultaneous in ~10%, and **arthritis precedes skin disease** in ~10% (“psoriatic arthritis sine psoriasis”).
- ▶ Cardinal musculoskeletal features: **peripheral arthritis** (early oligoarticular/asymmetric → later polyarticular/symmetric), **DIP-joint involvement** (typical, linked to nail disease), **axial arthritis/spondylitis** (5% early, ~50% after 20 years), **dactylitis** (“sausage digit” — inflammatory swelling of an entire digit; marker of severity), **enthesitis** (commonest at plantar fascia and Achilles insertion on calcaneum), and **tenosynovitis**.

2. **Ocular** — **uveitis** in ~5% (commonly **unilateral acute anterior uveitis**; posterior/bilateral also reported); conjunctivitis rare.

3. **Gastrointestinal** — **inflammatory bowel disease** (Crohn’s disease, rarely ulcerative colitis) may coexist; mucous-membrane inflammation with painful mouth ulcers, rarely urethritis.

4. **Cardiometabolic / systemic** — increased risk of **metabolic syndrome** with raised cardiovascular morbidity and mortality. Patients with psoriasis + PsA have CV risk as **high as in diabetes mellitus**, independent of conventional risk factors, with more severe subclinical atherosclerosis; higher prevalence of **hypertension, type 2 diabetes, obesity, fatty liver, angina and MI**. Obesity worsens disease activity and treatment response. Malignancy is **not** increased.

5. **Psychiatric** — increased rates of **depression and suicidality**.

Psoriatic arthritis — phenotypes, criteria & imaging

Five clinical phenotypes (Moll & Wright)	Notes
Symmetric polyarticular (~50%)	Resembles rheumatoid arthritis

Five clinical phenotypes (Moll & Wright)	Notes
Asymmetric oligoarticular (~35%)	Any joint; “sausage digits”; early-stage pattern
Distal (DIP) arthritis (~5%)	Classic form; dystrophic nails, pitting
Spondylitis (axial) (~5%)	Inflammatory back/neck pain; sacroiliitis often unilateral
Arthritis mutilans (<5%)	Severe, deforming; small joints of hands/feet; end-stage with osteolysis

- ▶ **CASPAR criteria** (Table 374-6): in a patient with **inflammatory articular disease** (joint, spine or enthesal), need **≥3 points** from — current psoriasis (2) / personal or family history of psoriasis (1), typical **nail dystrophy** (1), **RF negative** (1), **dactylitis** (1), **juxta-articular new bone formation** on X-ray (1). **Specificity 98.7%, sensitivity 91.4%.**
- ▶ **Radiology:** marginal erosions with adjacent “fluffy” new bone formation (characteristic), “pencil-in-cup” deformity, bony ankylosis in a “ray” distribution, **acro-osteolysis**; **chunky nonmarginal syndesmophytes** and (usually unilateral) sacroiliitis. MRI/ultrasound detect synovitis, enthesitis and erosions earlier than X-ray.
- ▶ **Labs:** ESR/CRP raised in ~50%; **RF negative** (low-titre RF or anti-CCP in <10%); **HLA-B27** positive in ~20% (≈50% of axial PsA).

Management (overview)

- ▶ **Cutaneous, localised:** skin hydration; **mid-potency topical glucocorticoids** (limited by tachyphylaxis and atrophy); **vitamin D analogue** (calcipotriene) and **retinoid** (tazarotene) — have largely replaced coal tar, salicylic acid and anthralin.
- ▶ **Phototherapy** for widespread disease: **UV-B, narrowband UV-B, and PUVA** (UV-A + psoralens); mutagenic (skin-cancer risk); **contraindicated with cyclosporine** and in the immunocompromised.
- ▶ **Systemic agents** (Table 60-3): **methotrexate** (weekly; especially with PsA), **acitretin** (teratogenic), **cyclosporine**, **apremilast** (PDE-4 inhibitor; for psoriasis and PsA), **deucravacitinib** (TYK2 inhibitor — blocks IL-23/IL-12/type-1-IFN; plaque psoriasis). **Oral glucocorticoids must NOT be used** — withdrawal can trigger **life-threatening generalised pustular psoriasis**.
- ▶ **Biologics** (Table 60-4): **Anti-TNF-α** (etanercept, adalimumab, certolizumab, infliximab, golimumab); **Anti-IL-12/23** (ustekinumab); **Anti-IL-23** (risankizumab, tildrakizumab, guselkumab); **Anti-IL-17** (secukinumab, ixekizumab, brodalumab). Screen for **TB, HIV, hepatitis B/C** before starting; TNF-α inhibitors may worsen **CHF** and cause **paradoxical psoriasiform lesions**.
- ▶ **PsA-specific** (Table 374-7): “**treat-to-target**” (minimal disease activity/remission); **NSAIDs** short-term; **local glucocorticoid injections** (avoid weight-bearing lower-limb entheses — rupture risk); **avoid systemic steroids**; **csDMARDs** (methotrexate preferred if relevant skin disease,

sulfasalazine, leflunomide); **bDMARDs** (TNF/IL-12-23/IL-17/IL-23 inhibitors), **PDE-4/TYK2 inhibitors**; **JAKi after TNFi failure** (CV black-box warning). For predominant **skin + joint** disease prefer IL-12/23, IL-17 or IL-23 inhibitors over TNF; **avoid IL-17i in active IBD**; prefer **TNF mAbs** for uveitis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled cutaneous psoriasis plaque (cross-section/surface)** — labels: *silvery micaceous scale, sharply demarcated erythematous plaque, Auspitz sign (pinpoint bleeding), Koebner phenomenon at trauma site, extensor distribution (elbows, knees, scalp, gluteal cleft).*
- ▶ **Psoriatic nail + DIP joint schematic** — labels: *nail pitting, onycholysis, oil-drop sign, subungual hyperkeratosis, splinter haemorrhage, DIP arthritis, dactylitis (“sausage digit”), “pencil-in-cup” deformity.*

Clinical / Diagnostic significance

- ▶ Recognise the **clinical variants** — guttate (post-streptococcal, young), inverse (flexural), pustular (febrile, can be erythrodermic) — as each alters prognosis and therapy.
- ▶ **Nail disease and dactylitis** are red flags for psoriatic arthritis; examine **hidden sites** (scalp, umbilicus, natal cleft, nails) when arthritis precedes obvious skin disease.
- ▶ **Screen every patient** for cardiometabolic risk (BP, lipids, glucose, weight), IBD, uveitis and **depression/suicidality** — psoriasis is a systemic disease.
- ▶ Biopsy (acanthosis, dermal vascular proliferation, Munro microabscesses) helps when the presentation is atypical; **CASPAR criteria** confirm PsA.
- ▶ A **multidisciplinary team** (dermatology, rheumatology, ophthalmology, gastroenterology, psychiatry, cardiology) optimises outcomes.

High-yield exam pointers

- ▶ Prevalence ~2%; **immune-mediated**, T-cell driven via the **IL-23/IL-17 axis**; family history in 30–50%.
- ▶ **Koebner phenomenon**; drug triggers — **lithium, beta blockers, antimalarials**; never use systemic steroids (rebound **pustular flare**).
- ▶ **Auspitz sign, silvery micaceous scale, extensor/scalp distribution**; **Munro microabscess** on histology.
- ▶ Variants: **plaque (commonest)**, guttate (post-streptococcal), inverse, pustular/erythrodermic.
- ▶ **PsA in up to 30%**; five Moll–Wright phenotypes; **psoriasis precedes arthritis in ~80%**; nail change in ~90% of PsA.
- ▶ **CASPAR criteria** (≥ 3 points; specificity 98.7%); radiology — “**pencil-in-cup**”, fluffy new bone, **acro-osteolysis**, asymmetric (often unilateral) sacroiliitis.

- ▶ Extra-cutaneous: **anterior uveitis**, **IBD**, **metabolic syndrome**, **CV disease** (risk like diabetes), **depression**.
- ▶ Therapeutic ladder — topical steroids/calcipotriene/tazarotene → phototherapy (NB-UVB/PUVA) → MTX/acitretin/cyclosporine/apremilast/deucravacitinib → **biologics** (TNF, IL-12/23, IL-17, IL-23 inhibitors).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 60 “Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders”** (cutaneous variants, nail disease, treatment) and **Ch 374 “Spondyloarthritis”** (psoriatic arthritis, extra-cutaneous/systemic manifestations, CASPAR criteria, PsA management).

Coverage note: **Auspitz sign** and **Munro microabscess** are not stated verbatim in the provided chapters but are included as universally-accepted standard dermatology; histology in Table 60-2 explicitly supports **acanthosis with dermal vascular proliferation**. The pithy ranges for PsA phenotype proportions and subtype names are drawn from Ch 60 (symmetric ~50%, asymmetric ~35%, distal ~5%, spondylitis ~5%, arthritis mutilans <5%); Ch 374 frames the same as the five Moll–Wright phenotypes. All drug names, criteria, and numerical figures are taken directly from the two chapters.



Schizophrenia

Asked in: Paper IV Jun 2024 · Paper IV Dec 2023 (2×) — RGUHS MD General Medicine

Definition / Introduction — Schizophrenia is a chronic, heterogeneous psychotic syndrome characterised by perturbations of perception, thinking, language, affect, social activity and volition, in which the patient progressively loses contact with reality. There is **no pathognomonic feature and no confirmatory laboratory test**; diagnosis is clinical and one of exclusion. It typically begins in late adolescence/early adulthood, has an insidious (less often acute) onset and a frequently poor outcome, and is best conceptualised as a **neurodevelopmental disorder** of multifactorial (genetic, environmental and neurotransmitter) origin. Lifetime prevalence is ~0.3–1.5% (Harrison quotes 0.85% worldwide; CMDT ~1%), and ~10% of patients die by suicide.

Epidemiology and risk factors

- ▶ **Prevalence:** ~0.85% worldwide; lifetime ~1–1.5% (Harrison). DSM-5-TR lifetime estimate 0.3–0.7%. ~300,000 acute episodes/year in the USA.
- ▶ **Age/sex at onset:** late teens to mid-30s; peak in early–mid 20s in **men** (~18 yr) and late 20s in **women** (~25 yr), with a second mid-life peak in women. Onset before adolescence is rare.

- ▶ **Genetic susceptibility** (strongest risk factor): present in ~6.6% of first-degree relatives; risk ~40% if both parents affected; monozygotic twin concordance 50% vs 10% for dizygotic. Sibling of a proband → ~10-fold risk. Most affected individuals nonetheless have no family history.
- ▶ **Environmental/developmental**: early developmental insults, winter/early-spring birth, advancing paternal age, obstetric complications with hypoxia, prenatal infection/malnutrition/maternal diabetes, urban upbringing, migration/refugee status, childhood trauma and social adversity.

Clinical features

- ▶ **Positive symptoms** (added experiences) — *delusions* (often persecutory/somatic), *auditory hallucinations* (characteristically third-person/derogatory; visual hallucinations suggest an organic state), *conceptual disorganisation*, *disorganised (formal thought-disordered) speech* with derailment, neologisms, echolalia and verbigeration, and *grossly disorganised or catatonic behaviour*.
- ▶ **Negative symptoms** (lost function) — *affective flattening/diminished emotional expression*, *avolition*, *anhedonia*, *alogia/poverty of speech*, *asociality* and impaired concentration. Predominate in ~one-third of patients and predict **poor long-term outcome and poor drug response**.
- ▶ **Cognitive symptoms** — deficits in working/declarative memory, attention, processing speed and executive function; strongly linked to functional/vocational disability and often precede frank psychosis.
- ▶ **Schneiderian first-rank symptoms** (classically supportive, not specific) — thought insertion, withdrawal and broadcasting; delusions of control/passivity; third-person auditory hallucinations; delusional perception. **Bleuler's "4 A's"** (loosening of Associations, Affect incongruity, Ambivalence, Autism) and Kraepelin's *dementia praecox* are the classical descriptions.
- ▶ **Catatonia** — a non-specific syndrome (≥3 of stupor, cataplexy, mutism, waxy flexibility, stereotypy, etc.) that may complicate schizophrenia but also occurs in mood and medical disorders.
- ▶ **Course**: chronic with relapses; positive symptoms attenuate with age while negative/cognitive features persist. Pooled first-episode remission ~56% and recovery ~30%. **Anosognosia (lack of insight)** is the commonest predictor of non-adherence and relapse. ~5–10% commit suicide (20% attempt).

DSM-5-TR diagnostic criteria

Criterion	Requirement
A (core)	≥2 of the following for ≥1 month (active phase), at least one being 1, 2 or 3: (1) delusions; (2) hallucinations; (3) disorganised speech; (4) grossly disorganised/catatonic behaviour; (5) negative symptoms
B	Marked decline in functioning (work, relationships, self-care) below premorbid level
C	Continuous signs ≥6 months, including ≥1 month of active-phase (Criterion A) symptoms; may include prodromal/residual phases
D	Schizoaffective and mood disorder with psychotic features excluded
E	Not due to a substance or another medical condition
F	If autism/childhood communication disorder, diagnosis only if prominent delusions/hallucinations also present ≥1 month

- ▶ **Related spectrum disorders by duration/content:** *brief psychotic disorder* (>1 day, <1 month, full recovery); *schizophreniform disorder* (1–6 months); *schizoaffective disorder* (mood episode plus active-phase psychosis, with ≥2 weeks of psychosis without mood symptoms); *delusional disorder* (≥1 month delusions, Criterion A never met).
- ▶ DSM-5-TR abandoned the classical subtypes (paranoid, disorganised/hebephrenic, catatonic, undifferentiated, residual) in favour of a **dimensional 0–4 severity rating** of psychotic domains.

Etiopathogenesis

- ▶ **Dopamine hypothesis (four pathways):** clinical antipsychotic potency parallels affinity for D2/D3 receptors in the ventral striatum. Mesolimbic hyperdopaminergia → positive symptoms; mesocortical hypodopaminergia → negative/cognitive symptoms; blockade of the nigrostriatal pathway → extrapyramidal symptoms; blockade of the tuberoinfundibular pathway → hyperprolactinaemia.
- ▶ **Other neurotransmitters:** glutamatergic (NMDA) hypofunction and serotonergic (5-HT_{2A}) signalling — atypical agents have high 5-HT₂:D₂ ratios; newer targets include D₃, 5-HT_{1A}/5-HT₇, mGlu_{2/3} and muscarinic M₁/M₄ receptors.
- ▶ **Neurodevelopmental/structural changes (ch462):** enlarged lateral ventricles, reduced cortical and subcortical grey matter in frontal/temporal lobes and limbic system, reduced neuropil with increased cell-packing density (no neuronal loss), hypofrontality (reduced dorsolateral prefrontal cortex metabolism at rest and on executive/working-memory tasks), and reduced expression of *GAD1* (GABA-synthesising enzyme) in prefrontal interneurons.

- **Genetics:** large GWAS show hundreds of small-effect risk loci plus rare large-effect copy-number variants; pathways involve **immunity, inflammation and cell signalling**. The strongest signal lies at the **complement component 4 (C4)** locus — increased C4A expression is hypothesised to drive **excessive synaptic pruning by microglia**, supporting a neurodevelopmental/neurodegenerative model.

Differential diagnosis

- **Primary psychiatric:** mood disorder (depressive/bipolar) with psychotic or catatonic features, schizoaffective disorder, delusional disorder, brief psychotic disorder, schizotypal personality disorder.
- **Substance-induced:** chronic amphetamine/cocaine/stimulant psychosis (formication, stereotypy), phencyclidine, cannabis; and prescription drugs (anti-parkinsonian agents, clonidine, quinacrine, procaine derivatives) — *rule out drug causes in any new-onset psychosis*.
- **Organic/medical:** thyroid, adrenal and pituitary disease, temporal-lobe (complex partial) seizures, CNS tumour/encephalitis/haemorrhage, metabolic derangements, heavy-metal/industrial toxicity. A full medical work-up with **CT/MRI brain** is advised at first episode of psychosis.

Management

- **Antipsychotics are the cornerstone** of acute and maintenance treatment. ~70% of first-episode patients respond; improvement begins within days but full remission needs **6–8 weeks**. Therapeutic doses produce **>80% D2 occupancy** (e.g. haloperidol 4–6 mg/d, olanzapine 10–15 mg/d, risperidone 4–6 mg/d); higher doses add toxicity, not efficacy.

Class	Examples	Key features
First-generation (typical)	Low-potency: chlorpromazine, thioridazine; mid: perphenazine, loxapine; high: haloperidol , fluphenazine, thiothixene	High-potency → more EPS; low-potency → more anticholinergic/orthostatic/sedative effects
Second-generation (atypical)	Clozapine , risperidone, olanzapine , quetiapine, ziprasidone, aripiprazole, paliperidone, lurasidone, asenapine, cariprazine, lumateperone	Higher 5-HT ₂ :D ₂ ratio; better for negative/cognitive symptoms; metabolic risk (weight gain, dyslipidaemia, type-2 DM)
Novel mechanism (2024)	Xanomeline/trospium (M1/M4 muscarinic agonist)	First agent acting <i>without</i> D ₂ /5-HT ₂ blockade → no EPS or metabolic complications

- **Clozapine** — drug of choice for **treatment-resistant schizophrenia** (~30% of non-responders improve) and uniquely **reduces suicidality**; needs a 6–9-month trial. Risks: **agranulocytosis**

(~1%, mandatory WBC monitoring), dose-related seizures (~10% at high dose), weight gain, drooling, hyperthermia; does **not** raise prolactin.

- ▶ **Long-acting injectables (LAI)** — risperidone, paliperidone, olanzapine, aripiprazole, haloperidol/fluphenazine decanoate — for **non-adherence**; reduce relapse. If medication is fully stopped, relapse rate is ~60% within 6 months.
- ▶ **Adverse effects:** EPS (acute dystonia, akathisia, parkinsonism) → benztropine 1–2 mg bid or trihexyphenidyl 2 mg bid; akathisia → beta-blocker. **Tardive dyskinesia** (incidence 2–4%/yr, prevalence ~20%; *buccolinguo-masticatory triad*) → treat with the VMAT2 inhibitor **valbenazine**. **Neuroleptic malignant syndrome** — hyperthermia, autonomic instability, rigidity, raised CPK (a medical emergency). Hyperprolactinaemia, QT prolongation, metabolic syndrome — monitor glucose/lipids/ECG. The CATIE trial showed high real-world discontinuation; olanzapine had the lowest discontinuation but most metabolic effect, and perphenazine performed comparably to newer agents.
- ▶ **Psychosocial/non-pharmacological:** family psychoeducation, assertive community treatment, social-cognition and skills training, cognitive remediation; ECT for catatonia and treatment-resistant cases. Lorazepam 1–2 mg rapidly relieves catatonia.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Dopaminergic pathways in schizophrenia** — midbrain origins (VTA, substantia nigra) projecting along four tracts, labelled: *Mesolimbic* (VTA → *nucleus accumbens*) — *positive symptoms* (hyperactive); *Mesocortical* (VTA → *prefrontal cortex*) — *negative/cognitive symptoms* (hypoactive); *Nigrostriatal* (SN → *striatum*) — *EPS on blockade*; *Tuberoinfundibular* (hypothalamus → *pituitary*) — *hyperprolactinaemia on blockade*.
- ▶ **Positive vs negative symptoms schematic** — two columns: *Positive* (Delusions, Hallucinations, Disorganised speech, Catatonia) and *Negative* (Affective flattening, Avolition, Anhedonia, Alogia, Asociality), with *Cognitive deficits* bridging both.

Clinical / Diagnostic significance

- ▶ Diagnosis is **clinical and longitudinal** — repeated observation improves reliability; reconsider the diagnosis (often → bipolar disorder) if the course is atypical.
- ▶ First episode mandates a **full medical work-up + neuroimaging** and a urine drug screen to exclude organic/substance causes.
- ▶ Patients have **reduced life expectancy** from suicide and from antipsychotic-associated **metabolic syndrome and cardiovascular disease** — metabolic monitoring is integral to care.
- ▶ Treatment failure is most often due to **inadequate dosing or non-adherence**; LAIs and clozapine are the structured responses to each.

High-yield exam pointers

- ▶ DSM-5-TR: ≥ 2 **Criterion A** symptoms ≥ 1 month + ≥ 6 months total, with ≥ 1 of delusions/hallucinations/disorganised speech.
- ▶ Positive = mesolimbic **hyperdopaminergia**; negative = mesocortical **hypodopaminergia**.
- ▶ Genetics: MZ concordance 50%, DZ 10%; both parents affected $\rightarrow \sim 40\%$.
- ▶ Strongest molecular signal = **C4 complement** $\rightarrow$ **excess synaptic pruning** (microglia); imaging = **ventriculomegaly + hypofrontality**.
- ▶ **Clozapine** = treatment-resistant disease and anti-suicidality; watch **agranulocytosis (1%)** with WBC monitoring; no prolactin rise.
- ▶ **Tardive dyskinesia** $\rightarrow$ valbenazine (VMAT2 inhibitor); **NMS** = hyperthermia + rigidity + autonomic instability + $\uparrow$ CPK.
- ▶ DSM-5 **dropped classical subtypes**; **xanomeline/trospium (M1/M4 agonist, 2024)** is the first non-dopaminergic antipsychotic.
- ▶ **Auditory** hallucinations favour schizophrenia; **visual** hallucinations favour an organic/toxic cause.
- ▶ $\sim 10\%$ die by suicide; anosognosia is the chief driver of non-adherence and relapse.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "Psychiatric Disorders" (Schizophrenia: clinical manifestations, epidemiology, differential diagnosis, antipsychotic pharmacology, CATIE, tardive dyskinesia, NMS) and "Biology of Psychiatric Disorders" (structural imaging, hypofrontality, GAD1, C4 complement and synaptic pruning).
- ▶ **DSM-5-TR** — "Schizophrenia Spectrum and Other Psychotic Disorders" (diagnostic criteria, course, prognosis, suicide risk, spectrum definitions).
- ▶ **Kaplan & Sadock's Comprehensive Textbook of Psychiatry** — dopaminergic pathway/neurochemistry and Schneiderian first-rank symptom framing.
- ▶ **CMDT 2026** — "Psychiatric Disorders" (classification, mesolimbic vs mesocortical D2 correlation, current drug regimens/doses, LAIs, xanomeline/trospium, ECT).

Coverage note: Schneiderian first-rank symptoms and Bleuler's "4 A's"/Kraepelin (dementia praecox) are given as universally-accepted standard psychiatry; the corpus references "schneiderian first-rank symptoms" but does not enumerate them, and the nigrostriatal/tuberoinfundibular limbs of the four-pathway model are standard pharmacology stated to frame Harrison's EPS/hyperprolactinaemia data.



Toxic epidermal necrolysis

Asked in: Paper IV 17 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Toxic epidermal necrolysis (TEN), originally described by *Lyell* (1956), is the most extensive form of a single severe mucocutaneous reaction spectrum, **Stevens-Johnson syndrome / toxic epidermal necrolysis (SJS/TEN)**, characterised by widespread blistering and **full-thickness epidermal necrosis** with detachment of skin and erosion of two or more mucosal surfaces. It is almost always **drug-induced** (a culprit drug is identified in ~85% of cases), is mediated by drug-specific cytotoxic CD8+ T cells, and is a dermatological emergency with mortality reaching ~30% in TEN. Cases are classified by **maximal body-surface-area (BSA) detachment**: SJS <10%, SJS/TEN overlap 10–30%, and TEN >30%.

Nomenclature, spectrum and epidemiology

- ▶ SJS = epidermal detachment <10% BSA with widespread purpuric macules / flat atypical targets; SJS/TEN overlap = 10–30%; TEN with spots = >30% with purpuric macules/targets; TEN without spots = >30% with loss of large epidermal sheets, no discrete lesions.
- ▶ SJS and TEN are now regarded as one entity separated from **erythema multiforme (EM) major**, which is HSV-driven, has true/raised *typical targets* on the extremities, and is rarely drug-related.
- ▶ Incidence ~1–2 cases per million per year; occurs at all ages (rises in the elderly); female:male ~2:1; increased risk in HIV infection.

Pathogenesis and genetic predisposition

- ▶ A delayed (type IV) hypersensitivity reaction: MHC class I-restricted presentation of a drug/metabolite-altered antigen by keratinocytes/APCs drives clonal expansion of CD8+ cytotoxic T lymphocytes (CTLs) that infiltrate the skin.
- ▶ Keratinocyte apoptosis/necroptosis is effected by soluble mediators — **granulysin** (secretory 15-kDa form; the *key* mediator, high in blister fluid), **soluble Fas ligand (Fas-FasL)**, **perforin/granzyme B**, TNF- α , IFN- γ and inducible nitric oxide synthase. **Annexin A1** acting via **formyl-peptide receptor 1** and overexpressed **RIP kinase 3 (RIP3)** implicate *necroptosis*.
- ▶ Mechanistic models of drug-HLA-TCR interaction: **hapten/pro-hapten** (covalent binding), **p-i (pharmacologic interaction)** concept (non-covalent binding to HLA/TCR), and **altered peptide repertoire** (classically *abacavir* in HLA-B*57:01).
- ▶ Pharmacogenetic HLA associations (drug- and phenotype-specific):

HLA allele	Drug	Population/notes
*HLA-B15:02**	Carbamazepine (SJS/TEN, not DRESS)	Han Chinese, Thai, Malaysian
*HLA-B58:01**	Allopurinol (SJS/TEN & DRESS)	Han Chinese; ACR advises pre-screening
*HLA-B57:01**	Abacavir hypersensitivity	100% NPV; screening abolishes AHS

HLA allele	Drug	Population/notes
*HLA-A32:01**	Vancomycin (DRESS)	—
*HLA-B13:01**	Dapsone / sulfonamide	cost-effective screening in leprosy

- ▶ Non-MHC factors also matter, e.g. slow-metaboliser *CYP2C93** raises risk of phenytoin-induced SJS/TEN.

Causative drugs

- ▶ A short list accounts for ~half of all cases. **High-risk culprits (Rook's Box 118.3):** allopurinol, carbamazepine, lamotrigine, nevirapine, oxicam NSAIDs, phenobarbital, phenytoin, sulfamethoxazole/other sulfa antibiotics, and sulfasalazine.
- ▶ Harrison additionally emphasises trimethoprim-sulfamethoxazole, β -lactam antibiotics and other antiepileptics.
- ▶ Typical **latency** from drug start to onset is **7–10 days (range 5–28 days)**. Paracetamol/aspirin/ibuprofen/corticosteroid are often confounders (used to treat the prodrome). In a minority (especially children) *Mycoplasma pneumoniae* is the trigger and no drug is found.

Clinical features

- ▶ **Prodrome:** malaise, fever, sore throat and upper-respiratory symptoms for a few days, often with conjunctivitis.
- ▶ **Skin:** fever $>39^{\circ}\text{C}$ then acute painful, **dusky atypical targets / purpuric macules** beginning on the face and upper trunk, spreading to involve trunk and limbs (palms/soles often prominent); lesions coalesce, blister and lead to confluent dusky erythema and **sheet-like epidermal detachment** over 5–10 days. Marked **skin pain** is characteristic.
- ▶ **Nikolsky sign positive** — gentle lateral pressure slides lesional epidermis off the dermis (detachable epidermis); not specific (also positive in pemphigus). Asboe-Hansen (bulla-spread) phenomenon may be present.
- ▶ **Mucosal involvement (≥ 2 sites, near-universal):** painful haemorrhagic erosive stomatitis/cheilitis with crusted lips; ocular chemosis, conjunctivitis, pseudomembranes, corneal/conjunctival epithelial defects; **urogenital** erosions; and **respiratory** tract sloughing (cough, dyspnoea, haemoptysis) in up to 25%.

Histopathology and investigations

- ▶ **Skin biopsy (lesional, adjacent to a blister):** full-thickness/confluent epidermal necrosis with apoptotic keratinocytes (Civatte bodies), basal vacuolar degeneration and **subepidermal split**, with only a sparse perivascular lymphocytic dermal infiltrate. **Frozen-section biopsy** allows rapid diagnosis.

- ▶ A second **peri-lesional biopsy for direct immunofluorescence** (negative) excludes autoimmune bullous disease.
- ▶ **Bloods at presentation:** FBC (anaemia, leukopenia), urea & electrolytes, glucose, **bicarbonate**, LFTs, amylase, CRP/ESR, coagulation, **Mycoplasma serology**, ANA/ENA, complement, indirect immunofluorescence. Skin swabs for bacteriology, and a **chest X-ray** are mandatory. A **body map** records redness and detachment separately.

Prognosis — SCORTEN

- ▶ Overall SJS/TEN mortality ~22% (SJS <10%, TEN ~30%); death is usually from **septicaemia-induced multiorgan failure**.
- ▶ **SCORTEN** (*Bastuji-Garin, 2000*) is the validated severity score, calculated on **admission and again within day 1–5**; one point each for seven independent parameters:

SCORTEN parameter (1 point each)
Age >40 years
Presence of malignancy
Heart rate >120/min
Epidermal detachment >10% BSA at admission
Serum urea >10 mmol/L (BUN >28 mg/dL)
Serum glucose >14 mmol/L (>252 mg/dL)
Bicarbonate <20 mmol/L

- ▶ Predicted in-hospital mortality rises steeply with score (classically ~3% at 0–1 points, ~12% at 2, ~35% at 3, ~58% at 4, and >90% at ≥5). The newer **ABCD-10** score is an alternative (CMDT).

Management

- ▶ **Immediate withdrawal of the culprit drug** is the single most important intervention — early stoppage (before/at blistering) is a strong predictor of survival; delay increases mortality. Continue essential non-suspect medicines. **ALDEN** (Algorithm of Drug causality in Epidermal Necrolysis) aids *retrospective* culprit attribution.
- ▶ **Care setting:** detachment >10% BSA → transfer to an **ICU or burns unit**; barrier-nurse on a pressure-relieving mattress at ambient 25–28°C, managed by an MDT (dermatology/burns, intensive care, **ophthalmology**, skin-care nursing, etc.).
- ▶ **Supportive care (the proven cornerstone):**
 - **Fluids:** crystalloid at ~2 mL/kg/%BSA detached (less than for thermal burns), titrated to urine output; avoid over-resuscitation.

- *Nutrition*: early **enteral/NG feeding** (20–25 kcal/kg/day catabolic phase, rising to 25–30 kcal/kg/day).
- *Skin*: atraumatic handling (avoid BP cuffs/adhesive leads/wrist tags); emollient (50/50 white-soft/liquid paraffin); leave detached epidermis as a biological dressing or use non-adherent **silicone dressings**; topical antibiotic only on infected/crusted areas.
- *Mucosae*: daily **ophthalmology review**, 2-hourly ocular lubricant, lysis of conjunctival adhesions, topical steroid drops ± **amniotic membrane transplantation** for severe ocular surface loss; mouth care and **urinary catheterisation** to prevent strictures.
- *Other*: opioid **analgesia** (± ketamine for procedures), **PPI** stress-ulcer prophylaxis, **LMWH** thromboprophylaxis, vigilant **sepsis** surveillance (commence antibiotics only on clinical signs — *S. aureus* early, then *Pseudomonas*/Gram-negatives), and **macrolide** if Mycoplasma-triggered.
- ▶ **Immunomodulatory (adjunctive, unproven — no therapy has unequivocal RCT benefit)**:
 - **Ciclosporin** 3–5 mg/kg/day for ~7–10 days then taper — most favoured in current practice; cohort data suggest faster re-epithelialisation and below-SCORTEN-predicted mortality.
 - **Systemic corticosteroids** — early high-dose (prednisone 1–2 mg/kg/day, or pulsed IV dexamethasone/methylprednisolone); benefit conflicting, risk of sepsis/impaired healing.
 - **IVIg** 0.5–1 g/kg/day for 3–4 days (total ~3–4 g/kg) — anti-Fas rationale; meta-analysis showed **no clear mortality benefit** in adults.
 - **Etanercept** (TNF- α inhibitor) — treatment of choice in some centres; faster healing in uncontrolled studies.
 - **Thalidomide** is contraindicated — the only RCT was stopped early for *excess deaths*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **SJS/TEN classification spectrum bar**: a horizontal axis of % BSA detachment with three zones labelled — “SJS <10%”, “SJS/TEN overlap 10–30%”, “TEN >30%”; annotate “atypical targets / purpuric macules” and “sheet-like epidermal detachment, Nikolsky +”.
- ▶ **Pathogenesis schematic**: *Drug/metabolite* → **HLA class I + altered peptide** on keratinocyte → recognised by CD8+ CTL (TCR) → release of **granulysin, Fas–FasL, perforin/granzyme B, TNF- α** → **keratinocyte apoptosis/necroptosis** → full-thickness epidermal necrosis & detachment.

Clinical / Diagnostic significance

- ▶ Recognise the **red-flag features** (skin pain, dusky/target lesions, blisters, positive Nikolsky, mucosal erosions, fever) early — they distinguish SJS/TEN from benign morbilliform eruptions and mandate urgent specialist referral.

- ▶ A frozen-section/biopsy confirms full-thickness necrosis and excludes **staphylococcal scalded skin syndrome** (subcorneal split, no mucosal involvement), pemphigus, bullous pemphigoid, paraneoplastic pemphigus, bullous lupus, linear IgA disease and generalised bullous fixed drug eruption.
- ▶ **HLA pharmacogenetic screening** (e.g. HLA-B15:02 before carbamazepine in South-East/East-Asian patients, HLA-B58:01 before allopurinol, HLA-B*57:01 before abacavir) prevents cases.
- ▶ **Long-term sequelae** drive morbidity: chronic **ocular** disease (dry eye, symblepharon, entropion/trichiasis, corneal scarring, blindness — the most disabling), **bronchiolitis obliterans**, oesophageal/vaginal strictures, dyspigmentation, **onychomadesis**, telogen effluvium, and PTSD. Issue a **MedicAlert card/bracelet** naming the culprit drug; lifelong avoidance of it and cross-reacting congeners (e.g. aromatic antiepileptics).

High-yield exam pointers

- ▶ TEN = >30% BSA detachment; SJS <10%; overlap 10–30% — *Lyell syndrome*.
- ▶ Culprits mnemonic — **allopurinol, anticonvulsants (carbamazepine, lamotrigine, phenytoin, phenobarbital), sulfonamides, oxicam NSAIDs, nevirapine**; latency 5–28 days.
- ▶ **Granulysin** is the *key* cytotoxic mediator; effector cells are CD8+ CTLs (MHC-I restricted).
- ▶ *HLA-B15:02 → carbamazepine; HLA-B58:01 → allopurinol; HLA-B57:01 → abacavir.**
- ▶ **Nikolsky sign positive**; biopsy = **full-thickness epidermal necrosis, subepidermal split**.
- ▶ SCORTEN = 7 parameters; ≥5 predicts >90% mortality.
- ▶ **Stop the drug + ICU/burns-unit supportive care** are the only measures with clear survival benefit; **ciclosporin** is the most favoured adjunct; **thalidomide is harmful**.
- ▶ Commonest cause of death = **sepsis** → **multiorgan failure**; commonest disabling sequela = **chronic ocular scarring**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Cutaneous Drug Reactions” (SJS/TEN spectrum, immunopathogenesis, HLA pharmacogenetics, culprit drugs, ALDEN); “Immunologically Mediated Skin Diseases” (blistering differential).
- ▶ **Rook's Textbook of Dermatology, 10e** — “Severe Cutaneous Adverse Reactions to Drugs” (definition/nomenclature, classification, histopathology, SCORTEN parameters, investigations, detailed supportive and active-therapy management ladder, complications/prognosis).
- ▶ **CMDT 2026** — “Erythema Multiforme / Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis” (BSA criteria, current drug doses — corticosteroids, IVIG, ciclosporin, etanercept; ABCD-10/SCORTEN).



Treatment and Complications of Psoriasis Vulgaris

Asked in: Paper IV Oct 2025 — RGUHS MD General Medicine

Definition / Introduction — Psoriasis vulgaris (chronic plaque psoriasis) is a common, immune-mediated, genetically determined inflammatory disease affecting up to 2% of the population, characterised by sharply demarcated, erythematous plaques bearing **silvery micaceous scale**, typically over extensor surfaces (elbows, knees), scalp and the gluteal cleft. It is driven by IL-23/Th17-axis cytokines causing keratinocyte hyperproliferation; trauma reproduces lesions (**Koebner/isomorphic phenomenon**). It is no longer regarded as a skin-limited disorder but a *systemic inflammatory disease* with major cardiometabolic, articular and psychological comorbidity. Treatment is selected by **disease severity, extent (BSA), site and comorbidity**.

Assessment of severity (governs treatment choice)

- ▶ **PASI (Psoriasis Area and Severity Index)** — the standard trial and clinical tool. Erythema, scaling (infiltration/thickness) and induration are each graded 0–4, multiplied by an **area score** 0–6, across four regions — head & neck, trunk, upper limbs, lower limbs — weighted $\times 0.1$, $\times 0.2$, $\times 0.3$, $\times 0.4$ respectively; total range 0–72. Response is reported as **PASI-75/90/100** (% improvement).
- ▶ **BSA** estimated by patient's palm $\approx 1\%$. **DLQI** (Dermatology Life Quality Index, 0–30) measures quality-of-life impact; score >10 = very large effect.
- ▶ **Severe disease** variously defined as **PASI >10 –12, or DLQI ≥ 10 , or BSA $>10\%$** , or involvement of high-impact sites (face, palms/soles, genitalia, nails). Practically, patients split into **candidates for topical therapy** vs **candidates for systemic therapy** (BSA $\geq 10\%$, high-impact site, or topical failure).
- ▶ General measures: emollients/adequate hydration, avoid skin drying and irritation, treat streptococcal triggers, and avoid known aggravators — **lithium, beta-blockers, antimalarials, NSAIDs, statins, and systemic glucocorticoid withdrawal**.

Topical therapy (mild/limited disease, BSA $<10\%$)

- ▶ **Topical corticosteroids** — potent/very-potent agents are first-line for limited plaque, trunk and limb disease; mild–moderate potency for face, flexures and genitalia. Limitations: cutaneous **atrophy, striae, tachyphylaxis and rebound flare**; do not induce lasting remission.
- ▶ **Vitamin D analogues** — *calcipotriol* (50 $\mu\text{g/g}$, restrict to <100 g/week to avoid hypercalcaemia/hypercalciuria), *calcitriol* (3 $\mu\text{g/g}$), *tacalcitol*. The **calcipotriol + betamethasone dipropionate** fixed combination (ointment/gel/foam) is the most effective short-term topical strategy and is excellent for scalp disease.

- ▶ **Coal tar** (Goeckerman regimen with UVB) and **dithranol/anthralin** (Ingram regimen, Lassar's paste 0.05–4%) — older keratolytic/antiproliferative agents giving long remissions but messy/staining; largely replaced.
- ▶ **Topical calcineurin inhibitors** (tacrolimus 0.1%/0.03%, pimecrolimus) — preferred for **face, flexures and genitalia** (no atrophy).
- ▶ **Salicylic acid** keratolytic for thick scalp/plaque; newer non-steroidals **tapinarof 1%** (aryl-hydrocarbon-receptor agonist) and **roflumilast 0.3%** (topical PDE4 inhibitor).

Phototherapy (moderate disease, ~10–30% BSA)

- ▶ **Narrowband UVB (NB-UVB, 311–313 nm)** — first-line phototherapy, given **thrice weekly**, MED-based dosing; clearance >90%, non-immunosuppressive and safe in pregnancy. Treatment of choice for widespread **guttate psoriasis**. **Avoid in patients on ciclosporin** (carcinogenesis risk).
- ▶ **PUVA** (oral/topical 8-methoxypsoralen 0.6 mg/kg + UVA) — highly effective; cumulative dose causes **non-melanoma skin cancer (SCC > BCC)**, hence lifetime limit ~200 treatments; *Re-PUVA* (with acitretin) is dose-sparing and synergistic.

Systemic (non-biologic) therapy (moderate-to-severe / BSA >30% / topical & phototherapy failure)

Agent	Class / mechanism	Dose	Key toxicity to monitor
Methotrexate	Antimetabolite (DHFR)	≤25 mg once weekly + folic acid 1–2 mg/d	Hepatic fibrosis (cumulative 3.5–4 g → hepatology/PIIINP/elastography), pancytopenia, pneumonitis, mucositis, teratogenic
Ciclosporin	Calcineurin inhibitor	≤5 mg/kg/day	Nephrotoxicity, hypertension, hyperkalaemia/uricaemia, gum hyperplasia ; for induction only , rebound on stopping
Acitretin	Oral retinoid	0.5–0.75 mg/kg/day	Teratogenic (avoid pregnancy 3 yr) , mucocutaneous dryness, hyperlipidaemia, hepatitis, hyperostosis; non-immunosuppressive — useful in pustular psoriasis & HIV
Fumaric acid esters (dimethyl fumarate)	Immunomodulator	up to 240 mg tds	GI upset, flushing, lymphopenia (→ rare PML), proteinuria
Apremilast	Oral PDE4 inhibitor	30 mg BD	Diarrhoea, weight loss, depression ; minimal

Agent	Class / mechanism	Dose	Key toxicity to monitor
			immunosuppression, no lab monitoring
Deucravacitinib	Oral TYK2 inhibitor	6 mg daily	URTI, raised CPK, herpes reactivation, folliculitis

- ▶ Oral glucocorticoids must NOT be used for plaque psoriasis — withdrawal precipitates life-threatening generalised pustular or erythrodermic flares.

Biologic therapy (severe disease, inadequate response/intolerance to standard systemics)

- ▶ TNF- α inhibitors — *etanercept*, *adalimumab*, *infliximab*, *certolizumab* (and *golimumab* for PsA). *Infliximab* (5 mg/kg IV, weeks 0, 2, 6 then q8w) gives the most rapid response — preferred for erythrodermic and pustular flares. TNFi can worsen heart failure and paradoxically induce psoriasis.
- ▶ IL-12/23 p40 inhibitor — *ustekinumab* (45 mg if <100 kg, 90 mg if >100 kg; weeks 0, 4, then q12w). Response is enhanced in *HLA-C06:02-positive** patients.
- ▶ IL-17 inhibitors — *secukinumab*, *ixekizumab* (anti-IL-17A), *brodalumab* (anti-IL-17RA), *bimekizumab* (anti-IL-17A/F). Very rapid, high PASI-90/100 rates; risks: mucocutaneous candidiasis, may unmask/worsen inflammatory bowel disease; *brodalumab* carries a suicidality black-box warning.
- ▶ IL-23 p19 inhibitors — *guselkumab*, *risankizumab*, *tildrakizumab*. Highest sustained efficacy, infrequent dosing, and no signal for candidiasis or IBD.
- ▶ Spesolimab (anti-IL-36 receptor) — approved specifically for generalised pustular psoriasis (linked to *IL36RN* mutations).
- ▶ Biologic safety rules: screen for latent TB (IGRA/CXR), hepatitis B/C and HIV before starting; do not start with active severe infection; serious-infection rate ~1.4–1.8 per 100 patient-years; rare reports of demyelination, drug-induced lupus and PML.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ PASI scoring schematic — body divided into 4 regions with weighting factors: *Head & neck* $\times 0.1$, *Upper limbs* $\times 0.2$, *Trunk* $\times 0.3$, *Lower limbs* $\times 0.4$; annotate each region with *Erythema* (0–4) + *Induration* (0–4) + *Scaling* (0–4) $\times$ *Area* (0–6); final box PASI = A + B + C + D (range 0–72).
- ▶ Treatment pyramid / IL-23–Th17 target map — base *General measures* + *Topicals* (*steroid*, *vitamin D analogue*, *calcineurin inhibitor*) $\rightarrow$ *Phototherapy* (NB-UVB, PUVA) $\rightarrow$ *Conventional systemics* (MTX, ciclosporin, acitretin) $\rightarrow$ apex *Biologics*; side ladder showing

cytokine targets: *TNF- α* , *IL-12/23p40*, *IL-17A/F*, *IL-23p19*, *IL-36R* with the drug at each node.

Clinical / Diagnostic significance

- **Complications of the disease itself:** progression to **erythrodermic psoriasis** (>90% BSA — impaired thermoregulation, high-output cardiac failure, fluid/protein/electrolyte loss, sepsis, rare ARDS) and **generalised pustular psoriasis** (fever 39–40°C, sterile pustules, systemic upset, life-threatening).
- **Psoriatic arthritis** in up to 30% (onset 30–50 yr) — five patterns: **symmetric** (~50%), **asymmetric** (~35%), **distal interphalangeal** (classic, ~5%), **spondylitic** (~5%), **arthritis mutilans** (<5%); “sausage digits” (dactylitis), nail dystrophy. Joint damage is erosive and deforming — early recognition is mark-worthy.
- **Systemic comorbidity** (screen actively): **metabolic syndrome** (obesity, hyperlipidaemia, hypertension, diabetes); **cardiovascular disease** with increased MI/stroke/peripheral-vascular/atrial fibrillation/VTE risk and excess mortality; **NAFLD**; other immune-mediated diseases (**Crohn’s**, **ulcerative colitis**, **coeliac disease**, **uveitis**); **anxiety**, **depression** and **suicidality**; increased non-melanoma skin cancer and lymphoma; gout and (rarely) secondary amyloidosis. **Ocular:** blepharitis, conjunctivitis, uveitis.
- **Complications of therapy** are exam-critical: topical-steroid atrophy/tachyphylaxis/rebound; vitamin-D-analogue hypercalcaemia; MTX hepatic/marrow/pulmonary toxicity and teratogenicity; ciclosporin nephrotoxicity, hypertension and malignancy; acitretin teratogenicity and hyperlipidaemia; PUVA-induced SCC/melanoma; biologic-associated serious infection, **TB** and **hepatitis B reactivation**, IL-17-related candidiasis and IBD.
- **Investigations:** usually clinical; **skin biopsy** (acanthosis with regular elongation of rete ridges, parakeratosis, Munro microabscesses, dilated dermal papillary vessels) when atypical. Baseline screen before systemics: FBC, LFTs, U&E, lipids/glucose, hepatitis & HIV serology, IGRA/CXR, pregnancy test.

High-yield exam pointers

- **PASI 0–72**, four regions weighted 0.1/0.2/0.3/0.4; treatment endpoints **PASI-75/90/100**; severe = PASI >10–12 or DLQI $\geq$ 10 or BSA >10%.
- **First-line by extent:** topical steroid $\pm$ vitamin D analogue (limited) $\rightarrow$ NB-UVB (moderate/guttate) $\rightarrow$ MTX/ciclosporin/acitretin or biologic (severe).
- **Never give systemic steroids** for plaque psoriasis — rebound pustular/erythrodermic flare on withdrawal.
- **Acitretin** = drug of choice in **pustular** psoriasis and when immunosuppression must be avoided; **teratogenic** for 3 years.

- ▶ **Infliximab** = fastest-acting biologic, best for **erythrodermic/pustular** flares; **spesolimab** (anti-IL-36R) specifically for GPP.
- ▶ Screen TB, HBV/HCV, HIV before any biologic/immunosuppressant; **IL-17 inhibitors** → **candidiasis & IBD**; **brodalumab** → **suicidality warning**.
- ▶ **HLA-C06:02** predicts good *ustekinumab* response; IL36RN* mutation underlies generalised pustular psoriasis.
- ▶ Treat psoriasis as a **systemic disease** — screen for psoriatic arthritis, metabolic syndrome, cardiovascular risk and depression; address weight and smoking.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders” (clinical types, FDA-approved systemic agents and biologics tables, PsA subtypes).
- ▶ **Rook's Textbook of Dermatology, 10e** — “Psoriasis and Related Disorders” (PASI methodology, severity classification, comorbidity Box, full topical/phototherapy/systemic/biologic pharmacology, generalised pustular psoriasis and *IL36RN*).
- ▶ **CMDT 2026** — “Dermatologic Disorders: Psoriasis” (current treatment ladder by BSA, drug doses and monitoring, spesolimab for GPP).



Vitamins, minerals, nutrition & electrolytes



Beer Potomania

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — *Beer potomania* is a distinctive form of **hypotonic, dilutional hyponatremia** caused by **very low dietary solute intake** rather than by excess antidiuretic hormone (AVP/ADH). It classically occurs in chronic heavy beer drinkers whose near-sole calorie source is beer — a beverage rich in water and carbohydrate but almost devoid of protein and salt (only **1–2 mmol/L of Na⁺**). Because renal free-water excretion is *obligately coupled to urinary solute (osmole) excretion*, an extremely low solute load shrinks the maximum volume of water the kidney can clear, so that even a modest fluid (beer) load overwhelms it and dilutional hyponatremia ensues despite **maximally suppressed AVP and maximally dilute urine**. The same physiology underlies the “*tea-and-toast*” syndrome in malnourished, non-alcoholic patients on protein-poor diets.

Pathophysiology — why low solute intake causes hyponatremia

- ▶ **Free-water excretion is solute-limited.** The kidney can excrete free water only in proportion to the solute (mainly urea + electrolytes) delivered to and excreted by the distal nephron. Maximum urine output $\approx$ (daily solute excreted) $\div$ (minimum achievable urine osmolality).
- ▶ **Minimum urine osmolality** the human kidney can achieve with full AVP suppression is **~ 50 mOsm/kg**.
- ▶ **Quantitative illustration (CMDT):**
 - A normal Western diet generates **~ 1000 mOsm of solute/day** $\rightarrow$ at a minimum Uosm of 50 mOsm/kg the kidney can put out up to **~ 20 L of dilute urine/day**, so ordinary water loads are easily cleared.
 - A beer-only / “tea-and-toast” diet generates only **~ 200 mOsm/day** $\rightarrow$ maximum urine output falls to **~ 4 L/day**. Once daily fluid (beer) intake exceeds this ceiling, electrolyte-free water is retained and serum Na^+ falls.
- ▶ **AVP is appropriately suppressed** (or rapidly suppressible) — this is an *ADH-independent* hyponatremia. The defect is inadequate substrate (solute) for water excretion, **not** inappropriate antidiuresis.
- ▶ Contributory factors in alcoholics: **poor protein/salt intake**, beer-induced **carbohydrate load** (further suppresses ureagenesis and lowers urinary solute), and often coexisting **GI losses, hypokalemia and malnutrition**.

Etiology and predisposing settings

- ▶ **Chronic heavy beer drinkers** whose only nutrient is beer — the eponymous setting (beer = high water + carbohydrate, minimal protein/ Na^+).
- ▶ **“Tea-and-toast” diet** — elderly, frail or non-alcoholic patients on very low-protein, low-salt diets.
- ▶ **Extreme/restricted diets** — e.g. extreme vegetarian or nutrient-restricted “fad” diets with high water intake.
- ▶ Common background of **malnutrition, thiamine deficiency, hypokalemia, hypomagnesemia and alcoholic liver disease**, all of which heighten the risk during correction.

Clinical and biochemical profile

Feature	Typical finding in beer potomania
Volume status	Clinically euvolemic (often mildly hypovolemic)
Serum osmolality	Low (hypotonic, <275 – 280 mOsm/kg)
Urine osmolality	Very low — <100 mOsm/kg to low 200s (dilute urine; suppressed AVP)
Urine Na^+	<20 mmol/L (often <10 – 20)

Feature	Typical finding in beer potomania
Serum AVP/ADH	Suppressed or rapidly suppressible with saline
Serum K ⁺	Frequently low (poor intake, GI losses)
Serum uric acid	Variable; not the hypouricemia typical of SIAD
Response to saline/diet	Hyponatremia corrects rapidly (often dangerously fast)

- **Symptoms** track the rate and depth of the fall in Na⁺: anorexia, nausea, headache, lethargy, gait unsteadiness/falls; with severe or acute drops — confusion, seizures, obtundation, coma (cerebral oedema).
- Many cases are **chronic** (>48 h), so the brain has osmotically adapted and the patient may be only mildly symptomatic despite Na⁺ <120 mmol/L — which is precisely what makes overcorrection dangerous.

Diagnostic approach and differential diagnosis

- **Step 1 — confirm true hypotonic hyponatremia:** measure serum osmolality to exclude *pseudohyponatremia* (hyperlipidemia/hyperproteinemia) and *hypertonic (translocational)* hyponatremia (hyperglycemia, mannitol).
- **Step 2 — measure urine osmolality:** Uosm <100 mOsm/kg places the patient in the *ADH-independent* group (suppressed AVP) — the bracket that contains beer potomania, primary polydipsia and tea-and-toast diet. Uosm >100 implies a continuing AVP effect (SIAD, hypovolemia, oedematous states).
- **Step 3 — measure urine Na⁺ and assess volume/diet:** low Uosm + low urine Na⁺ + a corroborating dietary history clinches low-solute hyponatremia.

Parameter	Beer potomania / low solute	Primary (psychogenic) polydipsia	SIAD
Mechanism	Low solute → low free-water clearance	Massive water intake > excretory capacity	Inappropriate AVP (water retention)
AVP	Suppressed	Suppressed	Inappropriately high
Urine osmolality	<100 → low 200s	<100 mOsm/kg	>100 (usually >300) mOsm/kg
Urine Na ⁺	<20 mmol/L	Low	Usually >30–40 mmol/L
Serum uric acid	Not characteristically low	Normal	Low (<4 mg/dL)
Dietary clue	Beer-only / “tea & toast”	Polydipsia, psychiatric illness	None

Treatment and the critical danger of overcorrection

- ▶ **Mainstay:** simply resuming a normal diet $\pm$ isotonic (0.9%) saline restores urinary solute excretion and the kidney rapidly dumps the retained free water — so the Na^+ tends to **self-correct very quickly and unpredictably**.
- ▶ This is the central exam point: **patients with beer potomania carry a HIGH risk of osmotic demyelination syndrome (ODS / central pontine myelinolysis)** because they combine *every* major ODS risk factor — **alcoholism, malnutrition, hypokalemia, severe chronic hyponatremia, and a strong tendency to overcorrect** once solute is restored and AVP shuts off.
- ▶ **Correction-rate limits (chronic hyponatremia):** do not exceed $\sim 8 \text{ mmol/L}$ in 24 h (some texts $8\text{--}10 \text{ mmol/L/24 h}$, and $<18 \text{ mmol/L/48 h}$). In high-risk patients (which beer potomania is), aim lower — $4\text{--}6 \text{ mmol/L/day}$; this is a *limit, not a target*.
- ▶ **Anticipate and pre-empt the auto-correction:** monitor serum Na^+ frequently (**every 1–2 h** initially). If a brisk water diuresis begins, *re-lower* Na^+ with hypotonic fluid (D5W) and/or use a DDAVP (desmopressin) “clamp” to stop the free-water diuresis and keep correction within limits.
- ▶ **Correct hypokalemia cautiously** — K^+ repletion itself raises serum Na^+ and can precipitate overcorrection.
- ▶ **Give thiamine** before/with any dextrose-containing fluids in alcoholics (prevent Wernicke encephalopathy).
- ▶ For genuinely *symptomatic/severe acute* hyponatremia, hypertonic 3% NaCl (e.g. 100 mL boluses over ~ 10 min, targeting a prompt $4\text{--}5 \text{ mmol/L}$ rise) is used — but in chronic beer potomania the threat is usually too-rapid correction, not under-correction.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Flow diagram of solute-limited water excretion:** boxes/arrows — *Low dietary solute (beer: low protein, Na^+ $1\text{--}2 \text{ mmol/L}$) $\rightarrow$ Low urinary solute excretion ($\sim 200 \text{ mOsm/day}$) $\rightarrow$ Reduced maximum free-water clearance (max urine $\sim 4 \text{ L/day}$ at $\text{U}_{\text{osm}} 50 \text{ mOsm/kg}$) $\rightarrow$ Beer (water) intake exceeds ceiling $\rightarrow$ Free-water retention $\rightarrow$ Dilutional hyponatremia (with AVP suppressed, $\text{U}_{\text{osm}} < 100$, $\text{U}_{\text{Na}} < 20$). Add a side note: “Normal diet $\approx 1000 \text{ mOsm/day}$ $\rightarrow$ up to $\sim 20 \text{ L/day}$.”*
- ▶ **Hyponatremia work-up algorithm:** Serum osmolality (exclude pseudo/hypertonic) $\rightarrow$ if hypotonic, Urine osmolality: $< 100 \text{ mOsm/kg}$ branch $\rightarrow$ ADH-independent $\rightarrow$ label the three boxes *Primary polydipsia | Beer potomania | Tea-and-toast diet*; > 100 branch $\rightarrow$ assess volume status $\rightarrow$ hypovolemic / SIAD (euvolemic) / hypervolemic. Labels to include: *S_{osm}, U_{osm} $50\text{--}100 \text{ mOsm/kg}$, U_{Na} $< 20 \text{ mmol/L}$, suppressed AVP.*

Clinical / Diagnostic significance

- ▶ A correctable, **diet-related** cause of hyponatremia that must be distinguished from SIAD — misclassifying it as SIAD and fluid-restricting/giving hypertonic saline can drive dangerous overcorrection.
- ▶ The triad **low Uosm + low urine Na⁺ + suggestive dietary history** is diagnostic; serum uric acid and volume assessment help separate it from SIAD.
- ▶ Illustrates a key renal-physiology teaching point: **free-water clearance is rate-limited by solute delivery**, not by water intake alone.
- ▶ A *sentinel* condition for **ODS prophylaxis** — anticipate spontaneous overcorrection, monitor intensively, and be ready with DDAVP/D5W re-lowering.

High-yield exam pointers

- ▶ Beer potomania = **low-solute, ADH-INDEPENDENT hypotonic hyponatremia**; AVP is *suppressed*, urine is *maximally dilute*.
- ▶ Beer is essentially salt- and protein-free — only **1–2 mmol/L Na⁺**; high water + carbohydrate load.
- ▶ Biochemistry: **Uosm <100 (to low 200s) mOsm/kg, urine Na⁺ <20 mmol/L, low serum osmolality**.
- ▶ Mechanism number to quote: normal diet ~1000 mOsm/day → **up to ~20 L urine**; beer diet ~200 mOsm/day → **only ~4 L**.
- ▶ Differential = **primary polydipsia** and “**tea-and-toast**” diet (other ADH-independent, low-Uosm causes).
- ▶ Treatment = **normal diet + isotonic saline** → corrects fast → **highest risk of ODS/central pontine myelinolysis**.
- ▶ Correction limit **~8 mmol/L/24 h** (high-risk target **4–6 mmol/L/day**); monitor Na⁺ **1–2 hourly**; consider **DDAVP clamp** and D5W to prevent/treat overcorrection.
- ▶ Co-manage **hypokalemia, magnesium, and thiamine**; cautious K⁺ replacement (raises Na⁺).

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Fluid and Electrolyte Disturbances” (hyponatremia: low solute intake / beer potomania; SIAD; osmotic demyelination syndrome and correction limits).
- ▶ **CMDT 2026** — “Electrolyte & Acid-Base Disorders” (hypotonic hyponatremia diagnostic algorithm; ADH-independent low-solute causes — beer potomania and tea-and-toast diet; solute-dependent maximum urine volume; Furst ratio; correction rate, ODS risk factors, and DDAVP clamp).



Beri Beri

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — *Beriberi* is the clinical syndrome of **thiamine (vitamin B1) deficiency**. Because thiamine pyrophosphate is the coenzyme that drives oxidative decarboxylation and the pentose-phosphate transketolase reaction, its lack cripples aerobic energy generation in the most metabolically active tissues — heart, peripheral nerve and brain. Prolonged deficiency therefore produces a high-output cardiac failure (**wet beriberi**), a symmetric sensorimotor polyneuropathy (**dry beriberi**) and a central neuropsychiatric disorder (**Wernicke-Korsakoff syndrome**), with considerable clinical overlap between these forms.

Thiamine: biochemistry and why deficiency causes disease

- ▶ **Vitamin B1** was the *first vitamin to be identified*; it is a water-soluble vitamin with small body stores that deplete within **weeks** of a deficient diet (unlike B12/vitamin A, which last ≥ 1 year).
- ▶ Active cofactor = **thiamine pyrophosphate (TPP)**. Functions:
 - Coenzyme for **decarboxylation of α -keto acids** (pyruvate, α -ketoglutarate) and branched-chain amino acids $\rightarrow$ essential for ATP/energy generation.
 - Coenzyme for the **transketolase** reaction, interconverting hexose and pentose phosphates (basis of the diagnostic enzyme assay).
 - Postulated role in **peripheral nerve conduction**.
- ▶ **Food sources**: yeast, organ meat, pork, legumes, beef, whole grains, nuts. *Milled/polished rice and processed grains contain very little thiamine* — hence endemic beriberi in rice-eating populations. Food processing removes it and high-heat/prolonged cooking destroys it.
- ▶ **Anti-thiamine factors**: heat-labile **thiaminases** (raw fish, shellfish) destroy the vitamin; heat-stable **polyhydroxyphenols/tannins** (coffee, tea, Brussels sprouts, betel nut) inactivate it.
- ▶ Overt deficiency develops at a dietary level < 0.3 mg/1000 kcal.

Aetiology and at-risk groups

- ▶ **Developing world / classic beriberi**: disproportionate reliance on **polished rice** and highly processed staples; famine, refugee and displaced populations.
- ▶ **Western world (commonest causes)**: **chronic alcohol use disorder** and chronic illness (e.g., cancer). Alcohol *directly impairs intestinal thiamine absorption, blocks TPP synthesis and increases urinary excretion*.
- ▶ **Refeeding/carbohydrate load**: giving a large carbohydrate load (oral, enteral or **parenteral glucose**) to a thiamine-depleted patient can precipitate **acute thiamine deficiency with lactic acidosis** — thiamine must always be given *before/with* refeeding.

- ▶ **Other groups:** prolonged hyperemesis gravidarum, anorexia and eating disorders, post bariatric/metabolic surgery (“bariatric Wernicke”), dialysis, chronic diuretic therapy (increased urinary thiamine loss in heart failure/hypertension).
- ▶ **Drugs** that inhibit the intestinal thiamine transporter ThTR2 — **metformin, verapamil** — raise deficiency risk.
- ▶ **Maternal thiamine deficiency** → **infantile beriberi** in breast-fed babies.

Clinical types — Wet vs Dry beriberi

Feature	Wet (cardiovascular) beriberi	Dry (neurological) beriberi
Dominant system	Heart and circulation	Peripheral (± central) nervous system
Precipitating setting	Deficiency + severe physical exertion + high carbohydrate intake	Deficiency + inactivity + low-calorie intake
Mechanism	Impaired myocardial energy metabolism + dysautonomia; marked peripheral vasodilatation	Energy failure in peripheral nerve → axonal degeneration
Onset	Can appear after ~3 months of deficient diet	Insidious
Cardiac features	High-output congestive heart failure , enlarged heart/cardiomegaly, tachycardia, pulmonary oedema, peripheral oedema with warm extremities (mimics cellulitis)	Usually absent
Neurological features	Peripheral neuritis may coexist	Symmetric motor + sensory polyneuropathy , pain/paraesthesia, diminished/absent reflexes , <i>legs affected more than arms</i> , difficulty rising from a squatting position
Reference	High-output failure listed among nutritional (beriberi) causes	Distal, length-dependent neuropathy

- ▶ The two forms **overlap**; pain and paraesthesiae occur in either. An acute fulminant cardiovascular collapse with lactic acidosis (*acute pernicious* / “*Shoshin*” beriberi) is the most dramatic cardiac presentation — see Coverage note.

Wernicke-Korsakoff syndrome (central nervous beriberi)

- ▶ Seen especially in **alcoholic** patients with chronic thiamine deficiency; the brain counterpart of beriberi.
- ▶ **Wernicke's encephalopathy** — classic triad:
 - **Ophthalmoplegia** (weakness of one or more extraocular muscles) and **horizontal nystagmus**
 - **Cerebellar / truncal ataxia**
 - **Global confusion / mental impairment**
- ▶ When there is additional **memory loss with confabulatory psychosis** → **Wernicke-Korsakoff syndrome** (Korsakoff = amnesia, confabulation, impaired new learning).
- ▶ Despite the characteristic picture, the syndrome is frequently **underdiagnosed**; a high index of suspicion in any malnourished, alcoholic, post-bariatric or hyperemetic patient is essential.

Investigations / Diagnosis

- ▶ Largely **clinical**, supported by a **therapeutic response to empirical thiamine**.
- ▶ **Erythrocyte transketolase activity** measured *before and after* adding TPP: a **>25% stimulation** (activity coefficient ≥ 1.25) indicates deficiency.
- ▶ **Direct thiamine assay** — serum/whole-blood thiamine or its phosphate esters by **HPLC**; normal $\approx 70\text{--}180\text{ nmol/L}$.
- ▶ Urinary thiamine excretion is also used.
- ▶ Always assess **co-existing deficiencies** (other B vitamins, magnesium) and look for the underlying cause (alcohol, malabsorption, bariatric surgery, hyperemesis).

Treatment

- ▶ **Acute beriberi / Wernicke's (Harrison regimen):** **thiamine 200 mg IV three times daily** until there is no further improvement in acute signs, then **oral thiamine 10 mg/day** until recovery is complete. (CMDT: **50–100 mg/day IV** initially, then oral **5–100 mg/day**.)
- ▶ **Cardiovascular and ophthalmoplegic features improve within 24 hours**; neuropathy clears gradually; Korsakoff psychosis may be **permanent** or persist for months.
- ▶ **Give glucose only after/with thiamine** in at-risk patients to avoid precipitating acute deficiency and lactic acidosis.
- ▶ **Replete magnesium** — it is a required cofactor for thiamine activation; thiamine supplementation is ineffective if magnesium is depleted. Co-administer other water-soluble (B-complex) vitamins.
- ▶ **Liberal prophylactic thiamine** (e.g., **50–100 mg oral thiamine daily for ≥ 1 week** in alcohol withdrawal; generous parenteral cover in the emergency setting) for all patients with alcohol use disorder.
- ▶ **Outcome:** roughly one-fourth recover immediately, one-fourth over days, and about half achieve only partial or no benefit — underscoring the value of *early* treatment.

- ▶ **Toxicity:** essentially none from food/supplements; rare hypersensitivity/anaphylaxis has followed high-dose IV thiamine.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Two-circle “Wet vs Dry beriberi” overlap (Venn) diagram.** Labels — *Common stem:* “Thiamine (B1) deficiency → ↓TPP → impaired oxidative decarboxylation/transketolase → energy failure”; *Wet circle:* “High-output cardiac failure, cardiomegaly, tachycardia, warm peripheral oedema, pulmonary oedema”; *Dry circle:* “Symmetric sensorimotor polyneuropathy, legs > arms, absent ankle reflexes, foot/wrist drop”; *Overlap:* “pain, paraesthesia, peripheral neuritis”; *Central extension:* “Wernicke-Korsakoff syndrome”.
- ▶ **Wernicke triad triangle.** Three vertices labelled **Ophthalmoplegia / nystagmus**, **Cerebellar (truncal) ataxia**, **Confusion (global)**; arrow to a fourth box “+ amnesia & confabulation = Korsakoff”.

Clinical / Diagnostic significance

- ▶ Beriberi is a key **reversible cause of high-output heart failure** (alongside anaemia, thyrotoxicosis, AV shunts, Paget’s disease, cirrhosis) — suspect it in dilated cardiomyopathy/CCF with warm extremities in a malnourished or alcoholic patient.
- ▶ Wet beriberi oedema with **warm, well-perfused extremities** is a clinical clue distinguishing it from low-output failure and from cellulitis.
- ▶ **Refeeding syndrome:** never load carbohydrate into a chronically malnourished or alcoholic patient without prior thiamine — iatrogenic Wernicke’s and lactic acidosis are classic, examinable pitfalls.
- ▶ A **rapid response to IV thiamine** (ocular signs within 24 h) is both therapeutic and diagnostic.
- ▶ Post-**bariatric surgery** patients are a modern high-risk group; persistent vomiting in such a patient mandates parenteral thiamine.

High-yield exam pointers

- ▶ Thiamine = **vitamin B1**, the *first vitamin identified*; cofactor **TPP** for pyruvate/α-ketoglutarate dehydrogenase, branched-chain ketoacid dehydrogenase and **transketolase**.
- ▶ **Polished/milled rice** diets and **chronic alcoholism** are the prototypical causes; **thiaminases** (raw fish) and **tannins** (tea, betel nut) are dietary antagonists.
- ▶ **Wet** = **cardiac** (high-output failure, warm oedema); **Dry** = **neuropathy** (symmetric, legs > arms, lost ankle jerks).
- ▶ **Wernicke triad** = **ophthalmoplegia/nystagmus** + **ataxia** + **confusion**; add **amnesia** + **confabulation** = **Korsakoff**.
- ▶ **Diagnosis:** erythrocyte transketolase activity with >25% **TPP stimulation** (coefficient ≥1.25); blood thiamine by HPLC (≈70–180 nmol/L).

- ▶ **Treatment:** high-dose parenteral thiamine first, glucose later; replete magnesium; ocular/cardiac signs reverse within 24 h, Korsakoff amnesia may be permanent.
- ▶ **Carbohydrate repletion without thiamine** → acute deficiency + lactic acidosis (refeeding Wernicke).
- ▶ **Infantile beriberi** results from maternal thiamine deficiency in breast-fed infants.
- ▶ Thiamine has **no significant toxicity**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Vitamin and Trace Mineral Deficiency and Excess*” (thiamine biochemistry, food sources, wet/dry beriberi, Wernicke-Korsakoff, transketolase diagnosis, treatment regimen); “*Alcohol and Alcohol Use Disorders*” (alcohol-related thiamine deficiency, prophylactic thiamine in withdrawal); “*Heart Failure*” chapter (beriberi as a cause of high-output cardiac failure).
- ▶ **CMDT 2026** — “*Nutrition, Nutritional Disorders, & Obesity*” (clinical features of wet vs dry beriberi, biochemical tests, normal thiamine 70–180 nmol/L, parenteral treatment doses, magnesium dependence, referral).
- ▶ **Coverage note:** The eponym “**Shoshin**” (**acute fulminant cardiac**) beriberi is standard internal-medicine terminology but is **not named in this corpus**; it is included only as universally accepted teaching. No dedicated subspecialty textbook was specified for this nutrition topic (specialty_books empty), so depth is drawn from Harrison + CMDT, which cover the topic adequately.



Evaluation and management of Hyponatremia

Asked in: Paper IV Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Hyponatremia is a serum sodium concentration <135 mEq/L (mmol/L) and is the commonest electrolyte disorder in clinical practice. It usually represents **excess water relative to sodium**, not true total-body sodium deficiency; therefore serum sodium must be interpreted with serum osmolality, urine osmolality, urine sodium, volume status, symptoms, and duration. Acute hypotonic hyponatremia causes cerebral edema, whereas chronic hyponatremia is dangerous mainly because rapid correction can cause **osmotic demyelination syndrome (ODS)**.

Pathophysiology and clinical severity

- ▶ Plasma sodium reflects the ratio of exchangeable $\text{Na}^+ + \text{K}^+$ to **total body water**. Hyponatremia develops when water intake, oral or intravenous, exceeds renal free-water excretory capacity, most often because **arginine vasopressin/ADH** is present when it should be suppressed.

- ▶ **Acute hyponatremia** is usually <48 h in duration. Brain cells swell before adaptive osmolyte loss occurs; symptoms include headache, nausea, vomiting, confusion, seizures, coma, respiratory failure, brainstem herniation, and death.
- ▶ **Chronic hyponatremia** is usually >48 h. Brain cells lose inorganic ions and organic osmolytes, so severe cerebral edema is less likely; however, chronic “asymptomatic” hyponatremia is associated with impaired attention, gait instability, falls, fractures, osteoporosis, and increased morbidity.
- ▶ Severity by sodium level: **mild 130-134, moderate 125-129, severe <125 mEq/L**. Clinical urgency is decided more by **neurologic symptoms and acuity** than by the number alone.
- ▶ **ODS risk** rises with chronic severe hyponatremia and overcorrection, especially when serum Na⁺ is very low, or with **hypokalemia, alcoholism, malnutrition, advanced liver disease, or liver transplantation**. ODS may present days later with dysarthria, dysphagia, quadriparesis, parkinsonism, catatonia, impaired consciousness, or locked-in syndrome.

Etiological classification

Step	Pattern	Important causes / clues
1. Serum osmolality	Normal osmolality: pseudohyponatremia	Severe hypertriglyceridemia or hyperproteinemia; confirm with direct ion-selective electrode if suspected.
	High osmolality: translocational hyponatremia	Hyperglycemia, mannitol, glycine/maltose; sodium falls approximately 1.6-2.4 mEq/L per 100 mg/dL glucose rise above normal.
	Low osmolality: true hypotonic hyponatremia	Most clinically important cases; proceed to urine osmolality and volume assessment.
2. Urine osmolality	<100 mOsm/kg	ADH appropriately suppressed: primary polydipsia, beer potomania, low-protein “tea and toast” diet.
	>100 mOsm/kg	Impaired urinary dilution due to ADH effect, renal failure, diuretics, endocrine disease, or SIADH.
3. Volume status / urine Na ⁺	Hypovolemic	Vomiting, diarrhea, sweating, burns, third spacing, thiazides, renal salt wasting, adrenal insufficiency; urine Na ⁺ often <20-30 mEq/L in extrarenal loss.

Step	Pattern	Important causes / clues
	Hypervolemic	Heart failure, cirrhosis, nephrotic syndrome, advanced kidney disease; low effective arterial blood volume drives nonosmotic ADH.
	Euvolemic	SIADH, glucocorticoid deficiency, severe hypothyroidism/myxedema, reset osmostat, drugs, nausea, pain, postoperative state.

- ▶ Important acute settings: postoperative hypotonic fluids, recent thiazide use, colonoscopy preparation, glycine irrigation, endurance exercise, psychogenic polydipsia, and MDMA/ecstasy.
- ▶ Common SIADH associations: small-cell carcinoma lung and other tumors, CNS disorders, pulmonary infections, positive-pressure ventilation, HIV, pain, nausea, stress, SSRIs, tricyclics, carbamazepine, antipsychotics, cyclophosphamide/ifosfamide, vincristine, NSAIDs, opioids, nicotine, and AVP analogues.

Evaluation

- ▶ **First triage:** check airway, breathing, circulation, seizures, mental status, vomiting, respiratory distress, and evidence of raised intracranial pressure. Treat severe symptoms while the diagnostic workup proceeds.
- ▶ **History:** duration, prior sodium values, fluid intake, low-solute diet/alcohol, hypotonic IV fluids, GI losses, urine output, surgery, exercise, pain/nausea, pulmonary/CNS disease, malignancy risk, adrenal/pituitary/thyroid symptoms, and a complete drug history including thiazides, SSRIs, antiepileptics, antipsychotics, NSAIDs, opioids, chemotherapy, desmopressin, and MDMA.
- ▶ **Examination:** volume status is mandatory but imperfect; look for orthostasis, tachycardia, dry mucosa, low JVP, edema/ascites, heart failure, cirrhosis, nephrotic syndrome, and neurologic signs.
- ▶ **Initial laboratories:** serum electrolytes, glucose, urea/BUN, creatinine, measured serum osmolality, serum uric acid, potassium, calcium/magnesium as needed, urine osmolality, urine Na⁺, urine K⁺, and urine creatinine. Use measured/effective osmolality to exclude pseudo- and hypertonic hyponatremia.
- ▶ **Urine interpretation:** urine osmolality <100 mOsm/kg suggests primary polydipsia or low solute intake; >400-500 mOsm/kg indicates strong ADH effect and predicts poor response to simple fluid restriction. Urine Na⁺ <20-30 mEq/L supports low effective arterial volume unless diuretics or renal salt loss confound interpretation; urine Na⁺ >30 mEq/L supports SIADH, renal salt wasting, diuretics, or adrenal insufficiency.

- ▶ **SIADH diagnosis:** hypotonic hyponatremia with inappropriately concentrated urine, clinical euvolemia, urine Na⁺ usually >20-30 mEq/L, absence of heart/liver/kidney failure, and normal adrenal and thyroid function. Supportive clues are low BUN and **hypouricemia <4 mg/dL**. Plasma AVP or copeptin is generally not useful for routine differential diagnosis.
- ▶ **Targeted tests:** morning cortisol and/or cosyntropin test when adrenal insufficiency is possible; TSH/free T4 for severe hypothyroidism or to satisfy SIADH criteria; chest radiograph or CT thorax in unexplained SIADH, especially smokers or suspected small-cell lung carcinoma; neuroimaging when CNS disease is suspected.

Management principles

- ▶ Stop hypotonic fluids and offending drugs, restrict unnecessary free water, correct hypoxia and seizures, and treat the underlying cause. Admit patients with severe symptoms, Na⁺ <125 mEq/L with risk factors, uncertain cause, or need for hypertonic saline, vaptans, dialysis, or very frequent monitoring.
- ▶ **Severe symptomatic hyponatremia:** give 3% NaCl 100 mL IV bolus over 10-15 min, reassess clinically and recheck sodium; repeat up to two times if severe symptoms persist, aiming for an initial 4-6 mEq/L rise, not normalization. Hypertonic saline contains about 513 mEq/L NaCl.
- ▶ If symptoms are less severe but active correction is needed, 3% NaCl infusion may be used with close monitoring. Serum sodium should be checked every 1-4 h during active hypertonic saline therapy; change the infusion according to the observed sodium rise, not only formula predictions.
- ▶ After the initial symptom-relieving rise, use chronic correction limits: generally **do not exceed 8 mEq/L in 24 h**; Harrison recommends <6-8 mEq/L in the first 24 h and <6 mEq/L per subsequent 24 h, and <18 mEq/L in 48 h. In high-risk patients, target only 4-6 mEq/L/day.
- ▶ Replace potassium carefully because K⁺ repletion itself raises serum Na⁺. If overcorrection occurs or a brisk water diuresis begins, **stop active therapy**, give **desmopressin (DDAVP)** and/or D5W/free water to stabilize or relower sodium. A proactive DDAVP “clamp” may be considered in severe chronic hyponatremia at high risk of rapid aquaresis.
- ▶ **Do not use vaptans for acute symptomatic hyponatremia;** they may overcorrect unpredictably and do not replace emergency hypertonic saline.

Management by cause

- ▶ **Hypovolemic hyponatremia:** restore effective circulating volume with **0.9% saline** and stop losses/diuretics. As volume is restored, ADH may shut off and a brisk dilute diuresis can rapidly overcorrect sodium; monitor closely, especially if duration >48 h or risk factors for ODS are present.
- ▶ **Thiazide-associated hyponatremia:** stop the thiazide, replace K⁺, avoid premature SIADH diagnosis until at least **1-2 weeks** after withdrawal if urine studies mimic SIADH.

- ▶ **Low-solute intake / beer potomania:** increase dietary solute/protein and avoid uncontrolled saline correction; these patients often correct rapidly and have high ODS risk because alcoholism, malnutrition, and hypokalemia commonly coexist.
- ▶ **Hypervolemic hyponatremia:** treat heart failure, cirrhosis, nephrotic syndrome, or renal failure; restrict fluid and sodium as appropriate, use loop diuretics for congestion, and avoid routine isotonic saline because it worsens edema. Vaptans can raise Na^+ in selected euvoletic/hypervolemic patients but do not improve hard outcomes and require specialist-supervised monitoring.
- ▶ **SIADH / euvoletic chronic hyponatremia:** first treat the cause and restrict all fluids, usually **500-1000 mL/day**. If the urine/plasma electrolyte ratio ($\text{UNa} + \text{UK}$)/ PNa is >1 , fluid restriction alone is likely to fail and may need to be <500 mL/day; if ratio is about 1, restrict 500-700 mL/day; if <1 , <1 L/day may suffice.
- ▶ If fluid restriction fails: increase solute with oral salt and protein, use **oral urea 15-60 g/day** (often 30-60 g/day in SIADH), or consider loop diuretic plus salt tablets in selected cases. Demeclocycline is slow and nephrotoxic and should be avoided particularly in cirrhosis.
- ▶ **Tolvaptan** is an oral V_2 antagonist for selected persistent SIADH or hypervolemic hyponatremia; start in hospital, lift fluid restriction during active aquaresis, monitor Na^+ every 6-8 h or more often in high-risk patients, and avoid/limit use in liver disease because of hepatotoxicity concerns. Low-dose **7.5 mg** is often used to reduce overcorrection risk; conventional starting dose is 15 mg where used.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm for hyponatremia:** Serum $\text{Na}^+ <135$ -> serum osmolality (normal pseudo / high hyperglycemia-mannitol / low hypotonic) -> urine osmolality (<100 : polydipsia, beer potomania, tea-toast; >100 : ADH effect) -> volume status and urine Na^+ (hypovolemic, euvoletic/SIADH-endocrine-drugs, hypervolemic HF-cirrhosis-nephrotic).
- ▶ **Treatment flowchart:** severe neurologic symptoms -> 3% NaCl 100 mL bolus -> target $+4$ - 6 mEq/L -> chronic correction limits -> DDAVP/D5W if overcorrecting; no/mild symptoms -> classify by volume -> isotonic saline / fluid restriction-urea-vaptan / treat edematous state.

Clinical / Diagnostic significance

- ▶ Hyponatremia is often **multifactorial**; a patient may have thiazide use, low solute intake, nausea, pain, and hypotonic fluids simultaneously.
- ▶ In unexplained SIADH, actively search for **small-cell lung carcinoma**, other pulmonary disease, CNS disease, and causative drugs; a chest x-ray may miss small-cell lung cancer, so CT thorax is justified in high-risk patients.

- ▶ Differentiating **SIADH from cerebral salt wasting** matters: SIADH is clinically euvolemic and treated with water restriction/solute strategies; cerebral salt wasting is hypovolemic renal salt loss and needs salt and volume replacement, though true CSW is uncommon and controversial.
- ▶ Normal saline corrects hypovolemic hyponatremia but may fail or worsen SIADH because the kidney excretes the sodium while retaining water.
- ▶ Vaptans, hypertonic saline, glucocorticoid replacement, stopping thiazides, and treating hypovolemia can all trigger rapid aquaresis; sodium monitoring must intensify when the cause of ADH excess is abruptly removed.

High-yield exam pointers

- ▶ Write the definition: **serum Na⁺ <135 mEq/L**, usually due to **excess water**, not sodium lack.
- ▶ First decide whether it is **pseudo-, hypertonic, or hypotonic** hyponatremia.
- ▶ In hypotonic hyponatremia, the key urine tests are **urine osmolality** and **urine Na⁺**.
- ▶ **Uosm <100 mOsm/kg** means ADH is suppressed: primary polydipsia or low solute intake.
- ▶ **Uosm >100 mOsm/kg** means impaired dilution; then classify as hypovolemic, euvolemic, or hypervolemic.
- ▶ SIADH is a diagnosis of exclusion: euvolemia, low serum osmolality, urine not maximally dilute, urine Na⁺ usually >20-30, normal adrenal/thyroid function, and no heart/liver/kidney failure.
- ▶ Severe symptoms need **3% saline 100 mL bolus**, aiming only for **4-6 mEq/L** initial rise.
- ▶ Chronic correction limit: **do not exceed 8 mEq/L/24 h**; aim lower in alcoholism, malnutrition, hypokalemia, severe liver disease, or very low Na⁺.
- ▶ Overcorrection is treated/prevented with **DDAVP and/or D5W**, not by ignoring a rapid water diuresis.

SOURCE & COVERAGE

Harrison 22e — “Fluid and Electrolyte Disturbances”; Harrison 22e — “Disorders of the Neurohypophysis”; Brenner & Rector’s The Kidney — “Disorders of Water Balance”; CMDT 2026 — “Electrolyte & Acid-Base Disorders”.



Hyponatremia

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Hyponatremia is a plasma Na⁺ concentration <135 mmol/L and is the commonest electrolyte abnormality in clinical practice, occurring in up to **22% of hospitalised patients**. It is fundamentally a disorder of *water balance* — an **excess of body water relative to sodium** — and almost always reflects an increase in circulating arginine vasopressin (AVP/ADH) and/or increased

renal sensitivity to AVP, combined with continued free-water intake. The serum Na^+ therefore says *nothing* about total-body sodium or volume status, both of which must be assessed independently. The key clinical danger is **cerebral oedema** (acute) and **osmotic demyelination from over-rapid correction** (chronic).

Pathophysiology of water homeostasis

- ▶ Serum osmolality is normally held at 285–295 mOsm/kg by two effectors: **thirst** and **AVP** acting on renal V2 receptors (insertion of aquaporin-2 → free-water reabsorption).
- ▶ Hyponatremia develops when water intake exceeds the kidney's capacity to excrete electrolyte-free water — either because AVP is inappropriately high, renal diluting capacity is impaired, or solute delivery to the diluting segment is inadequate (low-solute states).
- ▶ **Non-osmotic AVP release** (hypovolemia, arterial underfilling in heart failure/cirrhosis, nausea, pain, stress, drugs) overrides osmotic suppression and is central to most hyponatremias.
- ▶ Estimated osmolality = $2[\text{Na}^+] + \text{glucose}(\text{mg/dL})/18 + \text{BUN}(\text{mg/dL})/2.8$. **Effective osmolality (tonicity)** subtracts urea (an ineffective osmole); true hypotonic hyponatremia has an effective osmolality <275 mOsm/kg.

Classification — first by tonicity, then by volume status

Step	Category	Serum osmolality	Mechanism / examples
1	Pseudohyponatremia (isotonic)	Normal	Lab artifact in severe hyperlipidemia / hyperproteinemia (↑ solid phase of plasma); excluded by measuring osmolality
1	Hypertonic (translocational)	High	Hyperglycemia, mannitol — osmotic water efflux from cells; Na^+ falls ~1.6 mmol/L per 100 mg/dL rise in glucose. <i>No cerebral oedema</i>
1	Hypotonic (“true”)	Low (<275)	Genuine water excess — subclassified by volume status (Step 2)
2	Hypovolemic	Low	↓ total body water, ↓↓ total body Na^+
2	Euvolemic	Low	↑ total body water, near-normal Na^+

Step	Category	Serum osmolality	Mechanism / examples
2	Hypervolemic	Low	↑↑ total body water, ↑ Na ⁺ (oedematous states)

Aetiology of hypotonic hyponatremia by volume status

Volume status	Urine Na ⁺	Causes
Hypovolemic	<20 mmol/L (extrarenal)	Vomiting, diarrhoea, GI/tube drainage, third-spacing (pancreatitis, burns, trauma), insensible/sweat loss with hypotonic replacement
Hypovolemic	>20 mmol/L (renal)	Thiazide diuretics, mineralocorticoid deficiency / primary adrenal insufficiency (Addison's → ↑K ⁺), salt-losing nephropathy, osmotic diuresis (glycosuria, ketonuria), bicarbonaturia (RTA, vomiting), cerebral salt wasting
Euvolemic	>20–30 mmol/L	SIAD (commonest), hypothyroidism, secondary (glucocorticoid) adrenal insufficiency, reset osmostat, drugs; beer potomania / low-solute (here UNa <20, U-osm <100–200)
Hypervolemic	<10 mmol/L (Na ⁺ -avid)	Congestive heart failure, cirrhosis, nephrotic syndrome
Hypervolemic	>20 mmol/L	Acute & chronic renal failure

- ▶ **Cerebral salt wasting** — hyponatremia with *true hypovolemia* and inappropriate natriuresis in intracranial disease (subarachnoid haemorrhage, TBI, craniotomy, meningitis, encephalitis). Distinction from SIAD is critical: it responds to **aggressive Na⁺-Cl⁻ repletion**, whereas SIAD requires water restriction.

Syndrome of Inappropriate Antidiuresis (SIAD/SIADH)

- ▶ **Commonest cause of euvolemic hyponatremia.** Patients are not strictly euvolemic but *subclinically volume-expanded* with “AVP escape” limiting further retention.
- ▶ **Bartter–Schwartz diagnostic criteria** (a diagnosis of exclusion): (1) hyponatremia with **hypo-osmolality** (<280 mOsm/kg); (2) **inappropriately concentrated urine** (U-osm >100); (3) **urine**

Na⁺ usually >20–30 mmol/L (euvolemic, normal salt intake); (4) **absence of cardiac, renal, hepatic, thyroid and adrenal disease**; (5) normal acid–base/potassium.

- ▶ Supportive: **low serum uric acid (<4 mg/dL)** and **low BUN (<10 mg/dL)** from dilution + enhanced clearance — distinguishes from hyperuricemic hypovolemic hyponatremia.
- ▶ **Causes (4 groups):** **Malignancy** — *small-cell lung carcinoma* (75% of malignancy-associated SIAD; ~10% have Na⁺ <130 at presentation), head & neck, GI; **Pulmonary** — pneumonia, TB, abscess, positive-pressure ventilation; **CNS** — tumour, SAH, meningitis, encephalitis, head trauma; **Drugs** — SSRIs, tricyclics, **carbamazepine, chlorpropamide**, cyclophosphamide/ifosfamide, vincristine, NSAIDs, antipsychotics, MDMA (“Ecstasy”), desmopressin/oxytocin.

Clinical features

- ▶ Symptoms are predominantly **neurological** (cerebral oedema within the rigid skull) and depend on **severity and rate of fall**.
- ▶ **Acute (<48 h) symptomatic hyponatremia — a medical emergency:** nausea, headache, vomiting → seizures, obtundation, **brainstem herniation**, coma, death; may cause **non-cardiogenic (“neurogenic”) pulmonary oedema** with respiratory failure. **Premenopausal women** are at highest risk of encephalopathy. Settings: post-operative hypotonic fluids, TURP/hysteroscopy glycine irrigation, exercise (marathon) and MDMA-associated, psychogenic polydipsia.
- ▶ **Chronic (>48 h):** brain adapts by extruding **organic osmolytes** (creatine, betaine, glutamate, myoinositol, taurine) — largely complete by 48 h — so patients are often paucisymptomatic, but show subtle gait/cognitive deficits, **falls**, and ↑ **fracture/osteoporosis** risk. This adaptation is the basis of ODS risk on correction.
- ▶ **Severity (CMDT):** mild 130–134, moderate 125–129, **severe <125 mmol/L**.

Diagnostic approach

- ▶ **Step 1 — measure serum osmolality** to exclude pseudo- and hypertonic hyponatremia; calculate effective osmolality (<275 confirms hypotonic).
- ▶ **Step 2 — clinical volume status** (JVP, orthostatic vitals, oedema).
- ▶ **Step 3 — urine osmolality and urine Na⁺:** U-osm <100 mOsm/kg → primary polydipsia / low-solute; U-osm >100 → AVP active. UNa <20–30 → hypovolemic or Na⁺-avid (CHF/cirrhosis); UNa >30 → SIAD-type.
- ▶ **Step 4 — targeted tests:** serum glucose (correct for translocation), **uric acid** (low in SIAD), TSH, 0900 cortisol / **cosyntropin (ACTH-stimulation) test** for adrenal insufficiency; chest/CNS imaging (CT thorax in smokers for small-cell carcinoma).
- ▶ “Gold standard” for hypovolemic hyponatremia = correction of Na⁺ after a normal-saline challenge.

Treatment

- ▶ **Three guiding principles:** symptom severity sets urgency; chronicity sets the *safe correction rate*; response to therapy is **unpredictable** → monitor Na^+ every 1–4 h.
- ▶ **Acute symptomatic (seizures/coma) — hypertonic 3% saline (513 mmol/L):** 100 mL bolus over 10 min, repeatable $\times 2$, aiming to raise Na^+ by 1–2 mmol/L/h for a total of only 4–6 mmol/L — enough to abort herniation; or infusion 0.5–2 mL/kg/h. Add O_2 /ventilatory support and IV loop diuretic if pulmonary oedema. Na^+ deficit = $0.6 \times \text{body weight} \times (\text{target} - \text{actual } \text{Na}^+)$.
- ▶ **Safe correction limits (avoid ODS):** <8–10 mmol/L in first 24 h and <18 mmol/L in 48 h; high-risk patients (alcoholics, malnourished, hypokalemic, $\text{K}^+ < 120$) target only 4–6 mmol/L/day. “Limit, not a goal.”
- ▶ **Chronic / aetiology-specific:**
 - **Hypovolemic** → isotonic 0.9% saline (shuts off AVP — watch for *auto-correction* and overshoot).
 - **Hypervolemic (CHF/cirrhosis)** → fluid + Na^+ restriction, treat underlying disease, loop diuretics, ACE inhibition.
 - **Euvolemic/SIAD** → **fluid restriction** guided by the **Furst / urine-to-plasma electrolyte ratio** ($\text{UNa} + \text{UK}$)/ PNa : ratio >1 restrict <500 mL/d, ~1 restrict 500–700 mL/d, <1 restrict <1 L/d. Add oral salt tablets + furosemide 20 mg BD, oral urea, SGLT2 inhibitors (osmotic glycosuric diuresis), or demeclocycline.
 - **Vaptans (V2 antagonists) — tolvaptan (oral) and conivaptan (IV, mixed V1A/V2) —** aquaretics for SIAD and hypervolemic hyponatremia; **contraindicated in hypovolemic and acute hyponatremia**, avoid in cirrhosis, limit to ≤ 30 days (hepatotoxicity); start in hospital with liberalised fluids.
- ▶ **Overcorrection rescue / prophylaxis:** if Na^+ rises too fast, re-lower with DDAVP (desmopressin) $\pm$ D5W; a planned “DDAVP clamp” with concurrent hypertonic saline gives controlled correction in high-risk patients.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagnostic algorithm box (Fig.):** Top — “Hyponatremia ($\text{Na}^+ < 135$)”. Branch 1 *Serum osmolality* → Normal = pseudohyponatremia / High = hyperglycemia, mannitol / Low = true hypotonic. From “Low”, branch on volume status → Hypovolemia ($\text{UNa} < 20$ extrarenal: GI loss, third-space; $\text{UNa} > 20$ renal: diuretics, Addison’s, CSW), Euvolemia (SIAD, hypothyroidism, glucocorticoid deficiency), Hypervolemia (CHF, cirrhosis, nephrotic — $\text{UNa} < 10$; renal failure — $\text{UNa} > 20$). Label arrows $\text{UNa} < 20$ / $\text{UNa} > 20$.
- ▶ **Brain-cell osmolyte diagram:** ICF cell with arrows — *acute* water influx → swelling/cerebral oedema; *chronic* efflux of organic osmolytes (taurine, myoinositol,

glutamate); on **over-rapid correction** → osmotic shrinkage → **osmotic demyelination** (pons). Labels: “cerebral oedema”, “osmolyte efflux (48 h)”, “central pontine myelinolysis”.

Clinical / Diagnostic significance

- ▶ **Osmotic demyelination syndrome (ODS)**: occurs 2–6 days after over-rapid correction; **central pontine myelinolysis** → flaccid then spastic quadriparesis, dysarthria, dysphagia, diplopia, “**locked-in syndrome**”; **extrapontine** lesions (cerebellum, lateral geniculate, thalamus, putamen, cortex) → ataxia, parkinsonism, dystonia, mutism. Often **irreversible** — prevention by rate control is paramount.
- ▶ A **low uric acid + low BUN** in a euvolemic hyponatremic patient strongly favours SIAD; **hyperuricemia** favours volume depletion.
- ▶ Hyponatremia is an independent **adverse prognostic marker** in heart failure and cirrhosis (degree reflects neurohumoral activation).
- ▶ Always recheck for **thiazide effect** and **adrenal insufficiency** before labelling SIAD; defer SIAD diagnosis 1–2 weeks after stopping a thiazide.

High-yield exam pointers

- ▶ Hyponatremia = **water problem**, not a salt problem; Na^+ value reflects nothing about volume status.
- ▶ Three-step work-up: **serum osmolality** → **volume status** → **urine Na^+ /osmolality**.
- ▶ **Translocational Na^+ correction**: subtract ~1.6 mmol/L per 100 mg/dL glucose above normal.
- ▶ SIAD = **Bartter–Schwartz criteria**; uric acid <4 mg/dL; commonest malignancy = **small-cell lung carcinoma**.
- ▶ **Acute symptomatic** → 3% saline 100 mL boluses, target rise only 4–6 mmol/L.
- ▶ **Correction ceiling**: <8–10 mmol/L/24 h, <18/48 h (high-risk 4–6/day) — exceeding this → ODS / central pontine myelinolysis.
- ▶ **Vaptans never in hypovolemic or acute hyponatremia**; isotonic saline corrects hypovolemic type.
- ▶ **Cerebral salt wasting** (hypovolemic, treat with salt) vs SIAD (euvolemic, restrict water) — opposite therapies.
- ▶ Overcorrection rescue = DDAVP + D5W; correct **hypokalemia** cautiously (it itself raises Na^+).

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Fluid and Electrolyte Disturbances” (sodium disorders; SIAD; ODS; hypertonic saline and vaptan therapy).

- **CMDT 2026** — “Electrolyte & Acid-Base Disorders” (osmolality formula, severity grading, Bartter–Schwartz criteria, 3% saline boluses, Furst ratio, SGLT2 inhibitors/oral urea, DDAVP clamp) and “Disorders of the Pituitary, Thyroid, & Adrenal Glands” (SIADH causes).



Parenteral Nutrition Therapy

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — Parenteral nutrition (PN) is the delivery of a nutritionally complete mixture of crystalline amino acids, glucose (dextrose), lipid emulsion, electrolytes, minerals, vitamins and trace elements **directly into the bloodstream**, bypassing the gastrointestinal (GI) tract. It is one of three forms of *specialized nutritional support* (SNS) — the others being optimized voluntary nutrition and enteral nutrition (EN). PN is reserved for patients in whom invasive support is indicated but the gut is non-functional, inaccessible or insufficient. The guiding principle is “*if the gut works, use it*”: EN is always preferred when feasible, and PN carries the higher burden of infectious, metabolic and mechanical complications.

Indications and Patient Selection

- PN is used **when invasive SNS is indicated and EN is impossible, inappropriate or insufficient** to meet nutritional needs.
- The decision to start instrumental SNS rests on four factors: (1) nutrient intake is likely to remain inadequate for **many days**; (2) there is important **muscle loss** (of any cause); (3) **nutrient requirements are increased** (inflammatory diarrhoea, enterocutaneous fistulas/exudates, a protein-catabolic inflammatory state); and (4) a reasoned judgment that SNS will improve clinical outcome or quality of life.
- **Conditions that contraindicate EN and thus favour PN**: intestinal ischaemia, mechanical bowel obstruction, peritonitis, GI haemorrhage, high-output proximal fistula, prolonged paralytic ileus, severe malabsorption (e.g., short-bowel syndrome), and intractable vomiting/diarrhoea where EN fails.
- In the **ICU**, current guidelines advise starting EN soon after resuscitation and stabilization; if the protein goal is not met after **7–10 days**, PN may be added — particularly if the catabolic state persists.
- **Perioperative**: patients with starvation-related malnutrition (SRM) or chronic disease-related malnutrition (CDM) awaiting major elective surgery benefit from **7–10 days** of preoperative SNS (EN/PN if voluntary intake is impractical).

- ▶ PN is generally **not** initiated in advanced incurable malignancy or advanced dementia with no interest in food, where it does not alter the disease trajectory.

Routes of Venous Access

- ▶ Because adult PN admixtures are **hyperosmolar** (>1200 mOsm/L, often >1800 mOsm/L) and frequently large-volume, they must be infused through a **dedicated central-vein port**.
- ▶ **Central (total) PN**: for malnourished patients needing support >7–14 days; catheter tip documented in the **superior vena cava** radiographically before infusion. The *subclavian route is preferred*; **jugular and femoral catheters should be avoided** because of difficulty keeping a dry, sterile dressing and higher complication rates.
- ▶ **Peripheral PN (PPN)**: for non-malnourished patients or **short-term** (<2 weeks) support; lower osmolarity solutions. Limited by a high incidence of **phlebitis**, line infiltration and volume overload.
- ▶ Lipid emulsions are **isotonic** and can be given via either a central or peripheral vein.

Composition of PN Admixtures

- ▶ Supplied as **ready-to-use 2-chamber (amino acids + glucose)** or **3-chamber (amino acids + glucose + lipid)** bags; vitamins, trace elements and extra electrolytes are added just before infusion. Complex needs (especially acute disease-related malnutrition, ADM) justify a **computer-controlled compounder** to individualize composition.

Component	Key points (faithful to source)
Amino acids	Free (hydrated) crystalline amino acids; energy density 3.3 kcal/g (vs 4.0 in formed protein). 100 g free amino acids $\approx$ 83 g protein substrate . Provide all essential amino acids + nonessential N. Typical bags 4–7% amino acids.
Carbohydrate (dextrose)	Dextrose monohydrate , 3.4 kcal/g . Bags 20–25% glucose. Initial dose $\leq$ 200 g/day ; main metabolic hazard = hyperglycaemia.
Lipid emulsion	~10 kcal/g ; supplies essential n-6 and n-3 fatty acids. Soybean-oil based, or mixed (olive/soybean; or SMOF = 30% soybean, 30% MCT, 25% olive, 15% fish oil). Standard infusion $\leq$ 8 g/h ($\approx$ 175 g = 1925 kcal/day in a 70-kg adult). Check triglycerides first; >400 mg/dL is a relative contraindication . To prevent essential fatty acid deficiency, give 250 mL of 20% soy lipid $\geq$ twice weekly (CMDT).
Electrolytes	Sodium and potassium 1–2 mEq/kg/day ; calcium 10–15 mEq/day ; magnesium 8–20 mEq/day ; phosphorus 20–40 mmol/day (CMDT).

Component	Key points (faithful to source)
Trace elements	Zinc, copper, manganese, selenium, chromium. Iron is NOT added (incompatible with lipid; risk of free-radical catalysis) — give IV iron separately if needed. Copper and manganese omitted in cholestatic liver disease (impaired excretion). Extra zinc for high-output diarrhoea/fistula (1 L secretory diarrhoea $\approx$ 12 mg zinc loss).
Vitamins	Injectable adult multivitamin daily (A, D, E, K, B1, B2, B6, B12, niacinamide, dexpantenol, biotin, folic acid, ascorbic acid). Parenteral water-soluble vitamin needs are higher (urinary loss); ascorbic acid degrades in the bag.

Energy, Protein and Fluid Prescription

- ▶ **Energy:** total daily energy expenditure of a healthy sedentary adult $\approx$ **36 kcal/kg** (resting energy expenditure $\approx$ 75%); weight-based estimate **25–35 kcal/kg/day**; indirect calorimetry is the gold standard. Energy doses **>70% of TEE confer no extra protein-sparing** and risk hyperglycaemia, dyslipidaemia and volume expansion.
- ▶ Non-critically ill patients rarely need **>500 g glucose (1700 kcal)/day**; in ADM, limit to **$\leq$ 350 g glucose (1200 kcal)/day** during the intense catabolic phase. *Hypocaloric, protein-generous* nutrition is recommended for the first $\sim$ 2 weeks in fat-sufficient/obese ADM patients.
- ▶ **Protein:** safe intake 0.8 g/kg; **critically ill 1.2–2.0 g/kg/day**. CMDT: stable 0.8–1.2; moderate–severe stress $\geq$ 1.5; trauma/burns up to $\sim$ 2.5 g/kg/day.
- ▶ **Fluid:** total provision should not normally exceed **$\sim$ 2 L/day** without abnormal losses; $\sim$ 25–35 mL/kg or $\sim$ 1 mL/kcal.

Initiation, Glycaemic Control & Monitoring

- ▶ Begin PN only after the patient is **haemodynamically stable**, with glucose/electrolyte/acid-base homeostasis established and able to tolerate the fluid load. Start at $\sim$ half the energy target ($\approx$ 100–150 g dextrose first 24 h), then advance as tolerated.
- ▶ **Insulin:** add subcutaneous/admixture regular insulin to keep glucose **<140 and >80 mg/dL** (180/100 mg/dL in critically ill diabetics). Benchmarks: basal endogenous secretion $\approx$ **30 U/day**; **$\sim$ 10 U insulin per 100 g glucose** in non-diabetic non-catabolic patients; **$\sim$ 20 U/100 g** in type 2 diabetes.
- ▶ **Monitoring:** baseline urea, creatinine, electrolytes, glucose, magnesium, phosphate, calcium, albumin, triglycerides and LFTs; then daily basic panel + Mg/PO₄ during initiation, easing to 1–2 $\times$ /week once stable; **triglycerides and LFTs weekly**; vitamins/trace elements every 3–6 months on long-term PN.

- ▶ **Nitrogen balance** (CMDT) = [24-h protein intake (g) ÷ 6.25] – [24-h urinary nitrogen (g) + 4]; a positive balance confirms adequate provision (Harrison: 1 g N = 6.25 g protein).
- ▶ **Discontinuation:** taper PN as oral/enteral intake rises; stop once the patient tolerates **one-half to two-thirds of requirements** enterally. Slow the rate to 50 mL/h before stopping to avoid reactive hypoglycaemia.

Complications

Category	Examples
Catheter-related (mechanical/insertion)	Pneumothorax, arterial laceration, air embolism, brachial plexus injury; catheter-related bloodstream infection (PN patients are at higher risk than other CVC patients); central venous thrombosis ; thrombotic/non-thrombotic occlusion.
Metabolic	Hyperglycaemia (most frequent); hypoglycaemia (reactive, on abrupt stop); hypertriglyceridaemia ; fluid/electrolyte and acid-base derangements; volume overload (mortality risk).
Hepatobiliary	Mild transaminase rise at 2–4 weeks (often self-limited); fatty liver from energy overfeeding; intrahepatic cholestasis after many weeks — reduced by cyclic PN (infused over only 12 h/day).
Refeeding syndrome	See below.
Long-term	Metabolic bone disease; micronutrient deficiencies (including iron).

Refeeding Syndrome

- ▶ Occurs in successfully adapted SRM during the **first week** when carbohydrate (± sodium) is introduced too rapidly. Carbohydrate → insulin surge → **antinatriuretic** ECF expansion (refeeding **oedema**) plus intracellular shift of electrolytes.
- ▶ Hallmark biochemistry: **hypophosphataemia**, **hypokalaemia**, **hypomagnesaemia**; can cause haemolysis, cardiac arrhythmias and **left heart failure** (volume load + insulin-driven rise in resting energy expenditure on an atrophic LV + myocardial K/PO₄/Mg deficiency).
- ▶ **Acute thiamine-deficiency encephalopathy (Wernicke)** is a devastating but preventable complication — give **thiamine 100 mg daily for 5–7 days** before/with refeeding.
- ▶ **Prevention:** start low (~5–20 kcal/kg/day), advance slowly, restrict sodium, and frequently measure and replace phosphate, potassium and magnesium. (Refeeding oedema is benign — treat with elevation and sodium restriction; *avoid diuretics*.)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Decision algorithm for nutritional support:** box flow — *Can the patient eat enough?* → No → *Is the gut functional & accessible?* → Yes = **Enteral nutrition**; No = **Parenteral nutrition** → branch to **Central PN** (>7–14 days, malnourished, hyperosmolar) vs **Peripheral PN** (<2 weeks, non-malnourished). Label EN contraindications (obstruction, ischaemia, peritonitis, GI bleed) as the arrow into PN.
- ▶ **Triple-chamber PN bag:** three labelled compartments — *Amino acids* (3.3 kcal/g), *Dextrose monohydrate* (3.4 kcal/g), *Lipid emulsion* (~10 kcal/g) — with add-on ports labelled *Vitamins*, *Trace elements*, *Electrolytes*, feeding into a *central venous catheter*, tip in SVC.

Clinical / Diagnostic significance

- ▶ Choosing **route** (central vs peripheral) hinges on osmolarity, expected duration and nutritional status — a frequent exam decision point.
- ▶ Pre-lipid **triglyceride** and baseline **electrolyte/phosphate/Mg** checks pre-empt the two commonest serious metabolic harms (hypertriglyceridaemia, refeeding syndrome).
- ▶ **Special populations:** *Renal failure* — do **not** restrict protein (RRT removes amino acids/vitamins/trace elements; increase provision). *Liver failure* — generous energy and protein, but spread protein through the day and tighten fluid/acid-base/electrolyte control to limit encephalopathy; omit copper/manganese. *Critical illness–nutrition paradox* — early energy provision matching expenditure may be **harmful**; avoid matching energy to expenditure while inflammation is severe.
- ▶ A multidisciplinary **nutrition support team** (physician, nurse, dietitian, pharmacist) demonstrably lowers complication rates.

High-yield exam pointers

- ▶ “*If the gut works, use it*” — EN is always first-line; PN only when the gut is unusable/inaccessible/insufficient.
- ▶ Adult PN is **hyperosmolar** → **central vein** (subclavian preferred; tip in SVC, X-ray confirmed; **avoid femoral/jugular**).
- ▶ Energy densities to memorize: amino acids 3.3, dextrose 3.4, lipid ~10 kcal/g; 100 g amino acids ≈ 83 g protein.
- ▶ Starting glucose ≤200 g/day; insulin target glucose 80–140 mg/dL; triglycerides >400 mg/dL = relative contraindication to lipid.
- ▶ **Iron is never added** to PN; copper/manganese omitted in cholestasis.
- ▶ **Refeeding syndrome triad:** ↓phosphate, ↓potassium, ↓magnesium; give **thiamine 100 mg/day**, start 5–20 kcal/kg/day.

- ▶ Cyclic PN (12 h/day) reduces PN-associated cholestasis; energy overfeeding causes fatty liver.
- ▶ Wean PN once $\frac{1}{2}$ – $\frac{2}{3}$ of needs are tolerated enterally; slow rate before stopping to prevent rebound hypoglycaemia.
- ▶ Nitrogen balance = (protein intake/6.25) – (urinary N + 4).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Enteral and Parenteral Nutrition*” (Hoffer & Bistrian) and “*Nutritional Assessment*” (body-composition/inflammation context).
- ▶ **CMDT 2026** — “*Nutrition, Nutritional Disorders, & Obesity*” — nutritional-support routes, requirements, parenteral electrolyte/trace-element doses, nitrogen-balance equation, refeeding-syndrome management.



Pellagra

Asked in: Paper I Jul 2021 · Paper I May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — Pellagra is the clinical deficiency syndrome of **niacin** (vitamin B3) and/or its precursor amino acid **tryptophan**. The name derives from the Italian *pelle agra* (“rough skin”). Niacin (nicotinic acid + nicotinamide) is the precursor of the coenzymes **NAD** and **NADP**, which drive numerous oxidation–reduction reactions and (as NAD) ADP-ribose transfer reactions in DNA repair and calcium mobilisation. Deficiency produces the classic photodistributed dermatitis, gastrointestinal and neuropsychiatric features summarised as the “**four Ds**”: **Dermatitis, Diarrhoea, Dementia and Death**.

Niacin metabolism and biochemical basis

- ▶ **Sources & forms** — *Niacin* is a generic term for **nicotinic acid** and **nicotinamide** and their active derivatives. Roughly half the body's niacin is supplied by diet (meat, fish, poultry, nuts, eggs, dairy, legumes, fortified cereals) and half is synthesised endogenously from **tryptophan**.
- ▶ **Tryptophan conversion** — Tryptophan is converted to niacin with an efficiency of **60 : 1 by weight**; requirements are therefore expressed as **niacin equivalents**. This conversion needs **vitamin B6 (pyridoxine)**, **riboflavin** and **iron** as cofactors — deficiency of any of these lowers niacin yield.
- ▶ **Coenzyme role** — Nicotinic acid and nicotinamide are precursors of **NAD** and **NADP**, central to redox metabolism; NAD also participates in **ADP-ribose transfer** (**DNA repair**, **Ca²⁺ mobilisation**). Cellular NAD⁺ declines with ageing.

- ▶ **Maize/corn factor** — Niacin in corn and maize is **tightly (chemically) bound** and is not absorbed unless released by **alkaline hydrolysis** (e.g. lime-water/*nixtamalization*). Diets based on unfortified maize therefore predispose to pellagra.
- ▶ **Sorghum (jowar) factor** — Jowar contains usable niacin but a **high leucine content** that inhibits the conversion of tryptophan to niacin — the basis of epidemic pellagra in sorghum-eating populations of the Indian Deccan.
- ▶ **Excretion / biomarkers** — Urinary excretion products **2-pyridone** and **N-methyl (2-methyl) nicotinamide** fall in deficiency and are used diagnostically.

Aetiology and predisposing causes

Category	Examples (source-grounded)
Dietary / endemic	Corn- or maize-based diets (China, Africa, India); sorghum (jowar)-based diets; famine, displacement, refugee/camp populations; restrictive/selective eating (e.g. autism spectrum disorder), eating disorders
Alcoholism	Commonest cause in industrialised settings (poor intake + impaired metabolism)
Malabsorption	Inflammatory bowel disease, jejunoileitis, gastrectomy/gastroenterostomy, bariatric (gastric bypass) surgery
Drugs	Isoniazid (structural analogue of niacin — also seen with mass scale-up of INH TB-preventive therapy); 5-fluorouracil; 6-mercaptopurine/azathioprine; anticonvulsants; antidepressants; sulfonamides; chloramphenicol
Inherited — Hartnup disease	Autosomal recessive defect of neutral amino-acid transport (SLC6A19 gene) → intestinal & renal malabsorption of tryptophan ; presents with cerebellar ataxia, psychiatric symptoms, aminoaciduria and pellagra-like rash
Carcinoid syndrome	Tumour diverts up to ~60% of tryptophan to serotonin (normally ~1%), depleting tryptophan available for niacin synthesis

Clinical features — the “four Ds”

- ▶ **Dermatitis (the hallmark)** — A **photosensitive eruption**: initially intermittent painful/pruritic erythema and oedema of **sun-exposed skin**, evolving into sharply margined, **hyperpigmented**, **scaling**, **keratotic plaques**; vesicles/bullae may form in severe cases.

- *Distribution*: **dorsa of the hands** (glove/gauntlet pattern), **face in a symmetrical butterfly/malar distribution**, and the **neck and upper chest forming a collar** — **Casal's necklace** (*after Gaspar Casal*).
- *Mucocutaneous*: **bright-red ("beefy") glossitis**, angular stomatitis, cheilitis, oral/perirectal ulcers; **half-and-half nails** described.
- ▶ **Diarrhoea** — From **proctitis and malabsorption** (atrophy of intestinal villi); often accompanied by anorexia, abdominal pain, nausea, vomiting; vaginitis and oesophagitis may occur.
- ▶ **Dementia / neuropsychiatric** — Early irritability, anxiety, insomnia, apathy, fatigue, depression and impaired memory progress to **confusion, hallucinations, psychosis, dementia**; seizures and, terminally, stupor and coma.
- ▶ **Death** — Untreated pellagra is progressive and **fatal within ~4–5 years**.
- ▶ **Early (non-specific) phase** — Loss of appetite, generalised weakness, irritability, mouth soreness, glossitis/stomatitis and weight loss precede the full triad.

Diagnosis and investigations

- ▶ **Primarily a clinical diagnosis** in advanced cases (characteristic photodistributed rash + GI + neuropsychiatric features); early deficiency requires a **high index of suspicion**.
- ▶ **Biochemical confirmation** — Reduced **urinary N-methylnicotinamide and 2-pyridone**; low **serum/plasma nicotinamide and nicotinic acid**. Reference deficiency threshold is **< 9.0 niacin equivalents** (recommended daily intake ~13–20 mg).
- ▶ **Therapeutic trial** — Rapid response to niacin supports the diagnosis: **neuropsychiatric symptoms improve within 24–48 h**, whereas cutaneous lesions take weeks to resolve.
- ▶ **Differential diagnosis** — Pyridoxine (B6) deficiency (pellagra-like dermatitis), porphyrias, polymorphous light eruption, chronic actinic dermatitis, photosensitive drug eruptions, cutaneous lupus; consider underlying carcinoid or Hartnup disease where diet is adequate.

Treatment and prevention

- ▶ **Replacement** — **Nicotinamide is preferred** over nicotinic acid because it does not cause flushing/headache.
 - *Harrison*: oral **nicotinamide or nicotinic acid 100–200 mg three times daily for up to 4 weeks**.
 - *Rook's*: **~500 mg/day** of nicotinamide (or nicotinic acid) over several weeks.
 - *CMDT*: oral **nicotinamide 10–150 mg/day**; advanced pellagra may be treated with parenteral nicotinic acid initially, then oral.
- ▶ **Supportive** — Treat coexisting deficiencies (general undernutrition, alcohol-use disorder) and correct precipitants (stop offending drug, manage malabsorption/carcinoid). Co-administer **pyridoxine with isoniazid** to prevent INH-induced pellagra/neuropathy.

- ▶ **Prevention** — Dietary diversification away from monotonous maize/sorghum; **niacin fortification of flour/cereals**; alkaline (lime) treatment of maize; treat at-risk groups (alcoholics, famine/displaced populations).

Niacin toxicity (pharmacologic high-dose, not deficiency)

- ▶ High-dose **nicotinic acid** (≈ 2 g/day, sustained-release) is used for **hypertriglyceridaemia / low HDL** (useful in statin intolerance) but lacks proven cardiovascular benefit; **nicotinamide does not lower lipids**.
- ▶ **Flushing** — Prostaglandin-mediated (GPCR binding), starts in the face, with itching/paraesthesia/headache; subject to **tachyphylaxis**; mitigated by **aspirin pre-medication** and extended-release forms.
- ▶ **Hepatotoxicity** — Most serious effect of sustained-release niacin (raised AST/ALT, jaundice; rare fulminant hepatitis at 3–9 g/day). Other effects: **glucose intolerance, hyperuricaemia/gout, macular oedema**; combined with statins increases **rhabdomyolysis** risk. **Upper limit for non-therapeutic intake = 35 mg/day**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Casal's necklace / photodistributed dermatitis (front of body)**: Label — *symmetrical butterfly (malar) facial rash; Casal's necklace (collar over neck and upper chest); V of the neck; dorsa of hands — glove/gauntlet pattern; bright-red (beefy) glossitis & angular stomatitis; sun-exposed = photodistribution*.
- ▶ **Tryptophan–niacin pathway**: Boxes — *Dietary niacin (NAD/NADP in food) and Tryptophan $\rightarrow$ (60:1, needs B6 + riboflavin + iron) $\rightarrow$ Nicotinic acid / Nicotinamide $\rightarrow$ NAD / NADP $\rightarrow$ redox + DNA-repair reactions. Add block-arrows: Isoniazid (analogue, blocks), Carcinoid (diverts Trp $\rightarrow$ serotonin), Hartnup / SLC6A19 (blocks Trp absorption), Maize bound-niacin & sorghum-leucine (reduce availability)*.

Clinical / Diagnostic significance

- ▶ “4 Ds” mnemonic anchors recognition: photosensitive Dermatitis + Diarrhoea + Dementia $\rightarrow$ Death if untreated — an instantly examinable triad.
- ▶ **Casal's necklace** and **butterfly facial rash** in a photodistribution are pathognomonic visual clues at the bedside.
- ▶ Always seek a **precipitant**: alcohol, isoniazid therapy, maize/sorghum-predominant diet, malabsorption/bariatric surgery, carcinoid or Hartnup disease — deficiency in an apparently well-fed patient mandates this search.
- ▶ **Niacin-equivalents** concept explains why deficiencies of **B6, riboflavin and iron** (cofactors for tryptophan $\rightarrow$ niacin) and **carcinoid** can cause “secondary” pellagra.

- ▶ A prompt **therapeutic response** (neuropsychiatric within 48 h) is both treatment and confirmation.

High-yield exam pointers

- ▶ Niacin = **vitamin B3** = nicotinic acid + nicotinamide → coenzymes NAD/NADP.
- ▶ Tryptophan → niacin at **60 : 1 by weight**; cofactors **B6, riboflavin, iron**.
- ▶ **4 Ds** = **D**ermatitis, **D**iarrhoea, **D**ementia, **D**eath; dermatitis is **photosensitive**.
- ▶ **Casal's necklace** = pigmented scaly collar of neck/upper chest (eponym *Gaspar Casal*).
- ▶ **Maize (bound niacin)** and **sorghum/jowar (high leucine)** are classic dietary causes — relevant to India.
- ▶ Secondary pellagra: **alcoholism, isoniazid, Hartnup disease (SLC6A19), carcinoid syndrome, 5-FU/6-MP, malabsorption**.
- ▶ Tongue = **bright-red/beefy glossitis**; nails = **half-and-half**.
- ▶ Diagnosis mainly **clinical**; biomarkers = ↓ urinary **N-methylnicotinamide & 2-pyridone**, ↓ serum niacin.
- ▶ Treatment = **nicotinamide preferred** (no flushing); high-dose **nicotinic acid** toxicity = flushing, hepatotoxicity, hyperglycaemia, hyperuricaemia (UL **35 mg/day**).

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Vitamin and Trace Mineral Deficiency and Excess” (niacin/pellagra section: metabolism, four Ds, Casal's necklace, treatment, toxicity).
- ▶ **Rook's Textbook of Dermatology, 10e** — “Nutritional Disorders Affecting the Skin” (vitamin B3/niacin: maize & sorghum-leucine mechanisms, Hartnup/SLC6A19, carcinoid, photodistributed dermatitis, Casal's necklace, half-and-half nails, diagnosis and management).
- ▶ **CMDT 2026** — “Nutrition, Nutritional Disorders, & Obesity” (clinical findings, diagnosis, current treatment doses, niacin toxicity).

Coverage note: Corpus coverage is solid across all three texts. The etymology (*pelle agra*) and the attribution of “Casal's necklace” to *Gaspar Casal* are universally accepted standard medicine, included although not explicitly stated in the chapter text (Harrison/Rook's name the sign without the eponymous person). Stated treatment doses differ slightly between sources and are quoted per text rather than reconciled.



Thiamine Physiology and Deficiency

Asked in: Paper I Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Thiamine (**vitamin B1**) was the first vitamin to be identified. It is a water-soluble B-complex vitamin whose active coenzyme form, **thiamine pyrophosphate (TPP)**, is essential for carbohydrate and branched-chain amino-acid metabolism and for energy generation. Body stores are small and can be depleted within a few weeks of a deficient diet, so thiamine deficiency develops rapidly and produces the classic syndromes of **beriberi** (wet and dry) and **Wernicke–Korsakoff syndrome**. It is a readily treatable, frequently under-diagnosed condition.

Physiology and biochemical functions

- ▶ **Active form:** thiamine is phosphorylated to **thiamine pyrophosphate (TPP)**, the coenzyme responsible for virtually all of its metabolic actions. **Magnesium** is required for activation of thiamine — a key point in management.
- ▶ **Oxidative decarboxylation of α -ketoacids** — TPP is the coenzyme for the dehydrogenase complexes that decarboxylate **pyruvate** (pyruvate dehydrogenase) and **α -ketoglutarate** (α -ketoglutarate dehydrogenase), linking glycolysis to the citric-acid cycle, and for **branched-chain α -ketoacid dehydrogenase**. It is thus essential for **ATP/energy generation**.
- ▶ **Transketolase reaction** — TPP is the coenzyme for transketolase in the **hexose monophosphate (pentose phosphate) shunt**, mediating interconversion of hexose and pentose phosphates and generating ribose and NADPH-linked intermediates.
- ▶ Functionally, TPP is a coenzyme for the **cleavage of carbon–carbon bonds** in carbohydrate and amino-acid metabolism.
- ▶ **Peripheral nerve conduction** — thiamine is postulated to play a role in nerve conduction, although the exact chemical reactions are not established; this underlies the neuropathy of deficiency.
- ▶ **Stores and kinetics** — body stores are small (unlike B12 or vitamin A); thiamine and folate are among the vitamins that deplete within **weeks** on a deficient diet. Therapeutic losses occur with **haemodialysis and diuretics**, which remove water-soluble vitamins.

Dietary sources, requirement and anti-thiamine factors

- ▶ **Median dietary intake** in well-nourished adults is ~2 mg/day; overt deficiency is associated with intake <0.3 mg per 1000 kcal/day. (The conventional adult RDA of ~1.1–1.2 mg/day is standard medicine, not detailed in the corpus.)
- ▶ **Rich sources:** yeast, organ meat, **pork**, legumes, beef, whole grains and nuts. **Milled/polished rice and refined grains contain little thiamine**, so deficiency is commoner in cultures heavily reliant on polished-rice diets.
- ▶ **Food processing/cooking** removes or destroys thiamine (high-heat or long-duration cooking).
- ▶ **Anti-thiamine factors:**

- **Heat-labile thiaminases** — in **raw fish and shellfish** — enzymatically destroy the vitamin.
- **Heat-stable polyhydroxyphenols (tannins)** — in **coffee, tea, Brussels sprouts and betel nuts** — inactivate the vitamin; large amounts of tea/coffee can theoretically lower thiamine stores.
- ▶ **Intestinal transport** is via thiamine transporter **ThTR2**; drugs such as **metformin and verapamil** can inhibit it and increase deficiency risk.

Causes / at-risk groups

- ▶ **Inadequate intake** — famine, displaced/refugee populations, disproportionate reliance on highly processed/polished-rice staples (the major global cause).
- ▶ **Alcohol use disorder** — the leading cause in industrialised countries: alcohol **impairs thiamine absorption**, **inhibits synthesis of TPP**, and **increases urinary excretion**.
- ▶ **Chronic illness** — e.g., cancer and chronic protein–calorie undernutrition.
- ▶ **Refeeding / carbohydrate load** — giving a large carbohydrate load (enteral/parenteral glucose) to a thiamine-depleted patient can **precipitate acute deficiency with lactic acidosis**; thiamine must always be replenished when an alcoholic patient is refed.
- ▶ **Bariatric/metabolic surgery** (“**bariatric Wernicke**”), malabsorption, **dialysis**.
- ▶ **Prolonged hyperemesis gravidarum**, anorexia and other eating disorders, poor nutritional status with parenteral glucose.
- ▶ **Chronic diuretic therapy** (hypertension, systolic heart failure) — increased urinary thiamine loss.
- ▶ **Maternal deficiency** → **infantile beriberi** in breast-fed children.
- ▶ May be an overlooked factor in **motor-vehicle accidents/head injury**.

Clinical syndromes of deficiency

- ▶ **Early/subclinical deficiency** — non-specific: **anorexia**, irritability, decreased short-term memory, muscle cramps, paraesthesia. Hard to recognise.
- ▶ **Beriberi** — classically divided into **wet** and **dry**, with considerable overlap; pain and paraesthesia occur in both.

Feature	Wet beriberi	Dry beriberi
Dominant system	Cardiovascular (impaired myocardial energy metabolism + dysautonomia)	Nervous system (peripheral nerves)
Setting	Deficiency + heavy exertion / high carbohydrate intake; may appear after ~3 months	Deficiency + inactivity / low-calorie intake
Features	Peripheral vasodilation → high-output congestive heart failure ,	Symmetric motor + sensory peripheral neuropathy ,

Feature	Wet beriberi	Dry beriberi
	enlarged heart, tachycardia , dyspnoea, pulmonary and peripheral oedema with warm extremities (may mimic cellulitis); peripheral neuritis	diminished reflexes; legs > arms ; difficulty rising from a squatting position

- ▶ **Wernicke's encephalopathy (WE)** — the CNS manifestation, classically in alcoholics: the **triad** of (1) **ophthalmoplegia** (weakness of one or more extraocular muscles) with **horizontal nystagmus**, (2) **cerebellar/truncal ataxia**, and (3) **encephalopathy/global confusion** (mental impairment).
- ▶ **Wernicke-Korsakoff syndrome (WKS)** — WE plus the **amnesic-confabulatory** state: **severe retrograde and anterograde amnesia**, **confabulation** and impaired learning. About **1 in 500** persons with alcohol use disorder develop the full syndrome, particularly those with an inherited **transketolase** abnormality. WKS is typically **under-diagnosed**.
- ▶ **Classic neuropathology** (universally accepted standard medicine): symmetric lesions of the **mammillary bodies**, **periaqueductal grey matter** and **medial (dorsomedial) thalamus**; chronic alcohol use is associated with ventricular enlargement / widened sulci on CT/MRI (often reversible with abstinence).

Diagnosis / investigations

- ▶ **Erythrocyte transketolase activity** measured **before and after** addition of TPP — a **>25% stimulation** (an “activity coefficient” of ≥ 1.25) is abnormal and indicates deficiency.
- ▶ **Direct assay** of thiamine and its phosphate esters in serum/blood by **HPLC**; normal range **~70–180 nmol/L**.
- ▶ **Empiric response** to thiamine is, in practice, often used to support the diagnosis.
- ▶ Other deficiencies (especially **magnesium**, required for thiamine activation) and inflammatory status should be assessed.

Treatment

- ▶ **Acute deficiency with cardiovascular or neurological signs**: **thiamine 200 mg IV three times daily** until no further improvement in acute symptoms, then **oral thiamine 10 mg/day** until recovery is complete (Harrison). **CMDT regimen**: **50–100 mg/day IV** initially, then **5–100 mg/day orally**.
- ▶ **Cardiovascular and ophthalmoplegic improvement** typically occurs **within 24 hours**; other features clear gradually. **Korsakoff psychosis** may be **permanent** or persist for months.
- ▶ **Correct magnesium** concomitantly — thiamine is only effective if magnesium is replete — and give other water-soluble vitamins.

- ▶ Give thiamine **BEFORE** a glucose/carbohydrate load in at-risk patients (alcoholics, refeeding) to avoid precipitating acute deficiency / Wernicke's.
- ▶ **Prognosis (WKS)**: roughly one-fourth resolve immediately, one-fourth over days, and about half achieve only partial or no benefit — emphasising early treatment.
- ▶ **Toxicity**: essentially none from food or supplements; rare hypersensitivity/anaphylaxis after high IV doses.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Biochemical roles of thiamine pyrophosphate (TPP)**. Central box “Thiamine → Thiamine pyrophosphate (TPP)” with arrows to: “Pyruvate → Acetyl-CoA (pyruvate dehydrogenase)”; “ α -Ketoglutarate → Succinyl-CoA (α -ketoglutarate dehydrogenase)”; “Branched-chain α -ketoacids (branched-chain ketoacid dehydrogenase)”; and “Transketolase — HMP/pentose-phosphate shunt”. Side labels: “ Mg^{2+} required for activation”, “Energy/ATP generation”.
- ▶ **Diagram 2 — Clinical spectrum of thiamine deficiency**. Root “Thiamine deficiency” branching to: “Wet beriberi — high-output cardiac failure, oedema”; “Dry beriberi — symmetric sensorimotor neuropathy, legs > arms”; “Wernicke encephalopathy — ophthalmoplegia + nystagmus, ataxia, confusion”; “Korsakoff syndrome — amnesia + confabulation”; “Infantile beriberi (maternal deficiency)”.

Clinical / Diagnostic significance

- ▶ Always suspect thiamine deficiency in **alcoholics, post-bariatric, hyperemesis, refeeding and chronically ill/parenteral-nutrition** patients.
- ▶ Wernicke's encephalopathy is a **medical emergency** — treat empirically on clinical suspicion; do **not** wait for biochemistry, and **never give glucose first** in an at-risk patient.
- ▶ A patient on diuretics/dialysis with high-output cardiac failure unresponsive to standard therapy — consider **wet beriberi (Shoshin beriberi)**.
- ▶ Functional **erythrocyte transketolase activation coefficient** ≥ 1.25 is the classic confirmatory test.
- ▶ Co-existing **magnesium deficiency** causes apparent thiamine-refractoriness — always correct it.

High-yield exam pointers

- ▶ **Vitamin B1**; active coenzyme = **thiamine pyrophosphate (TPP)**; Mg^{2+} needed for activation.
- ▶ Coenzyme for **pyruvate dehydrogenase, α -ketoglutarate dehydrogenase, branched-chain ketoacid dehydrogenase and transketolase (HMP shunt)**.
- ▶ Deficiency threshold < 0.3 mg/1000 kcal/day; thiamine stores deplete within **weeks**.
- ▶ **Polished-rice diet, alcoholism, thiaminases (raw fish), tannins (tea/coffee/betel)** are key causes.

- ▶ **Wet beriberi** = high-output cardiac failure + oedema; **Dry beriberi** = symmetric peripheral neuropathy (legs > arms).
- ▶ **Wernicke triad** = ophthalmoplegia/nystagmus + ataxia + confusion; add amnesia + confabulation = Korsakoff.
- ▶ Diagnosis: erythrocyte transketolase, activation coefficient ≥ 1.25 ; thiamine 70–180 nmol/L by HPLC.
- ▶ Treatment: parenteral thiamine 200 mg IV TDS (or 50–100 mg/day), give before glucose, replace magnesium; CV/eye signs improve in 24 h, Korsakoff may be permanent.
- ▶ Refeeding an alcoholic with carbohydrate without thiamine can precipitate acute deficiency + lactic acidosis.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Vitamin and Trace Mineral Deficiency and Excess” (thiamine physiology, food sources, beriberi, transketolase assay, treatment) and “Alcohol and Alcohol Use Disorders” (Wernicke's and Korsakoff's syndromes, transketolase deficiency, neuroimaging).
- ▶ **CMDT 2026** — “Nutrition, Nutritional Disorders, & Obesity” (wet/dry beriberi distinction, thiamine reference range 70–180 nmol/L, parenteral thiamine regimen and prognosis, magnesium requirement).

Coverage note: The corpus details the clinical syndromes, biochemistry and management thoroughly. The classic neuropathologic localisation of Wernicke's encephalopathy (mammillary bodies, periaqueductal grey, dorsomedial thalamus) and the conventional adult RDA (~1.1–1.2 mg/day) are universally accepted standard internal medicine included for completeness but are not spelt out in these specific chapters.



Total Parenteral Nutrition

Asked in: Paper I Dec 2023 · Paper I Nov 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — Total parenteral nutrition (TPN) is the delivery of a *nutritionally complete admixture* — crystalline amino acids, glucose, lipid emulsion, electrolytes, minerals, vitamins and trace elements — **directly into the bloodstream through a central vein**, when the *entire* nutrient requirement is met intravenously. It is one of three forms of **specialized nutritional support (SNS)** — the others being optimized voluntary nutrition and instrumental enteral nutrition (EN) — and is reserved for patients whose gastrointestinal (GI) tract cannot be used or is insufficient. Because of its high osmolarity (>1200 mOsm/L) and large volume, adult PN must be infused into a central vein.

Indications and contraindications

- ▶ **Core rule:** PN is used when invasive SNS is indicated *and* EN is **impossible, inappropriate, or insufficient** to meet the patient's needs. *If the gut works and is accessible, use it (EN) — PN is the second choice.*
- ▶ The decision to give EN or PN rests on **four factors**: (1) nutrient intake will likely remain inadequate for **many days**; (2) there is important **muscle loss** of any cause; (3) requirements are **increased** (inflammatory diarrhoea, enterocutaneous fistulae/exudates, an inflammatory protein-catabolic state); and (4) reasoned judgement that SNS will **improve clinical outcome or quality of life**.
- ▶ **Typical PN indications (non-functioning / inaccessible gut):** mechanical **bowel obstruction**, **intestinal ischaemia**, **peritonitis**, **GI haemorrhage** (these four are absolute contraindications to EN), high-output **enterocutaneous fistula**, **short-bowel syndrome**, severe malabsorption, prolonged **paralytic ileus**; also when EN fails to achieve the protein goal after **7–10 days** in the ICU (PN is then added).
- ▶ **Not indicated / cautions:** a functioning accessible gut (EN preferred); terminal illness not mitigated by SNS; **advanced dementia** with little interest in food. PN must wait until the patient is **haemodynamically stabilized** and glucose/electrolyte/acid-base homeostasis is established. Serum triglyceride **>400 mg/dL** is a *relative contraindication* to lipid.

Composition and energy values of TPN

- ▶ Ready-to-use admixtures contain **4–7% hydrated amino acids** and **20–25% glucose**, supplied as **two-chamber** (amino acid + glucose) or **three-chamber** (amino acid + glucose + lipid) bags; vitamins, trace elements and extra electrolytes are added *just before infusion*. Individualized regimens use a **computer-controlled sterile compounder**.

Macronutrient	Form in PN	Energy yield	Key points
Amino acids	crystalline <i>free</i> amino acids	3.3 kcal/g	Hydration lowers density from 4.0 and cuts protein substrate ~17% — <i>100 g free AA = 83 g protein substrate</i> ; provide all essential AAs
Carbohydrate	dextrose monohydrate	3.4 kcal/g	Main energy source; hydration lowers density from 4.0; initial dose ≤ 200 g/day
Lipid emulsion	soybean / olive / MCT / fish-oil blends	~10 kcal/g	Supplies essential n-6 and n-3 fatty acids ; infuse at ≤ 8 g/h (pure fish-oil slower)

- ▶ **Lipid emulsions:** pure soybean oil is giving way to **mixed emulsions** (medium-chain triglycerides, n-9 monounsaturated, n-3). US options include 80% olive/20% soybean, and a 30% soybean/30% MCT/25% olive/15% fish-oil blend. **Fish oil** may reduce infections and length of stay in the critically ill; soy-based emulsions are best avoided in the **first week** of PN in critical illness.
- ▶ **Minerals / micronutrients:** default doses target a healthy adult and must be individualized. **Multivitamins are unstable** — added to the bag just before delivery; parenteral water-soluble vitamin needs *exceed* oral needs, and **ascorbic acid degrades spontaneously** in PN. **Iron is NOT added to PN** (iron dextran is incompatible with lipid emulsions and may catalyse free-radical formation); give IV iron separately, delayed in suspected infection.
- ▶ **Zinc:** 1 L of secretory diarrhoea loses ~12 mg zinc; because of low bioavailability 12 mg parenteral zinc ≈ 30 mg oral zinc (daily requirement ~15 mg).

Daily requirements and prescription targets

Parameter	Target (from chapter)
Total energy expenditure	~36 kcal/kg/day (resting EE ≈ 75% of total)
Protein / amino acids	0.8 g/kg (safe, healthy); 1.2–2.0 g/kg normal body weight (critically ill); minimum 0.65 g/kg
Glucose	start ≤200 g/day; ≤500 g/day (1700 kcal) non-critical; ≤350 g/day (1200 kcal) in acute disease-related malnutrition (ADM)
Lipid	≤50 g/day (500 kcal) in ADM; rate ≤8 g/h
Fluid	≤2 L/day unless abnormally high losses
Glucose control (insulin)	average 80–140 mg/dL (100–180 mg/dL in critically ill diabetics)

- ▶ **Insulin guidance:** regular insulin is added to the bag; ~10 units/100 g glucose for non-diabetic non-catabolic patients and ~20 units/100 g for type 2 diabetics; the next day's dose is based on today's requirement.
- ▶ **Permissive underfeeding** (under-provision of *all* nutrients) must not be confused with **hypocaloric nutrition** (reduced energy but *generous protein*). In fat-sufficient/obese ADM patients, hypocaloric, protein-generous PN is recommended for the first ~2 weeks; matching energy to expenditure early can be *harmful*.

Route, initiation, progression, monitoring and discontinuation

- ▶ **Access:** a dedicated lumen of a central venous catheter (subclavian or PICC preferred). **Jugular and femoral sites are avoided** — hard to keep a dry sterile dressing and higher complication rates.

- ▶ **Initiation:** begin only after haemodynamic stabilization and metabolic/acid-base homeostasis. Initial **glucose** ≤ 200 g/day to avoid hyperglycaemia and **refeeding syndrome**. **Lipids** are usually introduced *after the first week* to cover energy shortfalls (daily or 2–3×/week); check **triglycerides** first.
- ▶ **Monitoring:** urea, creatinine, electrolytes, glucose, **magnesium**, **phosphate**, **calcium** and **albumin** before starting; most monitored for the first few days then **twice weekly**. Capillary glucose several times daily. **Triglycerides** and **LFTs** at baseline and after PN is running. **Nitrogen balance** to gauge catabolism (urinary urea N: $N \text{ loss (g)} = \text{urea-N}/0.85 + 2$).
- ▶ **Discontinuation:** taper as oral/enteral intake rises; **stop once the patient tolerates one-half to two-thirds of requirement enterally**. Wean by optimizing voluntary nutrition — *do not* abruptly stop hoping to “stimulate appetite” (PN does not cause anorexia). **Cyclic PN** (infused over 12 h/day) reduces cholestasis with prolonged use.

Complications of TPN

Category	Complication	Prevention / management
Catheter	Insertion trauma (e.g., pneumothorax), catheter-related bloodstream infection (higher risk than other CVCs), central vein thrombosis	Aseptic insertion, dedicated port , meticulous dressing care, glycaemic control
Metabolic	Hyperglycaemia (most frequent), reactive hypoglycaemia , hypertriglyceridaemia , electrolyte/Mg/PO ₄ /acid-base derangement	Insulin to keep glucose 80–140; taper slowly; TG monitoring; limit lipid rate
Hepatobiliary	Transaminitis (within 2–4 weeks, usually self-limiting), hepatic steatosis (overfeeding), intrahepatic cholestasis (prolonged PN)	Avoid energy overfeeding; cyclic PN
Fluid	Volume overload (raises morbidity/mortality)	Limit fluid to ≤ 2 L/day; use a compounder; lowest appropriate glucose rate
Other	Toxic overfeeding (PN especially prone); artefactual hyperglycaemia/hyperkalaemia from sampling	Careful prescribing; clean blood draws from a dual-port CVC

- ▶ **Reactive hypoglycaemia** can follow abrupt stoppage of high-glucose, non-insulin PN — prevent by slowing the infusion to **50 mL/h for 1–2 h**, then 10% glucose or an oral snack.

- ▶ **Hypertriglyceridaemia** occurs when lipid infusion outpaces clearance (sepsis, renal failure, diabetes, glucocorticoids, multi-organ failure reduce clearance); risks include pancreatitis and impaired immunity — keep lipid ≤ 50 g/day in ADM.

Refeeding syndrome

- ▶ Occurs in patients with **successfully adapted starvation-related malnutrition (SRM)** during the first week of repletion when **carbohydrate and sodium** are reintroduced too rapidly.
- ▶ **Mechanism:** carbohydrate $\rightarrow$ **insulin surge** $\rightarrow$ (a) antinatriuretic effect $\rightarrow$ ECF expansion / **refeeding oedema**; (b) intracellular shift driving glucose-6-phosphate/glycogen synthesis $\rightarrow$ falling serum **phosphate, potassium and magnesium**, impairing skeletal/cardiac muscle and triggering **haemolysis**.
- ▶ **Left heart failure** has three causes: abrupt intravascular volume rise (insulin-mediated Na^+ retention); increased demand on an **atrophic left ventricle** from a higher resting EE; and myocardial $\text{K}^+/\text{PO}_4/\text{Mg}^{2+}$ deficiency. **Arrhythmias** may occur.
- ▶ **Acute thiamine-deficiency encephalopathy (Wernicke's)** is a devastating but **preventable** complication — can be precipitated even by simple glucose infusion.
- ▶ **Prevention:** restrict sodium, **advance carbohydrate slowly**, start glucose ≤ 200 g/day, and measure and replace phosphate, potassium, magnesium and thiamine frequently.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Labelled algorithm** — “Choosing the route of nutritional support”: boxes/arrows reading *Can patient eat enough?* $\rightarrow$ *Yes: Optimized voluntary nutrition* | *No* $\rightarrow$ *Is the gut functional and accessible?* $\rightarrow$ *Yes: Enteral nutrition (EN)* $\rightarrow$ *No (obstruction / ischaemia / peritonitis / GI haemorrhage / high-output fistula / failed EN)* $\rightarrow$ *Parenteral nutrition (PN/TPN)***. Label the four EN contraindications and the four-factor decision rule.
- ▶ **Labelled diagram** — “Central venous access for TPN”: label subclavian vein, SVC tip, **dedicated PN lumen**, sterile dressing; annotate “high osmolarity >1200 mOsm/L $\rightarrow$ central vein,” “avoid jugular/femoral.”

Clinical / Diagnostic significance

- ▶ TPN is **life-saving but high-risk** — EN and PN carry equivalent overall complication rates *except* that PN adds catheter and bloodstream-infection risk and is far more prone to **toxic overfeeding**; hence “*if the gut works, use it.*”
- ▶ **Glycaemic control** (80–140 mg/dL) and **strict catheter asepsis with a dedicated port** are the two interventions that most reduce TPN morbidity.
- ▶ **Baseline electrolytes, Mg, PO_4 , Ca, triglycerides and transferrin saturation** identify patients at risk of refeeding syndrome and functional iron deficiency before starting.

- ▶ In critical illness (ADM), early energy provision near/above expenditure is **not beneficial** and may be harmful; favour hypocaloric, protein-generous regimens while inflammation is severe.

High-yield exam pointers

- ▶ TPN = complete IV nutrition via a **central vein**; osmolality >1200 mOsm/L.
- ▶ Energy values: AA 3.3, dextrose monohydrate 3.4, lipid ~10 kcal/g; 100 g AA = 83 g protein substrate.
- ▶ **Initial glucose** ≤200 g/day; ADM ≤350 g; non-critical ≤500 g; **lipid** ≤8 g/h (≤50 g/day in ADM); **fluid** ≤2 L/day.
- ▶ Protein: 0.8 g/kg healthy, 1.2–2.0 g/kg critically ill.
- ▶ **Iron is never added** to PN; multivitamins added just before infusion; **ascorbic acid degrades** in the bag.
- ▶ Most frequent metabolic complication = **hyperglycaemia**; most feared early complication = **refeeding syndrome** (low PO₄/K⁺/Mg²⁺ + thiamine deficiency).
- ▶ **Triglyceride** >400 mg/dL = relative contraindication to lipid; transaminitis appears within 2–4 weeks; cyclic PN (12 h/day) for cholestasis.
- ▶ Stop PN once ½–⅔ of **requirement** is tolerated enterally; wean by optimizing voluntary intake, never abruptly.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 346 "Enteral and Parenteral Nutrition" (Hoffer & Bistrian).

Coverage note: All doses, energy values, osmolality, insulin ratios and complication data are taken verbatim from Ch 346. The chapter uses the term "PN"; "Total PN" (entire requirement given IV) is the universally accepted clinical term and is used here. A few standard-textbook specifics not stated explicitly in Ch 346 are flagged as universally accepted: the *subclavian/PICC* preference (the chapter states only that jugular/femoral are avoided), *short-bowel syndrome* as a classic PN indication (chapter lists fistulae/malabsorption), the *pneumothorax* example of insertion trauma, and naming acute thiamine-deficiency encephalopathy *Wernicke's*. Peripheral PN is implied by the chapter (high osmolality mandates a central vein) but not detailed.



Re-feeding Syndrome: Definition, Patients at Risk, Electrolyte Pathogenesis, Prevention and Treatment

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Re-feeding syndrome (RFS)* is a constellation of potentially fatal **fluid and electrolyte shifts** that occur when nutrition (oral, enteral or parenteral) is reintroduced too rapidly to a previously **starved or severely malnourished** patient. The hallmark biochemical lesion is **hypophosphataemia** developing in the first week of re-feeding, accompanied by **hypokalaemia, hypomagnesaemia, thiamine depletion, sodium-water retention and hyperglycaemia**. The clinical consequences—cardiac arrhythmia, heart failure, respiratory failure, neuromuscular and haematological dysfunction—are largely **preventable**, making early recognition of the at-risk patient the single most important step.

Pathophysiology — the metabolic switch and the electrolytes/minerals involved

- ▶ **Starvation (adaptation phase):** prolonged semi-starvation lowers insulin, raises glucagon, and switches metabolism from carbohydrate to **fat and protein (ketone/free-fatty-acid)** fuel. The body downregulates resting energy expenditure and conserves visceral mass at the cost of muscle. Crucially, **total-body phosphate, potassium and magnesium are progressively depleted**, yet *serum* levels are often maintained because these ions leave the shrinking intracellular compartment — masking the deficit.
- ▶ **Re-feeding (anabolic switch):** an abrupt carbohydrate (glucose) load **stimulates insulin secretion**. Insulin drives **glucose, phosphate, potassium and magnesium into cells** for glycogen and protein synthesis, and reactivates the depleted Na^+/K^+ -ATPase pump — unmasking the profound deficits as plasma levels crash.
- ▶ **Phosphate (the cardinal disturbance):** carbohydrate refeeding stimulates **intracellular glucose-6-phosphate and glycogen synthesis**, consuming phosphate to form phosphorylated intermediates and ATP/2,3-DPG, producing severe **redistributive hypophosphataemia** (movement of phosphate from ECF into cells/bone). This compromises every ATP-dependent process — skeletal and cardiac muscle function and red-cell integrity (haemolysis).
- ▶ **Potassium & magnesium:** insulin-driven cellular uptake produces **hypokalaemia and hypomagnesaemia**; hypomagnesaemia further impairs PTH function and renal K^+/PO_4 handling and is itself arrhythmogenic.
- ▶ **Thiamine (vitamin B₁):** re-introduced carbohydrate sharply increases demand for thiamine as the cofactor of pyruvate dehydrogenase/transketolase; in an already depleted patient this precipitates **acute thiamine-deficiency encephalopathy (Wernicke)** — *a devastating, preventable complication of refeeding, occurring even with simple glucose infusion* (Harrison).
- ▶ **Sodium, water and glucose:** carbohydrate-stimulated insulin has an **antinatriuretic effect**, expanding ECF volume, especially if sodium is given liberally → **refeeding oedema** and, in predisposed patients, **left heart failure**. Excess glucose provision also causes **hyperglycaemia**.

Mineral / factor	Direction in RFS	Mechanism	Main danger
Phosphate	↓↓ (hypophosphataemia)	Insulin-driven cellular uptake + consumption in glucose-6-P/ATP synthesis	ATP depletion → cardiac/respiratory/neuromuscular failure, haemolysis
Potassium	↓ (hypokalaemia)	Insulin shifts K ⁺ intracellularly via Na ⁺ /K ⁺ -ATPase	Arrhythmia, weakness, ileus
Magnesium	↓ (hypomagnesaemia)	Cellular uptake; total-body depletion	Arrhythmia, refractory hypo-K/hypo-Ca, tetany
Thiamine (B ₁)	depleted	Carbohydrate load increases coenzyme demand	Wernicke encephalopathy, lactic acidosis
Sodium / water	retained	Insulin antinatriuresis → ECF expansion	Refeeding oedema, congestive heart failure
Glucose	↑ (hyperglycaemia)	Excess CHO load + insulin resistance	Osmotic diuresis, hyperosmolar state, infection

Who is at risk

- ▶ **Core principle:** risk reflects the **degree of antecedent depletion** — the more malnourished/starved the patient, the greater the risk, and (in anorexia data) the degree of refeeding hypophosphataemia correlates with severity of malnutrition on admission more than with the calories prescribed.
- ▶ **Clinical high-risk groups (textbook):**
 - **Anorexia nervosa** and other eating disorders — *particularly high risk*; especially those <70–75% of expected body weight (Sleisenger).
 - **Starvation-related malnutrition (SRM) and chronic disease-related malnutrition / cachexia (CDM)** — malignancy, chronic infection (e.g. TB), inflammatory/autoimmune disease, advanced cardiac/renal/hepatic/pulmonary disease.
 - **Chronic alcohol use disorder** (combined phosphate/thiamine/Mg depletion).
 - **Prolonged fasting / starvation, hunger strikes, prolonged unfed ICU stay**, post-operative patients fed after long catabolic periods.
 - **Malabsorption / high GI losses** — short bowel, fistulae, chronic diarrhoea/vomiting, after bariatric surgery.
 - **Elderly with sarcopenia and comorbidities**; uncontrolled diabetes (insulin therapy causes redistributive hypophosphataemia, as in DKA treatment).

- ▶ ***NICE high-risk criteria** (*standard screening framework — see Coverage note*). A patient is high risk with one of: BMI <16 kg/m²; unintentional weight loss >15% in 3–6 months; little/no intake >10 days; low baseline K⁺, PO₄³⁻ or Mg²⁺. Or two* of: BMI <18.5 kg/m²; weight loss >10% in 3–6 months; little/no intake >5 days; history of alcohol misuse or drugs (insulin, chemotherapy, antacids, diuretics).

Clinical features / manifestations

- ▶ **Cardiac:** arrhythmias (atrial/ventricular), and **left heart failure** from three mechanisms — abrupt rise in intravascular volume (fluid + insulin-mediated Na⁺ retention), increased cardiac demand on an **atrophic left ventricle** from raised resting energy expenditure, and myocardial K⁺/PO₄/Mg deficiency; sudden cardiac death.
- ▶ **Neuromuscular (hypophosphataemia):** weakness, lethargy, confusion, dysarthria, dysphagia, ophthalmoplegia, nystagmus, ataxia, paraesthesiae, a **Guillain–Barré-like ascending paralysis**, seizures and coma; serious sequelae (paralysis, seizures) typically at phosphate <0.25 mmol/L (<0.8 mg/dL). **Rhabdomyolysis** may occur.
- ▶ **Respiratory:** diaphragmatic weakness and reversible respiratory failure at phosphate 0.5–0.8 mmol/L (1.5–2.5 mg/dL) — may impede ventilator weaning.
- ▶ **Haematological:** erythrocyte microspherocytosis and **haemolysis**, impaired oxyhaemoglobin dissociation (low 2,3-DPG), and defective leucocyte/platelet function.
- ▶ **Neurological (thiamine):** acute **Wernicke encephalopathy** — confusion, ophthalmoplegia, ataxia.
- ▶ **Fluid:** benign **refeeding oedema** (dependent, from renal Na⁺ reabsorption and poor vessel integrity) — must be distinguished from heart failure; **diuretics should not be used**.

Prevention

- ▶ **Identify the at-risk patient before feeding** and check baseline K⁺, PO₄³⁻, Mg²⁺, Na⁺, glucose and renal function.
- ▶ **Start low, go slow:** begin at only 5–20 kcal/kg/day for the first few days (depending on severity), advancing calories cautiously over ~7 days; once past the refeeding window, build to 30–35 kcal/kg/day and ~1.5 g protein/kg/day (CMDT). In enteral feeding, at-risk patients warrant conservative initiation/advancement; parenteral nutrition is begun at **about half the estimated energy requirement** (~100–150 g dextrose) for the first 24 h and increased daily as tolerated.
- ▶ **Give thiamine before/with the first feed:** thiamine 100 mg daily for at least 5–7 days (and other B vitamins) to prevent Wernicke encephalopathy.
- ▶ **Correct/replace electrolytes proactively** — supplement phosphate, potassium and magnesium and replete deficits, ideally before or alongside calories rather than withholding feed.
- ▶ **Restrict sodium and fluid** to minimise refeeding oedema and cardiac overload; increase carbohydrate provision slowly.

- ▶ **Monitor intensively:** serum phosphate and magnesium every 6–12 h (every 6–8 h after feeds begin) during at least the first week; daily weights, fluid balance, heart rate, respiratory rate and signs of failure; **cardiac telemetry** in severely malnourished patients.

Treatment

- ▶ **Slow or temporarily reduce the calorie load** if electrolytes fall, and aggressively replace phosphate, potassium and magnesium while continuing thiamine.
- ▶ **IV phosphate replacement** (Harrison) for severe hypophosphataemia <0.75 mmol/L (<2 mg/dL) — neutral sodium/potassium phosphate, initial **0.2–0.8 mmol/kg elemental phosphorus** over 6 h (e.g. 10–50 mmol/6 h); measure serum Ca^{2+} and PO_4^{3-} every 6–12 h; **reduce dose 50% if creatinine >2.5 mg/dL**, correct hypocalcaemia first:

Serum phosphorus	Infusion rate	Duration	Total administered
<0.8 mmol/L (<2.5 mg/dL)	2 mmol/h	6 h	12 mmol
<0.5 mmol/L (<1.5 mg/dL)	4 mmol/h	6 h	24 mmol
<0.3 mmol/L (<1 mg/dL)	8 mmol/h	6 h	48 mmol

- ▶ **Hypokalaemia / hypomagnesaemia:** replace with IV/oral KCl and magnesium; **correct magnesium** as it is required for sustained K^+ and PO_4 repletion and for PTH action.
- ▶ **Refeeding oedema:** elevate the area and **restrict sodium** — *do not give diuretics*; distinguish from true heart failure.
- ▶ **Heart failure / arrhythmia:** supportive management, telemetry, treat the underlying electrolyte deficits.
- ▶ **Glycaemic control:** keep glucose <140 – 180 mg/dL using hypocaloric glucose $\pm$ lipid and minimal-dose insulin.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **“Metabolic switch” flow diagram:** Starvation (low insulin, fat/ketone fuel, depleted total-body $\text{PO}_4/\text{K}^+/\text{Mg}^{2+}$) $\rightarrow$ **Carbohydrate re-feed** $\rightarrow$ $\uparrow$ **Insulin** $\rightarrow$ branches to: (1) cellular uptake of PO_4^{3-} $\rightarrow$ **hypophosphataemia** $\rightarrow$ $\downarrow$ ATP/2,3-DPG, (2) cellular uptake of K^+ $\rightarrow$ **hypokalaemia**, (3) cellular uptake of Mg^{2+} $\rightarrow$ **hypomagnesaemia**, (4) **thiamine consumption** $\rightarrow$ **Wernicke**, (5) **renal Na^+ /water retention** $\rightarrow$ **oedema/heart failure**. End-organ boxes labelled: *Cardiac arrhythmia/HF, Respiratory failure, Neuromuscular weakness/seizures, Haemolysis*.

- ▶ **Timeline bar:** Day 0 (start feed) → Days 1–3 (nadir phosphate, highest risk) → Day 7 (refeeding window closes); annotate “monitor $\text{PO}_4/\text{K}^+/\text{Mg}^{2+}$ every 6–12 h” and “thiamine 100 mg/day ×5–7 days”.

Clinical / Diagnostic significance

- ▶ **Diagnosis is biochemical + temporal:** a falling phosphate ($\pm \text{K}^+, \text{Mg}^{2+}$) within the **first week** of re-instituted nutrition in an at-risk patient. Serum phosphate at presentation can be normal (masked by prerenal azotaemia/depletion) and falls *hours* after feeding/insulin — so **serial** measurement, not a single baseline, is required.
- ▶ **Investigations:** daily basic metabolic panel, **phosphate and magnesium**, glucose; ECG/telemetry for arrhythmia and QTc; CK if rhabdomyolysis suspected (CK may peak 1–2 days after the phosphate nadir).
- ▶ **Management pearls:** the safe-feeding rule is *prevention beats rescue*; never withhold thiamine waiting for confirmation; replace electrolytes **before** escalating calories; refeeding can occur by **any route** including oral.

High-yield exam pointers

- ▶ **Cardinal lab abnormality = hypophosphataemia;** the triad $\text{PO}_4^{3-} \downarrow, \text{K}^+ \downarrow, \text{Mg}^{2+} \downarrow$ plus thiamine deficiency and fluid overload.
- ▶ **Trigger = carbohydrate/glucose load → insulin surge** driving intracellular shift of phosphate/potassium/magnesium.
- ▶ **Highest-risk group = anorexia nervosa, especially <70–75% expected body weight;** also chronic alcoholism, prolonged starvation, malabsorption, cancer cachexia, elderly.
- ▶ **NICE one-major criterion:** BMI <16, weight loss >15%/3–6 mo, intake >10 days, or low baseline $\text{K}/\text{PO}_4/\text{Mg}$.
- ▶ **Prevent:** start 5–20 kcal/kg/day, advance over 7 days; **thiamine 100 mg/day ×5–7 days;** restrict sodium; monitor PO_4/Mg 6–12 hourly.
- ▶ **Treat severe hypophosphataemia IV:** 0.2–0.8 mmol/kg elemental P over 6 h; replace K and Mg concurrently.
- ▶ **Refeeding oedema is benign — never treat with diuretics;** distinguish from heart failure.
- ▶ **Acute thiamine-deficiency (Wernicke) encephalopathy can follow plain glucose infusion —** always give thiamine first.
- ▶ Serious paralysis/seizures occur at phosphate <0.25 mmol/L (<0.8 mg/dL); respiratory/cardiac failure at 0.5–0.8 mmol/L.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Enteral and Parenteral Nutrition” (refeeding syndrome: carbohydrate–insulin mechanism, phosphate/potassium/magnesium deficiencies, left heart failure, thiamine encephalopathy) and “Malnutrition and Nutritional Assessment” (SRM/CDM/ADM and at-risk groups); “Disorders of Bone and Mineral Metabolism / Fluid and Electrolyte Disturbances” (redistributive hypophosphataemia, clinical thresholds, and IV phosphate therapy table).
- ▶ **Sleisenger & Fordtran's Gastrointestinal and Liver Disease** — “Feeding and Eating Disorders” (anorexia nervosa <70–75% expected body weight as highest-risk group; refeeding hypophosphataemia; 6–8-hourly electrolyte monitoring, telemetry).
- ▶ **CMDT 2026** — “Nutrition, Nutritional Disorders & Obesity” (definition, 5–20 kcal/kg/day initiation advancing to 30–35 kcal/kg/day and 1.5 g protein/kg/day, thiamine 100 mg/day ×5–7 days, refeeding oedema — avoid diuretics).
- ▶ *Coverage note:* The exact numerical **NICE 2006 (CG32) high-risk thresholds** (BMI/weight-loss/days-without-intake cut-offs) are not stated verbatim in this corpus; they are included as universally accepted standard internal-medicine screening criteria. All other figures (calorie ranges, thiamine dose, phosphate thresholds and IV phosphate dosing) are taken directly from Harrison/CMDT/Sleisenger as cited.



Miscellaneous



Anatomy of spinal cord

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — The spinal cord is the thin, tubular caudal extension of the central nervous system housed within the bony vertebral canal, carrying — within a small cross-sectional area — almost the entire motor output and sensory input of the trunk and limbs. It originates at the medulla, ends caudally as the **conus medullaris**, and is continued by the fibrous **filum terminale** to the coccyx. Because of this dense packing of ascending and descending tracts, focal cord lesions produce devastating, anatomically predictable syndromes, making cord anatomy the key to bedside lesion localisation.

Gross anatomy and vertebro-segmental relationships

- ▶ **Length & shape:** ~45 cm in the adult male and 42–43 cm in the adult female (Harrison quotes ~46 cm); the vertebral column is ~70 cm, so the cord fills only the upper two-thirds of the canal. It is oval/cylindrical, flattened dorsoventrally.
- ▶ **Enlargements:** the **cervical enlargement (C5–T1)** supplies the upper limbs (brachial plexus) and the **lumbosacral enlargement (L3–S2)** supplies the lower limbs (lumbosacral plexus).

- ▶ **Segments:** 31 segments — 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal — each defined by an exiting ventral (motor) root and an entering dorsal (sensory) root.
- ▶ **Conus & cauda equina:** because the cord grows more slowly than the vertebral column, the adult cord ends at ~L1–L2. *Descent of the conus:* L4–L5 at 20 weeks' gestation → L3 at term → adult L1–L2 by ~2 months of age. Below this, the lumbosacral roots travel a long intrathecal course as the **cauda equina** around the filum terminale — the safe target for lumbar puncture (below L2).
- ▶ **Cord-segment vs vertebral-body mismatch (localisation rule):** the first 7 cervical nerves exit **above** the same-numbered vertebra (8 cervical segments but 7 cervical vertebrae); all lower nerves exit **below** the same-numbered vertebra. Cord segments therefore lie progressively higher than their vertebral spinous processes — upper cervical ≈ same level, lower cervical ≈ 1 higher, upper thoracic ≈ 2 higher, lower thoracic ≈ 2–3 higher, lumbar cord ≈ T10–T12, sacral cord ≈ T12–L1.
- ▶ **External surface landmarks:** ventral (anterior) median fissure, dorsal (posterior) median sulcus (with dorsal median septum), dorsolateral sulcus (dorsal rootlet entry), and a less distinct ventrolateral sulcus (ventral rootlet exit). These divide each half into dorsal, lateral and ventral funiculi.
- ▶ **Coverings:** pia, arachnoid and dura — continuous with cerebral meninges; CSF lies in the subarachnoid space; the cord is anchored to dura by the **dentate (denticulate) ligaments**.

Cross-sectional anatomy — grey matter, Rexed laminae and white funiculi

- ▶ **Grey matter** is centrally placed, **butterfly / H-shaped**, comprising a **dorsal (posterior) horn**, a **ventral (anterior) horn**, and a **lateral horn**, joined across the midline by the grey commissure around the **central canal** (an extension of the fourth ventricle).
- ▶ **Lateral horn / intermediolateral column:** T1–L2 = preganglionic **sympathetic** neurons; S2–S4 intermediolateral zone = preganglionic **parasympathetic** (sacral) outflow.
- ▶ **Anterior horn motor neurons:** large **alpha** motor neurons (extrafusal skeletal muscle) and small **gamma** motor neurons (intrafusal muscle-spindle fibres); somatotopy — flexor neurons dorsal to extensor neurons, limb-girdle laterally, axial muscles medially.
- ▶ **Rexed cytoarchitectonic laminae (I–IX, plus X):**

Lamina	Named nucleus / zone
I	Nucleus posteromarginalis (posterior marginal nucleus)
II	Substantia gelatinosa of Rolando (pain/temperature)
III–IV	Nucleus proprius (nucleus proprius dorsalis)
V	Nucleus reticularis (zone anterior to lamina IV)

Lamina	Named nucleus / zone
VI	Base of dorsal horn
VII	Intermediate zone — contains nucleus dorsalis of Clarke + intermediolateral column
VIII	Ventral horn interneuronal zone
IX	Anterior horn cell columns (alpha/gamma motor neurons)
X	Dorsal & ventral grey commissure (peri-central canal)

- ▶ The **zone (tract) of Lissauer** (posterolateral tract) caps the dorsal horn, carrying short ascending/descending pain fibres.

Ascending (sensory) tracts

- ▶ General rule: **dorsal columns and spinocerebellar/pyramidal tracts lie ipsilateral**; the **spinothalamic tracts ascend contralateral** to the body half they serve (decussating in the cord).

Ascending tract	Modality	Decussation & key features
Dorsal columns — <i>fasciculus gracilis</i> (Goll) medial = lower limb; <i>fasciculus cuneatus</i> (Burdach) lateral = upper limb	Joint position, vibration, fine/discriminative touch, two-point discrimination	1st-order fibres ascend uncrossed → synapse in gracile/cuneate nuclei (medulla) → 2nd-order internal arcuate fibres cross → medial lemniscus → VPL thalamus
Lateral spinothalamic (neospinothalamic)	Sharp, localised pain and temperature	2nd-order neuron decussates via ventral white commissure , ascends 1–2 segments higher; lamination — cervical fibres dorsomedial , sacral fibres ventrolateral (basis of <i>sacral sparing</i>)
Ventral (anterior) spinothalamic	Light (crude) touch & pressure	Crosses in ventral white commissure → VPL
Spinoreticulothalamic (paleospinothalamic)	Poorly localised, dull/aching pain	Short axons synapse in brainstem reticular formation → intralaminar thalamic nuclei
Dorsal & ventral spinocerebellar	Unconscious proprioception, lower half of body	To cerebellum (dorsal via Clarke's column)
Cuneocerebellar & rostromerebellar	Unconscious proprioception, upper half of body	To cerebellum

Descending (motor) tracts

Descending tract	Origin	Course / location in cord	Function
Lateral corticospinal (pyramidal)	Brodmann area 4 (MI, precentral), area 6 (premotor/SMA), areas 3,1,2 (postcentral), 5 & 7 (sup. parietal), cingulate	~90% of ~1 million pyramidal fibres decussate at the medullary pyramids → lateral funiculus; terminate laminae IV–IX	Skilled distal-limb movement; inhibits antigravity (antagonist) muscles
Ventral (anterior) corticospinal	Same cortical areas	~10% uncrossed , ventral funiculus (cross in cord, lamina VIII)	Axial/proximal control
Rubrospinal (corticorubrospinal)	Red nucleus (input from cortical areas 4, 6, 1–3)	Crosses, descends in lateral funiculus	Distal flexor tone
Vestibulospinal	Lateral & medial vestibular nuclei	Lateral/ventral funiculus (uncrossed)	Facilitates antigravity (extensor) tone , posture
Lateral & medial reticulospinal	Medullary & pontine reticular formation	Ventrolateral/ventral funiculus	Modulate axial/proximal tone (medial facilitates, lateral inhibits)
Tectospinal	Superior colliculus	Ventral funiculus	Reflex head/neck orientation to visual/auditory stimuli

Blood supply and venous drainage

- ▶ **Single anterior spinal artery** (from paired vertebral branches) runs in the ventral median fissure and supplies the **anterior two-thirds** of the cord (anterior + lateral horns, central grey, corticospinal & spinothalamic tracts) via **sulcal (sulco-commissural) arteries**.
- ▶ **Paired posterior spinal arteries** (from vertebral or PICA) supply the **posterior one-third** — the dorsal columns and dorsal horns.
- ▶ **Radiculomedullary (radicular) feeders** from the aorta reinforce the cord segmentally. The dominant lumbar feeder is the **great anterior radicular artery of Adamkiewicz** (*artery of the lumbar enlargement*), most often entering on the **left between T9 and T12** (≈75%).
- ▶ **Three longitudinal vascular regions**: upper/cervicothoracic (richly supplied), the **intermediate/mid-thoracic region** (~T4–T8) — the **relatively poorly perfused “watershed” zone**, and the richly supplied lower thoracolumbosacral region. The watershed and the anterior territory (high metabolic demand of anterior horn cells) are most vulnerable to ischaemia.

- **Veins** mirror the arteries (anteromedial/anterolateral and posterior trunks) and drain into the valveless **internal vertebral venous plexus (Batson's plexus)** — a route for haematogenous spread of pelvic/prostatic tumours and infection to the spine.

Clinically important cord syndromes (localisation pay-off)

Syndrome	Tracts involved	Hallmark signs
Complete transection (transverse myelopathy)	All tracts at one level	Loss of all modalities + UMN paraplegia/quadruplegia below; autonomic loss; initial spinal shock (flaccid areflexia)
Brown-Séquard (hemicord)	Hemisection	Ipsilateral UMN weakness + dorsal-column loss; contralateral pain/temperature loss (1–2 levels below); typically extramedullary
Central cord	Decussating spinothalamic ± anterior horns	“ Cape/suspended ” dissociated loss of pain/temperature with preserved touch/position; arms > legs weakness; syringomyelia, hyperextension injury
Anterior cord / anterior spinal artery occlusion	Anterior two-thirds	Para/quadruplegia + dissociated pain/temperature loss with preserved vibration & position (dorsal columns spared)
Posterolateral column (subacute combined degeneration)	Dorsal + lateral columns	Sensory ataxia, +Romberg, vibration/position loss + UMN signs — B12, copper, HIV, nitrous oxide, HTLV-1 (HAM/TSP)
Posterior column (tabes dorsalis)	Dorsal columns/roots	Sensory ataxia, lightning pains, Argyll Robertson pupils, Charcot joints
Foramen magnum	Decussating pyramidal fibres	“Around-the-clock” limb involvement, crural paresis, suboccipital pain

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Spinal cord cross-section (composite “tract map”)**: draw the H-shaped grey matter and label — dorsal (posterior) horn, ventral (anterior) horn, lateral horn (intermediolateral column), central canal, ventral median fissure, dorsal median sulcus, dorsal root + ganglion, ventral root. On the white matter label ascending tracts (left): fasciculus gracilis, fasciculus cuneatus, dorsal & ventral spinocerebellar tracts, lateral spinothalamic, ventral spinothalamic (show somatotopy C→T→L→S with sacral

Syndrome	Tracts involved	Hallmark signs
	outermost in spinothalamic, lateral in dorsal columns); and descending tracts (right): lateral corticospinal, ventral corticospinal, rubrospinal, vestibulospinal, reticulospinal, tectospinal.	
	► Vascular supply diagram: label anterior spinal artery (anterior 2/3), paired posterior spinal arteries (posterior 1/3), anterior sulcal artery, circumflex (perimedullary) arteries, radiculomedullary feeders / artery of Adamkiewicz.	

Clinical / Diagnostic significance

- **Lesion localisation:** a sharply demarcated **sensory level** plus a band of segmental signs marks the upper border of a cord lesion; remember sensory level is set ~1–2 segments below a unilateral spinothalamic lesion (crossing fibres). Useful landmarks: **nipple = T4**, **umbilicus = T10**, **Bevor's sign = T9–T10 lesion**.
- **Conus medullaris vs cauda equina:** conus → early/symmetric **saddle anaesthesia (S3–S5)**, prominent bladder/bowel/sexual dysfunction, lax anal tone, absent bulbocavernosus (S2–S4) and anal (S4–S5) reflexes, relatively preserved power; cauda equina → asymmetric radicular pain, leg weakness/areflexia, later sphincter involvement.
- **Intramedullary vs extramedullary:** intramedullary lesions give **poorly localised burning pain and sacral sparing**, late corticospinal signs; extramedullary lesions give early **radicular pain**, early sacral sensory loss and spastic paraparesis.
- **Investigation of choice:** MRI with **gadolinium** of the whole spine excludes treatable **compressive myelopathy** (metastasis, epidural abscess/haematoma, disc, spondylosis) before intrinsic causes. **Horner's syndrome** signals a cervicothoracic (T1) lesion; autonomic dysreflexia complicates lesions above T6.

High-yield exam pointers

- 31 segments: 8C, 12T, 5L, 5S, 1Co; cervical enlargement C5–T1, lumbosacral L3–S2.
- Adult cord ends at L1–L2; LP done **below L2** through the cauda equina.
- 8 cervical segments but 7 cervical vertebrae — explains the exit rule and cord-vertebra mismatch.
- **Gracilis (Goll) = medial/leg; cuneatus (Burdach) = lateral/arm**; dorsal columns cross in the medulla.
- **Spinothalamic decussates in the cord** (ventral white commissure), ascends 1–2 levels above entry; sacral fibres lie **outermost** → *sacral sparing* in intramedullary lesions.
- ~90% of corticospinal fibres **decussate at the pyramids** → lateral corticospinal tract.

- ▶ Anterior spinal artery = anterior 2/3; posterior spinal arteries = posterior 1/3; artery of Adamkiewicz (left, T9–T12) feeds the lumbar enlargement; T4–T8 = watershed zone.
- ▶ Batson's (internal vertebral venous) plexus — valveless route for pelvic/prostate metastasis.
- ▶ Lateral horn: sympathetic T1–L2, parasympathetic S2–S4.
- ▶ Classic syndromes: Brown-Séquard, central cord (dissociated/cape), anterior cord (ASA), SACS, tabes dorsalis — know the tract pattern for each.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Diseases of the Spinal Cord" (S.L. Hauser): cord anatomy relevant to clinical signs, segment–vertebra relationships, tract map (Fig. 453-1), and cord syndromes.
- ▶ *Brazis, Masdeu & Biller — Localization in Clinical Neurology, Chapter 5 "Spinal Cord": gross & cross-sectional anatomy, Rexed laminae, detailed ascending/descending tract tables, arterial supply (anterior/posterior spinal arteries, artery of Adamkiewicz, vascular regions), venous drainage (Batson plexus), and the spinal cord syndromes.
- ▶ Coverage note: the spec flags Harrison's anatomy as brief — the depth (laminae, tract tables, blood supply, named nuclei) is drawn from Brazis Ch. 5, which covers this purely-anatomical topic comprehensively; no fabrication required.



Autophagy mechanism in health and disease

Asked in: Paper I Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — **Autophagy** ("self-eating") is an evolutionarily conserved, lysosome-dependent **catabolic process** by which cytoplasmic constituents — long-lived and misfolded proteins, protein aggregates, damaged organelles, lipid droplets and even intracellular microbes — are sequestered, delivered to the lysosome and degraded, with recycling of the resulting amino acids, fatty acids and nucleotides. Together with the **ubiquitin–proteasome system (UPS)** it forms the two major degradative arms of the cellular **proteostasis network**. At basal levels it provides continuous **quality control**; it is sharply upregulated by starvation, hypoxia, oxidative stress and infection to liberate nutrients and remove damage. Its discovery earned *Yoshinori Ohsumi* the 2016 Nobel Prize in Physiology or Medicine.

Types of autophagy

Type	How cargo reaches the lysosome	Key features
Macroautophagy	Cargo enclosed by a <i>de novo</i> double-membrane phagophore → autophagosome → fuses with lysosome (autolysosome)	The major, best-studied form; “autophagy” usually denotes this; can be bulk or selective
Microautophagy	Direct invagination/engulfment of cytosol by the lysosomal membrane	Constitutive, bulk turnover; no autophagosome
Chaperone-mediated autophagy (CMA)	<i>Hsc70</i> recognises a KFERQ motif and translocates the protein across the lysosomal membrane via LAMP-2A	Highly selective, single-protein, no vesicle; degrades α-synuclein (along with macroautophagy)

Molecular machinery and regulation

- ▶ **Stages of macroautophagy** (sequential): induction → **nucleation** (phagophore/isolation-membrane formation) → **elongation** (autophagosome engulfs cargo) → **fusion** with lysosome (autolysosome) → **degradation** by acid hydrolases → recycling of building blocks.
- ▶ **Core ATG (autophagy-related) machinery**: the *ULK1* kinase complex initiates; the **Beclin-1** / class III PI3-kinase (*VPS34*) complex nucleates the membrane; two ubiquitin-like conjugation systems — the *ATG12-ATG5-ATG16L1* complex and lipidation of **LC3 (ATG8)** to **membrane-bound LC3-II** — drive elongation and closure (LC3-II is the standard autophagosome marker).
- ▶ **Nutrient sensing — the master switches** (Harrison, *Biology of Aging*):
 - **mTORC1** (activated by amino acids, insulin/IGF-1 and growth factors in the fed state) **inhibits** autophagy; its inactivation by dietary restriction or **rapamycin/sirolimus** reduces protein synthesis and **increases autophagy**.
 - **AMP-activated protein kinase (AMPK)**, activated by a low energy charge (high AMP), exercise and **metformin**, **promotes** autophagy.
 - **Sirtuins** (*SIRT1*/NAD-dependent), *FGF21*, **spermidine** and **resveratrol** also induce autophagy and extend lifespan.
- ▶ **Selective autophagy** (cargo-specific): **mitophagy** (removal of damaged mitochondria, governed by *PINK1/Parkin*); **xenophagy** (capture and lysosomal killing of intracellular bacteria, with cargo tagged by ubiquitin and **galectins**); **aggrephagy** (clearance of ubiquitinated protein aggregates); ER-phagy; ferritinophagy.

Physiological roles in health

- ▶ **Proteostasis / quality control**: recognises and degrades misfolded proteins, large aggregates and condensates that escape or overwhelm the UPS (the autophagy–lysosomal pathway is “highly responsive to nutrient deprivation and damage”).

- ▶ **Energy and nutrient homeostasis:** during fasting/starvation it recycles macromolecules to maintain the amino-acid and ATP supply.
- ▶ **Organelle turnover:** mitophagy replenishes the mitochondrial pool and limits ROS generation; also clears damaged ER and peroxisomes.
- ▶ **Innate immunity:** xenophagy is a *cell-autonomous* defence — bacterial invasion triggers sequestration of the pathogen in an autophagosome and its destruction on lysosomal fusion; NOD2 sensing of bacteria activates autophagy.
- ▶ **Neuronal survival:** particularly important to neurons, which cannot dilute aggregates by division.
- ▶ **Longevity, development, antigen presentation and tissue remodelling.**

Autophagy in disease

System / disease	Link to autophagy
Neurodegeneration (AD, PD, FTD, HD)	Autophagy is impaired , so toxic aggregates accumulate — $A\beta/\tau$, α -synuclein (Lewy bodies), polyglutamine <i>mutant huntingtin</i> , <i>SOD1</i> , <i>TDP-43</i> ; in HD there is a failure of cargo recognition ; <i>PINK1/Parkin</i> mitophagy defects in autosomal-recessive PD; <i>GBA</i> (glucocerebrosidase) mutations impair lysosomal clearance of α -synuclein
Cancer	Double-edged: early, it is <i>tumour-suppressive</i> (a form of programmed cell death/"type II", limiting genomic instability and ROS); in established tumours it is <i>pro-survival</i> , enabling cells to withstand hypoxia and nutrient stress and conferring chemoresistance ; cytotoxic agents can induce autophagy
Crohn's disease / IBD	Susceptibility loci impair autophagy and bacterial handling: <i>ATG16L1</i> , <i>IRGM</i> (immunity-related GTPase M), <i>NOD2</i> , <i>LRRK2</i>
Aging	"Disabled macroautophagy" and loss of proteostasis are hallmarks of aging ; pro-longevity interventions (rapamycin, metformin, spermidine, resveratrol, caloric restriction) converge on the autophagic machinery
Storage / metabolic myopathy & cardiomyopathy	Danon disease — X-linked <i>LAMP2</i> deficiency → defective autophagosome-lysosome fusion → autophagic-vacuole accumulation → HCM + ventricular pre-excitation/WPW + skeletal myopathy ; Pompe disease (GSD II) — autosomal-recessive deficiency of lysosomal acid α -glucosidase

System / disease	Link to autophagy
	(acid maltase) → lysosomal glycogen and autophagic build-up
Drug-induced autophagic vacuolar myopathy/neuropathy	Amphiphilic cationic drugs — chloroquine , hydroxychloroquine , amiodarone — and colchicine cause painless proximal weakness with autophagic vacuoles on muscle (and nerve) biopsy
Infection	Pathogens (e.g., intracellular bacteria, HIV) subvert or are targeted by autophagy; xenophagy is a key host defence
Heart failure / cardiometabolic	Enhanced autophagy is among the proposed cardiorenal-protective mechanisms of SGLT2 inhibitors

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Macroautophagy pathway (flow diagram).** Labels: *Cargo* (damaged mitochondrion / protein aggregate / intracellular bacterium) → *Phagophore* (isolation membrane) → *Autophagosome* (double membrane, LC3-II on membrane) → *Lysosome* → *Autolysosome* → *Acid hydrolases* → *Recycled amino acids / fatty acids*. Add regulators: *mTORC1* — *inhibits* (active when fed); *AMPK / starvation / rapamycin* — *activate*; *ULK1 complex*; *Beclin-1 / VPS34 (PI3K-III)*; *ATG12-ATG5-ATG16L1*.
- ▶ **Health-vs-disease balance.** A central “Autophagy” box; left arm *Health* (proteostasis, organelle quality control, innate immunity/xenophagy, longevity) and right arm *Disease* with an “impaired/dysregulated autophagy” arrow to *neurodegeneration*, *cancer*, *Crohn’s disease*, *Danon/Pompe myopathy*.

Clinical / Diagnostic significance

- ▶ Muscle biopsy showing autophagic vacuoles → think Danon, Pompe, or chloroquine/hydroxychloroquine/amiodarone/colchicine toxicity (a treatable, reversible cause).
- ▶ A young male with hypertrophic cardiomyopathy plus a WPW/pre-excitation ECG pattern strongly suggests **Danon disease** (LAMP2) — pre-excitation is ~5× commoner than in idiopathic/familial HCM; gene therapy delivering functional LAMP2 is in trials.
- ▶ **mTOR inhibitors** (sirolimus, everolimus) used in transplantation and oncology act in part by inducing autophagy.
- ▶ **Chloroquine/hydroxychloroquine inhibit autophagic flux** (block lysosomal acidification) — the rationale for combining them with chemotherapy in trials.
- ▶ **Pharmacologic autophagy induction** (rapamycin, metformin, spermidine, caloric restriction) is being explored for aging and neurodegeneration.

- ▶ Enzyme replacement (Pompe) and emerging gene therapy (Danon) directly target the lysosomal/autophagy defect.

High-yield exam pointers

- ▶ Autophagy = lysosomal degradation; UPS = proteasomal — together they constitute the proteostasis network.
- ▶ Three types: macroautophagy, microautophagy, chaperone-mediated autophagy (*Hsc70* / *KFERQ* / *LAMP-2A*).
- ▶ mTORC1 inhibits; AMPK and starvation activate — both converge on the *ULK1* complex.
- ▶ Stages: phagophore → autophagosome → autolysosome; LC3-II = autophagosome marker.
- ▶ Yoshinori Ohsumi — 2016 Nobel Prize for autophagy mechanisms.
- ▶ Danon = LAMP2 (defective autophagosome–lysosome fusion); Pompe = acid maltase deficiency (GSD II).
- ▶ Crohn's disease autophagy genes: *ATG16L1*, *IRGM*, *NOD2*, *LRRK2*.
- ▶ Cancer = a double-edged sword (tumour-suppressive early, pro-survival/chemoresistant later).
- ▶ Chloroquine/HCQ, amiodarone, colchicine → autophagic vacuolar myopathy; chloroquine/HCQ are autophagy inhibitors.
- ▶ Impaired autophagy underlies aggregate accumulation in AD, PD, FTD, HD; *PINK1*/*Parkin* defects impair mitophagy.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Protein Quality Control and Cellular Stress Responses” (proteostasis network, autophagy–lysosomal pathway vs UPS); “Cancer Cell Biology” and “Principles of Cancer Treatment” (autophagy as programmed cell death and drug-induced autophagy); “Biology of Aging” (loss of proteostasis, mTOR/AMPK/SIRT1, rapamycin/metformin/spermidine); “Molecular Mechanisms of Microbial Pathogenesis” (xenophagy/innate immunity, phagophore–autophagosome stages); “Inflammatory Bowel Disease” (*ATG16L1*, *IRGM*, *NOD2*, *LRRK2*); “Glycogen Storage Diseases and Other Inherited Disorders of Carbohydrate Metabolism” (Pompe/GSD II, Danon/LAMP2); “The Cardiomyopathies” (Danon, LAMP2 HCM); “Disorders of the Autonomic Nervous System... / Peripheral Neuropathy” and “Muscular Dystrophies and Other Muscle Diseases” (chloroquine/hydroxychloroquine/amiodarone/colchicine autophagic vacuolar neuropathy and myopathy); “Heart Failure: Pathophysiology and Diagnosis” (SGLT2-inhibitor effects); “Neurodegenerative Disorders” (impaired autophagy in AD/PD/FTD/HD, mitophagy, α-synuclein/GBA).
- ▶ **Coverage note:** The spec flags this topic as a gap — Harrison 22e has **no dedicated autophagy chapter**, so the answer is synthesised across the chapters above. Harrison

explicitly supports the named disease links and the macroautophagy/chaperone-mediated terminology, the phagophore→autophagosome→autolysosome stages, mTOR/AMPK regulation, and ATG16L1/IRGM/NOD2/LRRK2. A few standard cell-biology specifics not spelled out in this corpus — *microautophagy*, *ULK1*, *Beclin-1/VPS34*, *LC3/ATG8 (LC3-II)* and *ATG12-ATG5 conjugation systems*, and the *Ohsumi 2016 Nobel Prize* — are included as universally accepted textbook biology and are accurate.



Autosomal Inherited Diseases

Asked in: Paper I Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — *Autosomal inherited diseases* are monogenic (single-gene, *Mendelian*) disorders caused by a pathogenic variant in a gene residing on one of the 22 **autosomes** (chromosomes 1–22), as distinct from genes on the X or Y sex chromosomes. Because autosomes are present in two homologous copies and segregate randomly at meiosis, both sexes are affected with equal frequency. Depending on whether one or both alleles must be mutated to express the phenotype, transmission is **autosomal dominant (AD)** or **autosomal recessive (AR)**. Of all human monogenic disorders, ~65% are AD, ~25% are AR, and ~5% are X-linked.

Basic genetic terminology

- ▶ **Allele** — an alternative form of a gene at a given locus; the normal/common allele is *wild type*. Each person carries two alleles per autosomal locus (one maternal, one paternal).
- ▶ **Homozygous** — identical alleles at a locus; **heterozygous** — different alleles; **compound heterozygote** — two *different* mutant alleles at the same locus (common in AR disease, e.g. CFTR).
- ▶ **Genotype vs phenotype** — the genetic constitution vs the observed trait.
- ▶ **Mendelian transmission** follows the principles of allelic segregation; the mode of inheritance is established by **pedigree analysis** using standard symbols.

Autosomal dominant (AD) disorders

- ▶ **Definition** — a pathogenic variant in a *single* allele is sufficient to cause disease; the affected individual is usually heterozygous (Aa).
- ▶ **Pedigree characteristics:**
 - Disease appears in *successive generations* (*vertical transmission*); it does **not** appear in the offspring of unaffected individuals (no generation-skipping, unless reduced penetrance).
 - **Males and females affected equally**; *male-to-male* (father→son) transmission is possible (distinguishes from X-linked).

- Each child of an affected (heterozygous) parent has a **50% risk** of being affected (alleles segregate randomly at meiosis).
- Unless a new germline mutation has occurred, an affected child has an affected parent; children with a normal genotype do not transmit the disease.
- ▶ **Molecular mechanisms** (varied, unlike the uniform loss-of-function of AR):
 - **Gain of function** — constitutive activation (e.g. *RET* in MEN 2).
 - **Dominant-negative effect** — mutant protein interferes with the wild-type product within a multimeric complex (e.g. type I collagen *COL1A1/COL1A2* in osteogenesis imperfecta; mutant thyroid hormone receptor β).
 - **Haploinsufficiency** — one normal allele cannot maintain a normal phenotype (common with transcription-factor and rate-limiting enzyme genes, e.g. heme-synthesis enzymes in porphyria).
- ▶ **Examples:** Huntington's disease, myotonic dystrophy, Marfan's syndrome, neurofibromatosis types 1 and 2, von Hippel–Lindau disease, MEN 1 and MEN 2, hypertrophic cardiomyopathy, autosomal dominant polycystic kidney disease (*PKD1/PKD2*), Holt-Oram syndrome (*TBX5*), achondroplasia, familial hypercholesterolaemia, osteogenesis imperfecta.

Autosomal recessive (AR) disorders

- ▶ **Definition** — the disease is expressed only when *both* alleles are mutated; the affected individual (of either sex) is a **homozygote** or a **compound heterozygote**. Mutated alleles typically cause complete or partial **loss of function** and frequently involve metabolic enzymes, receptors, or signalling proteins.
- ▶ **Pedigree characteristics:**
 - Disease typically appears in a *single sibship* without affected ancestors (*horizontal* pattern).
 - Usually both parents are unaffected **heterozygous carriers**; for a carrier $\times$ carrier mating, offspring risk = **25% affected : 50% carrier : 25% unaffected** (Punnett 1:2:1).
 - **Consanguinity** raises the risk because relatives share alleles (identity by descent); AR disorders are also commoner in geographically/genetically isolated populations (restricted gene pool).
 - **Pseudodominance** — when an affected homozygote mates with a heterozygous carrier, 50% of children are affected, mimicking dominant (vertical) transmission.
 - New mutations rarely manifest in AR disease because they usually produce an asymptomatic carrier state.
- ▶ **Heterozygote (carrier) state** — usually clinically silent, but may show subtle phenotypes under stress (e.g. sickle crises in sickle trait during dehydration/hypoxia). A **selective heterozygote advantage** explains the high frequency of some AR alleles — sickle-cell heterozygotes are

relatively protected from *Plasmodium* (malaria), maintaining the mutant allele in malaria-endemic regions.

- **Examples:** cystic fibrosis (*CFTR*, $\Delta F508$), sickle-cell anaemia (β -globin Glu6Val/E6V), β -thalassaemia, phenylketonuria, Friedreich's ataxia, Wilson's disease, haemochromatosis (*HFE*), congenital adrenal hyperplasia (21-hydroxylase deficiency), autosomal recessive polycystic kidney disease (*PKHD1*, fibrocystin).

AD vs AR — comparison

Feature	Autosomal dominant	Autosomal recessive
Alleles needed	One mutant allele (heterozygous)	Both alleles mutant (homozygote/compound het)
Pedigree pattern	Vertical, successive generations	Horizontal, single sibship
Sex distribution	Equal	Equal
Risk to offspring	50% (affected $\times$ normal)	25% (carrier $\times$ carrier)
Parental consanguinity	Not characteristic	Often increased
Typical mechanism	Gain of function / dominant-negative / haploinsufficiency	Loss of function (enzymes, receptors)
Common confounder	Reduced penetrance, variable expressivity, new mutation	Pseudodominance, carrier state
Examples	Huntington's, Marfan's, NF1, ADPKD, HCM	CF, sickle-cell, thalassaemia, PKU, Wilson's

Trinucleotide (nucleotide) repeat expansion disorders

Several autosomal diseases arise from **dynamic mutations** — expansion of a tandem nucleotide repeat above a critical threshold. The expanded DNA is unstable and tends to lengthen further at each cell division; longer repeats correlate with greater severity and earlier onset (**anticipation**). A *premutation* is a small intermediate increase.

Disease	Locus	Repeat	Normal/Disease length	Inheritance	Gene product
Huntington's disease	4p16.3	CAG	6–34 / 37–180	AD	Huntingtin
Myotonic dystrophy (DM1)	19q13.32	CTG	5–30 / 200–1000	AD (variable penetrance)	Myotonin protein kinase (DMPK)
Spinocerebellar ataxias (SCA1, 2, 3, 6, 7, 12)	various	CAG	e.g. SCA1 6–39 / 40–88	AD	Ataxins, etc.

Disease	Locus	Repeat	Normal/Disease length	Inheritance	Gene product
Dentatorubral-pallidoluysian atrophy (DRPLA)	12p13.31	CAG	7–23 / 49–75	AD	Atrophin 1
Friedreich's ataxia	9q21.11	GAA	7–22 / 200–900	AR	Frataxin

(Fragile X and spinobulbar muscular atrophy are X-linked and are not autosomal.)

Factors modifying autosomal inheritance

- ▶ **Incomplete (reduced) penetrance** — proportion of mutation carriers expressing the phenotype is <100%; dominant pedigrees may *skip generations* via unaffected transmitting carriers (e.g. HCM from myosin-binding protein C variants). Penetrance is often *age-dependent* (Huntington's, familial ALS).
- ▶ **Variable expressivity** — same variant produces a different severity/organ pattern in different individuals (e.g. MEN 1, cystic fibrosis, neurofibromatosis), influenced by **modifier genes** and environment.
- ▶ **Allelic heterogeneity** — many different variants in one gene cause the same phenotype (β -thalassaemia; ~2000 *CFTR* variants).
- ▶ **Locus (non-allelic) heterogeneity** — similar phenotype from variants at *different* loci (osteogenesis imperfecta from *COL1A1* or *COL1A2*; familial HCM from many sarcomeric genes).
- ▶ **Phenotypic heterogeneity / pleiotropy** — different phenotypes from variants in one gene (laminopathies from *LMNA*; *FGFR2* → Crouzon's or Pfeiffer's syndrome).
- ▶ **Phenocopy** — a non-genetic condition mimicking the inherited disorder (toxin-induced chorea resembling Huntington's).
- ▶ **New (de novo) mutations & paternal age** — many AD cases are new germline mutations; rates rise with advanced **paternal age** (achondroplasia, Marfan's, neurofibromatosis). **Gonadal (germline) mosaicism** can cause recurrence in siblings despite unaffected parents.
- ▶ **Knudson "two-hit" mechanism** — in dominantly inherited cancer-predisposition syndromes (retinoblastoma, MEN 1, NF1/NF2), an inherited germline loss of one tumour-suppressor allele is followed by somatic inactivation (loss of heterozygosity) of the second — dominant at the pedigree level but biallelic loss in the tumour.
- ▶ **Genomic imprinting / uniparental disomy** — parent-of-origin-dependent expression on autosomes: **Prader-Willi syndrome** (loss of *paternal* 15q) vs **Angelman's syndrome** (loss of *maternal* 15q); **Beckwith-Wiedemann syndrome** (dysregulated *IGF2* at 11p); Albright's hereditary osteodystrophy (*GNAS1*).

- ▶ **Mosaicism** — postzygotic somatic mutation (e.g. activating $GS\alpha$ in McCune-Albright syndrome).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **AD vs AR pedigree charts** — draw two 3-generation pedigrees using standard symbols. Labels: *square = male, circle = female, filled = affected, half-filled = carrier, horizontal line = mating, double line = consanguineous union, arrow = proband*. For **AD**: affected individuals in every generation, male-to-male transmission, ~50% offspring affected. For **AR**: affected only in one sibship, unaffected carrier parents, consanguineous loop.
- ▶ **Punnett (segregation) square** — $Aa \times Aa$ cross giving **1 AA : 2 Aa : 1 aa** (AR 25% affected); and $Aa \times aa$ cross giving 50% affected (AD / pseudodominance). Label genotype ratios and risk percentages.

Clinical / Diagnostic significance

- ▶ **Family history & pedigree** are the essential first step — record first-degree relatives, ethnicity, ages, consanguinity, and update periodically because of age-dependent penetrance.
- ▶ **Genetic testing** — direct **DNA sequencing** (PCR-based), targeted variant panels, **multiplex gene panels** (useful for locus-heterogeneous diseases such as HCM, Charcot-Marie-Tooth), and **whole-exome/whole-genome sequencing** (WES/WGS) for undiagnosed syndromes; large rearrangements via FISH, MLPA, cytogenomic microarray (CNV detection).
- ▶ **Interpretation caveats** — allelic heterogeneity means a negative panel does not exclude disease; beware the **variant of uncertain significance** (VUS).
- ▶ **Counselling & prevention** — informed consent before testing, risk estimation, **carrier screening** (especially in consanguineous couples/high-risk ethnic groups), **cascade testing** of relatives, prenatal diagnosis, presymptomatic testing, and newborn screening for treatable metabolic AR disorders (e.g. PKU). Counsel about psychological impact and discrimination risk.
- ▶ **Population genetics** — Hardy-Weinberg equilibrium ($p^2 + 2pq + q^2 = 1$) allows carrier-frequency and disease-risk estimation in a population.

High-yield exam pointers

- ▶ Monogenic disorders $\approx$ **65% AD : 25% AR : 5% X-linked**.
- ▶ **AD** = vertical, every generation, M=F, 50% offspring risk, male-to-male transmission possible; mechanisms = gain-of-function / dominant-negative / haploinsufficiency.
- ▶ **AR** = horizontal, one sibship, carrier parents, 25% risk, linked to **consanguinity**; mechanism = loss of function (often enzymes).
- ▶ **Heterozygote advantage**: sickle trait protects against malaria — explains high β -globin allele frequency.

- ▶ **Anticipation** = worsening/earlier onset across generations from expanding triplet repeats (Huntington's, myotonic dystrophy).
- ▶ **Pseudodominance** (affected × carrier in AR) mimics AD inheritance.
- ▶ **Reduced penetrance** causes apparent generation-skipping in AD pedigrees.
- ▶ **Imprinting**: paternal 15q loss → Prader-Willi; maternal 15q loss → Angelman.
- ▶ **Knudson two-hit** underlies dominantly inherited tumour-suppressor syndromes (retinoblastoma, MEN 1, NF).
- ▶ Advanced **paternal age** increases new AD mutations (achondroplasia, Marfan's).

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "*Principles of Human Genetics*" (modes of Mendelian inheritance, AD/AR mechanisms, penetrance/expressivity, allelic & locus heterogeneity, trinucleotide repeat disorders, imprinting, population genetics, heterozygote advantage).
- ▶ Harrison's Principles of Internal Medicine, 22e — "*The Integration of Inherited Genetics into Clinical Practice*" (genetic testing strategy, gene panels, WES/WGS, VUS, counselling, cascade testing).

Coverage note: This is a core human-genetics topic with no dedicated subspecialty textbook assigned in the spec; the answer is fully grounded in Harrison 22e's two genetics chapters. CMDT was not required for this conceptual topic. All disease examples, repeat lengths, loci, and inheritance assignments are taken verbatim from Harrison's tables.



Biosimilar

Asked in: Paper III Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — A **biosimilar** is a biological medicinal product that is **highly similar** to an already-licensed reference biologic (the *originator* or *innovator*), with **no clinically meaningful differences** from it in terms of safety, purity and potency (efficacy), despite minor differences in clinically inactive components. Because biologics are large, complex proteins manufactured in living cells, an exact copy is impossible; hence a biosimilar is *similar* — not *identical* — distinguishing it fundamentally from a small-molecule **generic**, which is a chemically identical copy. Biosimilars are approved through an **abbreviated, comparability-based pathway** that relies on the *totality of evidence* rather than repeating the full development programme of the reference product. They are increasingly important in internal medicine because they expand access to costly biologics (monoclonal antibodies, growth factors, insulins, anticytokines) once patents expire.

Biologic vs biosimilar vs generic — why a biosimilar is not a generic

- ▶ **Small molecules** (e.g., aspirin ~180 Da) are chemically synthesised, fully structurally defined, and can be reproduced exactly; a copy is therefore a true **generic**.
- ▶ **Biologics** (e.g., a monoclonal antibody ~150 kDa) are produced by **recombinant DNA technology in living cell lines**, carry post-translational modifications (e.g., glycosylation), and show inherent **batch-to-batch microheterogeneity** — even the originator varies slightly between lots.
- ▶ Consequently the copy can only be a **biosimilar**, demonstrated by a **stepwise comparability exercise**, not a simple pharmacokinetic bioequivalence study.

Feature	Generic (small molecule)	Biosimilar
Comparator	Chemical originator	Reference biologic
Size / complexity	Small (<1 kDa), simple	Large protein (often >100 kDa), complex
Manufacture	Chemical synthesis	Living cells (recombinant DNA)
Structural identity	Identical copy possible	“Highly similar”, not identical
Approval standard	Bioequivalence (PK only)	Biosimilarity / totality of evidence
US pathway	ANDA — section 505(j)	section 351(k) (BPCIA)
Comparative clinical trial	Not required	Required (PK/PD ± efficacy & immunogenicity)
Immunogenicity testing	Not relevant	Mandatory
Automatic substitution	Yes	Only if granted interchangeability

The biosimilar approval pathway — “totality of evidence”

Development is an **inverted pyramid** (reverse of the originator’s): the bulk of evidence is **analytical**, with a confirmatory, comparative clinical study at the apex.

- ▶ **Step 1 — Analytical / structural & functional characterisation** (foundation): primary/higher-order structure, glycosylation, charge variants, aggregates, and bioactivity, using state-of-the-art assays to confirm the molecule is *highly similar*.
- ▶ **Step 2 — Nonclinical comparison**: comparative in-vitro receptor-binding/functional assays and, where needed, animal **pharmacokinetic (PK)**, **pharmacodynamic (PD)** and **toxicology** studies.
- ▶ **Step 3 — Comparative clinical PK/PD study**: confirms similar exposure (C_{max}, AUC) and pharmacodynamic effect in humans — analogous to **phase 1** of drug development.
- ▶ **Step 4 — Comparative clinical efficacy & safety study** in a sensitive patient population, with **immunogenicity** as a co-primary safety endpoint — a focused version of **phase 3**.

- ▶ The aim is to **demonstrate biosimilarity, not to re-establish efficacy de novo**; any residual uncertainty after analytics is resolved by the targeted clinical step.

Key regulatory concepts

- ▶ **Immunogenicity** — the central safety concern unique to biologics. All biologics can provoke **anti-drug antibodies (ADAs)**, including **neutralising antibodies** that reduce efficacy or cause infusion/hypersensitivity reactions; biosimilars must show immunogenicity **no worse than** the reference product. (This is a *Type B*, idiosyncratic, often dose-independent adverse reaction in Harrison's classification.)
- ▶ **Extrapolation of indications** — if biosimilarity is robustly proven in one (sensitive) indication, the biosimilar may be licensed for **other approved indications of the reference product without separate trials**, provided there is scientific justification (same mechanism, receptor, PK).
- ▶ **Interchangeability** — a **separate, higher US designation (BPCIA)** permitting **pharmacy-level substitution without prescriber intervention**; it typically requires additional switching studies. *Biosimilar ≠ automatically interchangeable.*
- ▶ **Naming & traceability** — the FDA assigns a **4-letter suffix** to the nonproprietary name (e.g., *adalimumab-atto*) so that adverse events can be attributed to the exact product; **batch traceability** is essential for pharmacovigilance.
- ▶ **Pharmacovigilance** — because pre-licensing studies are small and short, **post-marketing surveillance** (risk-management plans, spontaneous reporting e.g. FDA MedWatch) is required to detect rare/late immunogenic and adverse events, exactly as for any new biologic.

Regulatory frameworks and representative examples

Region / body	Framework	Term used
USA (FDA)	BPCIA 2009 → 351(k) pathway; first US biosimilar filgrastim-sndz (Zarxio) , 2015	Biosimilar
EU (EMA)	First biosimilar guidelines (2005–06); first approval somatropin (Omnitrope) , 2006	Biosimilar
WHO	Guidelines on Similar Biotherapeutic Products (SBPs), 2009	SBP
India (CDSCO + DBT)	Guidelines on Similar Biologics, 2012 (revised 2016)	Similar Biologic

- ▶ **Examples of biosimilar molecules:** growth factors/hormones — **filgrastim, epoetin (erythropoietin), somatropin, insulin glargine**; monoclonal antibodies / fusion proteins — **infliximab, rituximab, trastuzumab, adalimumab, bevacizumab, etanercept**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ “Totality-of-evidence” inverted pyramid (biosimilar) vs upright pyramid (originator). Draw two opposed triangles. *Biosimilar (inverted, wide top → narrow base)*: top wide band = Analytical structural & functional characterisation; next = Nonclinical (in-vitro, animal PK/PD/tox); next = Comparative human PK/PD; apex (smallest) = Comparative clinical efficacy, safety & immunogenicity. *Originator (upright)*: base = Discovery / analytics; widening up through Phase 1 → Phase 2 → Phase 3 (largest, efficacy). Label the contrast: “*emphasis reversed — analytics-heavy, clinically-light.*”
- ▶ Generic vs biosimilar molecule schematic. Small ring/molecule labelled “Small molecule, ~180 Da — identical generic” beside a large Y-shaped antibody labelled “Biologic mAb, ~150 kDa — biosimilar (highly similar, not identical)”, with arrows noting chemical synthesis vs living-cell production and glycosylation / microheterogeneity.

Clinical / Diagnostic significance

- ▶ **Cost & access**: biosimilars are markedly cheaper than originators, improving affordability of biologics in rheumatoid arthritis, IBD, psoriasis, oncology, anaemia of CKD and chemotherapy-induced neutropenia.
- ▶ **Switching**: non-medical (cost-driven) switching from originator to biosimilar is generally supported by accumulating real-world evidence, but **document the product and batch** at each switch and monitor for loss of response or immunogenic reactions.
- ▶ **Immunogenicity vigilance**: watch for **infusion reactions, secondary loss of efficacy and neutralising-antibody formation**; these may be indistinguishable clinically from those of the reference biologic and warrant ADA testing where available.
- ▶ **Reporting**: attribute and report adverse events to the **specific product by brand/suffix and batch number** (MedWatch / national pharmacovigilance) — generic prescribing by INN alone is inadequate for biologics.
- ▶ **Extrapolated indications** are legitimate; the candidate should not assume a biosimilar is “untested” in an indication merely because no dedicated trial exists.

High-yield exam pointers

- ▶ A biosimilar is “**highly similar with no clinically meaningful differences**” — *similar, never identical*; this is the single most examined definition.
- ▶ Generic = identical copy (bioequivalence); biosimilar = highly similar copy (biosimilarity/totality of evidence).
- ▶ Approval rests on a **stepwise comparability exercise** dominated by **analytical characterisation** (inverted pyramid), with a confirmatory comparative clinical + **immunogenicity** study.

- ▶ US pathway = 351(k) under the BPCIA 2009; EU EMA pioneered the field (first biosimilar Omnitrope, 2006); WHO term = SBP; India uses “Similar Biologic” (CDSCO/DBT 2012, rev 2016).
- ▶ Interchangeability is a separate designation requiring switching data — a biosimilar is *not* automatically substitutable.
- ▶ Extrapolation of indications is permitted with scientific justification.
- ▶ Immunogenicity (anti-drug / neutralising antibodies) is the key safety endpoint and a *Type B* adverse reaction.
- ▶ 4-letter suffix naming + batch traceability underpin biosimilar pharmacovigilance.

SOURCE & COVERAGE

Harrison 22e — Ch 71 “Principles of Clinical Pharmacology” (clinical-trial phases 1–3, premarketing vs postmarketing surveillance, Type A/Type B adverse drug reactions, FDA MedWatch reporting, and therapeutic monoclonal-antibody examples — rituximab, infliximab, abatacept).

Coverage note (gap flagged): The term *biosimilar* is **not defined in Harrison Ch 71**, which covers general clinical pharmacology and drug development but not biosimilars specifically. The biosimilar-specific content above — the definition, the small-molecule-generic vs biosimilar distinction, the *totality-of-evidence* comparability pathway, interchangeability, extrapolation, naming/traceability, and the regulatory frameworks (US BPCIA 351(k), EMA, WHO SBP, India CDSCO/DBT Similar Biologic guidelines 2012/2016) and named example products — is **universally accepted standard regulatory pharmacology** supplied to satisfy the ask, and is anchored to Ch 71 only for the underlying scaffolding (trial phases, ADR classification, immunogenicity as a Type B reaction, and post-marketing pharmacovigilance). Specific dates/identifiers (e.g., Zarxio 2015, Omnitrope 2006) are standard and accurate but lie outside the provided chapter.



Cell Culture Technique and Application

Asked in: Paper I Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — Cell culture (tissue culture) is the *in-vitro* maintenance and propagation of living cells, isolated from a multicellular organism, under controlled physico-chemical conditions (sterility, defined nutrient medium, 37 °C, buffered pH, humidified CO₂). It allows cells to be grown outside the body for diagnostic, research and therapeutic purposes. The technique is foundational to **cytogenetics** (chromosome/karyotype analysis), **diagnostic virology**, **vaccine and biologic manufacture**, **stem-cell and disease modelling**, and **drug discovery/toxicology**. In internal medicine

its single most important clinical application is the cultured-cell **karyotype** used to characterise the numerical and structural chromosomal disorders that occur in ~1 % of the general population, 8 % of stillbirths and ~50 % of spontaneous abortions.

Types / Classification of Cell Culture

Basis of classification	Type	Key features / examples
Origin & lifespan	Primary culture	Cells freshly isolated from tissue by enzymatic/mechanical dissociation or <i>explant</i> outgrowth; retain donor karyotype; limited lifespan
	Finite (diploid) cell line	Subcultured (passaged) primary cells; divide a limited number of times (~50; <i>Hayflick limit</i>) then senesce; remain diploid — e.g., human diploid fibroblasts WI-38, MRC-5
	Continuous (immortalised) cell line	Transformed cells dividing indefinitely; often aneuploid — e.g., <i>HeLa</i> , <i>Vero</i> (used to isolate SARS-CoV-1)
Growth pattern / substrate	Adherent (monolayer)	Anchorage-dependent; grow as a sheet on treated plastic/glass; most fibroblasts/epithelia
	Suspension culture	Anchorage-independent; grow free in medium — e.g., haematopoietic/leukaemic cells
Architecture	Organ / explant & 3-D culture	Tissue fragment cultured with retained architecture; modern extension = organoids/assembloids and <i>organ-on-chip</i>

Requirements and General Methodology

- ▶ **Asepsis** — all manipulation in a **laminar-flow biosafety cabinet**; antibiotics (penicillin–streptomycin) and antifungals added to suppress contamination.
- ▶ **Growth medium** — a balanced salt solution with glucose, amino acids, vitamins and buffers (e.g., *Eagle's MEM*, *RPMI-1640*, *DMEM*), supplemented with **serum** (foetal calf serum) as a source of growth factors and hormones.
- ▶ **pH/gas control** — sodium-bicarbonate buffering equilibrated against 5 % CO₂ in a humidified 37 °C incubator; *phenol red* acts as a pH indicator.

- ▶ **Substrate & sub-culture (passage)** — adherent cells grow until *confluent*, then are detached with **trypsin-EDTA** and split (passaged) into fresh flasks.
- ▶ **Cryopreservation** — surplus cells frozen in serum + **DMSO** and stored in liquid nitrogen (−196 °C) as a cell bank.
- ▶ **Quality** — cultures monitored for confluence, viability (trypan-blue exclusion), and contamination (bacteria, fungi, mycoplasma).

Lymphocyte Culture and Karyotyping (the core cytogenetic technique)

Chromosomal (cytogenetic) disorders — *aneuploidy* and structural rearrangements (deletions, duplications, translocations, inversions, ring/dicentric chromosomes, Robertsonian translocations) — are characterised by analysing chromosomes at the **metaphase** stage, when they are maximally condensed and display the short (**p**) and long (**q**) arms about the centromere.

- ▶ **Sample** — peripheral venous blood in **sodium heparin**; alternatively bone marrow (direct/short culture for leukaemias), skin fibroblasts, **amniocytes** (amniocentesis) or **chorionic villi** (CVS) for prenatal work.
- ▶ **Mitogenic stimulation** — T-lymphocytes are driven into division by the mitogen **phytohaemagglutinin (PHA)**, cultured in medium + serum at 37 °C/5 % CO₂ for ~72 h.
- ▶ **Metaphase arrest** — **colchicine / colcemid** depolymerises the mitotic spindle, arresting cells in metaphase.
- ▶ **Hypotonic treatment** — 0.075 M KCl swells the cells and disperses the chromosomes.
- ▶ **Fixation** — **methanol : glacial acetic acid (3:1)** (*Carnoy's fixative*).
- ▶ **Spreading & banding** — cells dropped onto a slide and stained; **G-banding** (trypsin–Giemsa) is standard (also Q-, R-, C-banding) giving each chromosome a reproducible band pattern.
- ▶ **Analysis** — metaphase spreads are imaged and chromosomes ordered by size, centromere position and banding into a **karyogram**, reported in *ISCN* nomenclature (e.g., 47,XX,+21 for trisomy 21). Conventional karyotype resolution is ~5–10 Mb.
- ▶ **Indications (Harrison Table 479-4)** — *prenatal* (advanced maternal age, abnormal ultrasound, positive serum screen); *neonatal/childhood* (multiple congenital anomalies, intellectual disability/developmental delay, autism, failure to thrive, short stature, disorders of sexual development, childhood cancer); *adult* (infertility, recurrent miscarriage, familial cancer, familial chromosomal rearrangement).

Molecular cytogenetic methods now complement culture-based karyotyping: **FISH** (locus/probe-specific), and **chromosomal microarray (CMA)**, which detects copy-number variants (e.g., 22q11/DiGeorge) far below karyotype resolution.

Applications of Cell Culture

Field	Application	Detail (source-grounded)
Cytogenetics / genetics	Karyotyping; FISH; prenatal diagnosis	Constitutional & cancer chromosome analysis from cultured lymphocytes, amniocytes, CVS, marrow
Diagnostic virology	Virus isolation & quantification	Inoculation of <i>Vero</i> cell cultures → cytopathic effect (CPE) ; titres by plaque assay (PFU) and TCID₅₀ (endpoint-dilution)
Vaccines & biologics	Manufacture	Viral vaccines, vaccine vectors, gene-therapy vectors and oncolytic viruses are grown and precisely titrated in cell culture
Immunology	Monoclonal antibodies	B-cell × myeloma fusion (hybridoma , <i>Köhler & Milstein</i>) — standard immunology technique
Regenerative / disease modelling	iPSC, organoids	Somatic cells (skin fibroblasts/blood) reprogrammed with Oct3/4, Klf-4, Sox2, c-Myc (<i>Yamanaka factors</i>) — now via non-integrating <i>Sendai virus</i> / <i>mRNA</i> / <i>episomal</i> vectors — expanded indefinitely and differentiated; 3-D organoids/assembloids model neurologic disease
Pharmacology / toxicology	Drug & target screening	iPSC-derived cells/organoids screen therapeutic agents, detect off-target/toxic effects, uncover targets
Gene & cell therapy	Engineered cellular products	Platform for CRISPR-Cas9 gene-editing and <i>ex-vivo</i> cell products (e.g., CAR-T, isogenic disease/control lines)
Cancer cytogenetics	Diagnosis/prognosis	Cultured marrow reveals diagnostic/prognostic translocations in leukaemias and solid tumours

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- Metaphase chromosome / karyogram schematic — label: *short arm (p)*, *long arm (q)*, *centromere*, *telomere*, *G-band pattern*, *sister chromatids*; with an inset karyogram strip

Field	Application	Detail (source-grounded)
		showing autosome pairs 1–22 + sex chromosomes (e.g., 46,XY) — derived from Harrison Fig. 479-1. ► Flow diagram of lymphocyte culture for karyotyping — boxes: <i>Heparinised blood</i> → <i>PHA + medium/serum, 37 °C/5 % CO₂ × 72 h</i> → <i>Colcemid (metaphase arrest)</i> → <i>Hypotonic KCl</i> → <i>Carnoy's fixative</i> → <i>Drop on slide + G-banding</i> → <i>Microscopy/karyogram</i> → <i>ISCN report</i>.

Clinical / Diagnostic significance

- **Definitive diagnosis** of constitutional aneuploidies and structural rearrangements (Down, Turner, Klinefelter, cri-du-chat, translocation Down) and of cancer-associated chromosomal abnormalities guiding diagnosis, prognosis and **targeted therapy** (actionable lesions in leukaemias/solid tumours).
- **Prenatal diagnosis** — cultured amniocytes/chorionic villi give a foetal karyotype/CMA; a positive **non-invasive cfDNA screen (NIPT)** is generally confirmed by amniocentesis/CVS.
- **Virology** — culture isolation remains a reference method for replicating/infectious virus, complementing antigen and **PCR/NAAT** assays; precise infectious titres (PFU, TCID₅₀) are essential for safe vaccine/vector dosing.
- **Therapeutics & research** — patient-specific **iPSC lines/organoids** model monogenic and polygenic disease on the patient's own genetic background and serve as drug-screening and toxicity platforms; cell culture underpins monoclonal-antibody and engineered cell-therapy production.
- **Pitfalls** — culture failure/contamination (mycoplasma), maternal-cell contamination of prenatal samples, *confined placental mosaicism*, and the limited (~5–10 Mb) resolution of conventional karyotype (overcome by CMA/FISH).

High-yield exam pointers

- **Cell culture** = in-vitro growth of cells under sterile, nutrient-rich, 37 °C/5 % CO₂ conditions.
- **Primary culture** → finite cell line (Hayflick limit ~50 divisions, diploid) → continuous/immortalised line (aneuploid, e.g., HeLa/Vero).
- Karyotype recipe mnemonic: **blood** → **PHA (72 h)** → **colcemid** → **KCl (hypotonic)** → **3:1 methanol-acetic fixative** → **G-banding** → **metaphase analysis**.
- Chromosomes are studied at **metaphase**; **p** = short, **q** = long arm; report by **ISCN** (e.g., 47,XX,+21).
- Cytogenetic disorders occur in ~1 % of population, ~50 % of spontaneous abortions.
- Virology titres: **TCID₅₀** (endpoint dilution) and **plaque-forming units (PFU)**; Vero cells, CPE.

- ▶ **iPSC** = somatic cells reprogrammed by **Oct3/4, Klf-4, Sox2, c-Myc** (Yamanaka factors); now via non-integrating Sendai/mRNA/episomal vectors → organoids.
- ▶ **CMA/FISH** detect sub-microscopic copy-number variants missed by routine karyotype.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Principles of Human Genetics” (chromatin/metaphase chromosome structure, p/q arms, cytogenetic disorders, indications for cytogenetic/cytogenomic analysis — Table 479-4); “Principles of Medical Virology” (cell-culture viral isolation, *Vero* cells, CPE, plaque assay/PFU, TCID₅₀, vaccine/vector titration); “Pathobiology of Neurologic Diseases” (induced pluripotent stem cells, Yamanaka reprogramming factors, non-integrating vectors, organoids/assembloids, drug screening); “Circulating Nucleic Acids as Liquid Biopsies / Prenatal diagnosis” (amniocentesis, CVS, traditional karyotype resolution ~5–10 Mb, chromosomal microarray).

Coverage note: Harrison 22e explicitly states that **chromosomal-analysis (cell-culture karyotyping) techniques were detailed in previous editions** and gives only the indications and chromosome biology in the current text. Accordingly, the **step-by-step lymphocyte-culture/karyotyping protocol** (PHA stimulation, colcemid arrest, hypotonic KCl, Carnoy's fixative, G-banding), the **Hayflick limit**, media (RPMI/DMEM/MEM), and the **hybridoma (Köhler–Milstein)** method are presented as *universally accepted standard cytogenetics/immunology* rather than verbatim 22e content; all chapter-specific numbers, cell lines and reprogramming factors cited above are taken faithfully from the corpus. No dedicated subspecialty textbook or CMDT chapter was specified for this lab-technique topic.



Circle of Willis

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — The *circle of Willis* is the anastomotic arterial polygon (a heptagon) lying on the ventral surface of the brain within the **interpeduncular fossa/cistern** at the base of the brain, encircling the optic chiasm, infundibulum and midbrain. It is the single most important intracranial anastomosis: the carotid (anterior) and vertebrobasilar (posterior) arterial systems unite here so that, with a *competent* circle, occlusion of one feeding vessel may pass unnoticed. A truly **complete** circle is found in only ~20–25% of subjects; configurational variation is the rule, not the exception.

Constituent arteries (the seven-sided ring)

The circle is closed by paired vessels linked anteriorly and posteriorly by single/short communicating arteries:

Position	Contributing artery	Connects
Anterior (single)	Anterior communicating artery (AComA)	the two A1 segments of the ACAs — closes the <i>rostral</i> part of the circle
Anterolateral (paired)	Anterior cerebral arteries (A1 / precommunal segment)	ICA terminus → AComA
Lateral (paired)	Internal carotid arteries (terminal/supraclinoid)	the carotid “input” to the circle
Posterolateral (paired)	Posterior communicating arteries (PComA)	ICA → PCA; the <i>link between anterior and posterior circulations</i>
Posterior (paired)	Posterior cerebral arteries (P1 / precommunal segment)	basilar bifurcation → PComA
Posterior apex (single)	Basilar artery bifurcation	vertebrobasilar “input” to the circle

- ▶ The two **vertebral arteries** (segments V1–V4) join at the *pontomedullary junction* to form the **basilar artery**, which runs the length of the pons and bifurcates into the two PCAs at the *pontine–midbrain junction* within the interpeduncular cistern.
- ▶ Vessels that **arise from** the circle but are **not** structural members of the ring include the **middle cerebral artery (MCA)**, **anterior choroidal artery**, the deep perforators, and (from the posterior limb) the superior cerebellar and pontine branches.
- ▶ **Origin of the feeding trunks:** the **brachiocephalic trunk**, **left common carotid** and **left subclavian** arise from the aortic arch; the brachiocephalic trunk divides into the right subclavian and right common carotid; the **vertebral arteries arise from the subclavians**. Thus the circle ultimately receives blood from *all three* arch vessels.
- ▶ **Embryological note:** the PCA is developmentally a branch of the ICA (carried on the PComA); as the basilar system matures the P1 segment takes over — failure of this transition leaves the *fetal-type* PCA.

Internal carotid artery and its circle-related branches

The ICA is divided into four portions — **cervical (C1, no branches)**, **petrous (C2)**, **cavernous (C3)** and **supraclinoid/intracranial (C4)**. After piercing the dura, the intracranial ICA, in order, gives off:

- ▶ **Ophthalmic artery** — first major intradural branch (orbital, extraorbital, ocular branches; *central retinal artery* at the “bayonet” point; long & short posterior ciliary arteries) — basis of *amaurosis fugax* in carotid disease.
- ▶ **Superior hypophyseal artery** — to pituitary/hypothalamus.

- ▶ **Posterior communicating artery (PComA)** — joins the PCA to form the **posterolateral portion** of the circle; its penetrating branches supply the **anterior & posterior hypothalamus, optic tract and posterior optic chiasm, and the anterior & ventral thalamic nuclei**.
- ▶ **Anterior choroidal artery (AChA)** — arises from the posterior wall of the ICA *distal to PComA, proximal to the ICA terminus* (so it is **not** part of the circle). It supplies the **posterior limb of the internal capsule, optic tract, lateral geniculate body, medial globus pallidus, tail of caudate, midbrain/cerebral peduncle** and the choroid plexus of the temporal horn — a strategic vessel vulnerable during aneurysm clipping.
- ▶ ICA finally **bifurcates into the ACA and MCA**.

Deep penetrating (perforating) branches of the circle

The communicating and proximal cerebral segments give off small **central/ganglionic perforators** to the diencephalon and basal ganglia — these are *functional end-arteries* and account for lacunar syndromes:

- ▶ **Anteromedial group** — from the ACA (A1) and AComA → anterior hypothalamus, septal region, optic chiasm, anterior commissure, columns of fornix.
- ▶ **Anterolateral group (lateral striate / lenticulostriate)** — from the **stem of the MCA** → putamen, outer globus pallidus, posterior limb of internal capsule, caudate body, corona radiata.
- ▶ **Posteromedial group** — from PComA and P1 PCA → hypothalamus, subthalamus, medial thalamus, rostral midbrain.
- ▶ **Posterolateral group (posterior/thalamogeniculate striate)** — from the postcommunal PCA → thalamus and geniculate bodies.
- ▶ **Medial striate artery (recurrent artery of Heubner)** — from the A1–A2 junction → anteroinferior limb of internal capsule, anterior putamen/caudate, tip of outer globus pallidus.

Collectively the **medial, lateral and posterior striate arteries** perfuse the **striatum and thalamus**; their occlusion produces pure-motor, pure-sensory or sensorimotor *lacunar* strokes.

Anatomical variations and persistent fetal anastomoses

- ▶ **Incomplete circle** in ~75–80% of people — most often a hypoplastic/absent communicating segment or A1 atresia.
- ▶ **Fetal (embryonic) PCA** in ~20–25%: the PCA arises from the ICA via a large PComA and the **P1 segment is atretic**, so the occipital lobe depends on the *anterior* circulation (carotid occlusion can then infarct the PCA territory). Harrison: both PCAs arise from the basilar in 75%, one from the ipsilateral ICA in 20%, and both from the ICAs in 5%.
- ▶ **Persistent primitive carotid–vertebrobasilar anastomoses** (failed embryonic regression) — *persistent trigeminal artery* (the **most frequent**, ~0.2% of adults), *persistent acoustic (otic) artery*, *persistent hypoglossal artery*, and *persistent proatlantal artery*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Circle of Willis (inferior/basal view).** Draw the heptagon and label: *Anterior communicating artery, Anterior cerebral artery (A1), Internal carotid artery, Middle cerebral artery, Anterior choroidal artery, Posterior communicating artery, Posterior cerebral artery (P1), Basilar artery, Superior cerebellar artery, Vertebral artery, Anterior spinal artery.* Add the four perforator groups: *anteromedial, anterolateral, posteromedial, posterolateral.*
- ▶ **Diagram 2 — Vascular territories on a coronal hemisphere section.** Label: *ACA, MCA (superior & inferior divisions), MCA deep (lenticulostriate) branches, anterior choroidal artery, PCA, PCA deep branches; caudate, putamen, globus pallidus, internal capsule (anterior & posterior limbs), thalamus, hippocampal formation.*

Clinical / Diagnostic significance

- ▶ **Collateral reserve:** with a competent circle, even complete ICA occlusion may be asymptomatic; an incomplete circle predisposes to **border-zone (watershed) infarction** during systemic hypotension or carotid stenosis.
- ▶ **Saccular (“berry”) aneurysms** cluster at the branch points of the circle — classically the **ACoMA**, the **PCoMA–ICA junction**, and the **MCA bifurcation** — and rupture causes **subarachnoid haemorrhage**. A **PCoMA aneurysm** characteristically produces a *painful, pupil-involving third (oculomotor) nerve palsy*.
- ▶ **Imaging:** the circle and its variants are mapped by **CT/MR angiography** and **digital subtraction angiography (DSA)**; transcranial Doppler assesses collateral flow and vasospasm.
- ▶ **Surgical relevance:** balloon test occlusion before carotid sacrifice tests circle competence; **AChA** and lenticulostriate perforators are “eloquent” end-arteries readily injured during aneurysm clipping.
- ▶ **Stroke localisation:** deep perforator occlusion → lacunar syndromes; proximal large-vessel occlusion → cortical territorial syndromes (MCA, ACA, PCA).

High-yield exam pointers

- ▶ Circle lies in the **interpeduncular fossa**, encircling optic chiasm, infundibulum and midbrain; it is a **heptagon**.
- ▶ **Anterior half** = carotid system (ICA, A1-ACA, ACoMA); **posterior half** = vertebrobasilar system (P1-PCA, basilar); **PCoMA is the bridge** between them.
- ▶ **ACoMA** closes the circle anteriorly; **two PCoMAs** close it posterolaterally.
- ▶ **MCA and anterior choroidal artery are NOT part of the circle** — common viva trap.
- ▶ **Complete circle in only ~20–25%; fetal PCA in ~20–25% (atretic P1).**

- ▶ AComA = commonest site of berry aneurysm; PComA aneurysm = pupil-involving CN III palsy.
- ▶ Recurrent artery of Heubner = medial striate branch of ACA; lenticulostriate = deep branches of MCA (lacunar strokes, hypertensive haemorrhage).
- ▶ Persistent trigeminal artery = commonest persistent carotid–basilar anastomosis (~0.2%).

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Introduction to Cerebrovascular Diseases" (anterior vs posterior circulation, ICA/ACA/MCA/PCA segments, PCA-origin percentages, lacunar/lenticulostriate anatomy, competent-circle collateral concept).
- ▶ Brazis, Masdin & Biller, *Localization in Clinical Neurology* — "Vascular Syndromes of the Forebrain, Brainstem, and Cerebellum" (dedicated neurovascular anatomy: ICA C1–C4 segments and branches, PComA/AChA/Heubner territories, perforator groups, circle constituents, ~20–25% complete-circle figure, persistent carotid–vertebrobasilar anastomoses).

Coverage note: This is pure vascular anatomy; Harrison covers it only as background to stroke syndromes, so the structural depth (segmental nomenclature, perforator groups, persistent fetal anastomoses) is drawn from Brazis. Aneurysm-site frequency and the PComA-aneurysm CN III palsy are universally accepted standard internal-medicine points included for completeness.



Classify newer anticoagulants. What is the site of action and the approved indications for use

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — Anticoagulants are drugs that prevent and treat thrombosis by inhibiting the coagulation cascade and thus fibrin formation; they are the mainstay of venous thromboembolism (VTE) management because fibrin is the predominant component of venous thrombi. "Newer anticoagulants" denotes the agents introduced after unfractionated heparin and warfarin — the synthetic pentasaccharide (**fondaparinux**), the parenteral **direct thrombin inhibitors**, and, most importantly, the **direct oral anticoagulants (DOACs)**, formerly called novel/non-vitamin-K oral anticoagulants (NOACs): **dabigatran** (oral thrombin inhibitor) and **rivaroxaban, apixaban, edoxaban** (oral factor Xa inhibitors). Unlike warfarin, DOACs target a *single* clotting enzyme at its active site, have a rapid onset/offset, and are given in fixed doses without routine coagulation monitoring.

Classification of newer anticoagulants

Class	Mechanism / target	Agents	Route
Synthetic pentasaccharide (indirect Xa inhibitor)	Binds antithrombin → catalyses factor Xa inhibition only (too short to bridge thrombin)	Fondaparinux	SC
Parenteral direct thrombin (IIa) inhibitors	Bind thrombin directly	Argatroban (univalent, active site), Bivalirudin (bivalent, active site + exosite 1), Desirudin	IV / SC
Direct oral anticoagulants — oral thrombin inhibitor	Reversible active-site inhibition of thrombin (factor IIa)	Dabigatran etexilate	Oral
Direct oral anticoagulants — oral factor Xa inhibitors (“-xabans”)	Reversible active-site inhibition of factor Xa	Rivaroxaban, Apixaban, Edoxaban	Oral

- ▶ The unifying feature of the DOACs is that they are small molecules that bind **reversibly to the active site** of a single target enzyme, in contrast to warfarin (which lowers synthesis of factors II, VII, IX, X) and heparins (which act indirectly through antithrombin).
- ▶ Dabigatran is administered as the **prodrug dabigatran etexilate**, which is converted to the active moiety; the three factor Xa inhibitors are active drugs and are not prodrugs.

Site of action within the coagulation cascade

- ▶ **Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban):** directly and reversibly inhibit **factor Xa**, the enzyme at the convergence of the intrinsic and extrinsic pathways that assembles into the **prothrombinase complex** to convert prothrombin (II) to thrombin. A key pharmacodynamic advantage over heparin is that DOACs inhibit factor Xa **even when it is incorporated into the prothrombinase complex** — a site where the heparin–antithrombin complex is ineffective.
- ▶ **Direct thrombin inhibitor (dabigatran):** reversibly inhibits **thrombin (factor IIa)**, the final effector enzyme, blocking conversion of fibrinogen → fibrin and inhibiting thrombin-mediated feedback activation of factors V, VIII, XI and platelets. Unlike heparin, dabigatran also inhibits **fibrin-bound (clot-bound) thrombin**.
- ▶ **Fondaparinux:** an *indirect* inhibitor — it binds antithrombin via the pentasaccharide sequence, accelerating factor Xa inhibition; being only 5 saccharide units long it cannot bridge antithrombin to thrombin, so it has **no anti-IIa activity**.

Pharmacologic properties of the DOACs (Harrison Table 123-9)

Property	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin (IIa)
Prodrug	No	No	No	Yes
Bioavailability	80%	60%	50%	6%
Dosing	od (bid)	bid	od	bid (qd)
Half-life	7–11 h	12 h	9–11 h	12–17 h
Renal excretion	33% (66%)	25%	35%	80%
Drug interactions	CYP3A4 / P-gp	CYP3A4 / P-gp	P-gp	P-gp

- ▶ **Apixaban has the lowest renal clearance (25%)** and the lowest bleeding risk of the group, making it preferred in chronic kidney disease; **dabigatran is the most renally dependent (80%)** and is contraindicated/avoided in severe renal impairment.
- ▶ All are substrates of **P-glycoprotein (P-gp)**; the factor Xa inhibitors rivaroxaban and apixaban are additionally metabolised by **CYP3A4**. Strong dual P-gp/CYP3A4 *inducers* (rifampin, carbamazepine, phenytoin, St John's wort) reduce efficacy and should be avoided; potent *inhibitors* (ketoconazole, itraconazole, ritonavir) increase bleeding risk.

Approved indications and dosing

- ▶ **Stroke prevention in non-valvular atrial fibrillation (AF):** *all four* DOACs are licensed, *except* in patients with **mechanical heart valves or moderate–severe (rheumatic) mitral stenosis**, where warfarin remains mandatory.
 - Rivaroxaban **20 mg od** (15 mg od if CrCl 15–49 mL/min); take with food.
 - Dabigatran **150 mg bid** (75 mg bid if CrCl 15–30 mL/min).
 - Apixaban **5 mg bid**, reduced to **2.5 mg bid** if ≥ 2 of the “ABC” criteria — Age >80 y, Body weight <60 kg, serum Creatinine ≥ 1.5 mg/dL.
 - Edoxaban **60 mg od** (CrCl 50–95 mL/min); reduce to **30 mg od** if CrCl 15–50 mL/min, weight ≤ 60 kg, or concurrent potent P-gp inhibitor (verapamil, quinidine).
- ▶ **Treatment of VTE (DVT/PE):**
 - Dabigatran and edoxaban require a **≥ 5 -day parenteral (LMWH) lead-in** (dabigatran 150 mg bid if CrCl >30 ; edoxaban as for AF).
 - Rivaroxaban and apixaban are **all-oral, single-drug regimens**: rivaroxaban 15 mg bid $\times$ 21 days $\rightarrow$ 20 mg od; apixaban 10 mg bid $\times$ 7 days $\rightarrow$ 5 mg bid.
- ▶ **Extended/secondary VTE prevention** (after 6 months of full-dose therapy): apixaban **2.5 mg bid**; rivaroxaban **10 mg od**.

- ▶ **Thromboprophylaxis after elective hip or knee arthroplasty:** dabigatran 220 mg od, rivaroxaban 10 mg od, apixaban 2.5 mg bid (edoxaban licensed for this only in Japan); continued ~30 days after hip and 10–14 days after knee replacement.
- ▶ **VTE prophylaxis in selected adults hospitalised for acute medical illness:** rivaroxaban (per CMDT 2026).
- ▶ **Secondary prevention in stable coronary or peripheral artery disease: low-dose rivaroxaban 2.5 mg bid added to aspirin** (81–100 mg od) reduces major adverse cardiac and limb events; low-dose rivaroxaban added to dual-antiplatelet therapy also reduces recurrent ischaemic events after acute coronary syndrome.

Monitoring, reversal and safety

- ▶ **Routine coagulation monitoring is not required.** When assessment is needed (adherence, suspected overdose, before urgent surgery, in extremes of body weight or renal failure): qualitatively, PT screens for factor Xa inhibitors (rivaroxaban/edoxaban prolong PT more than apixaban, which needs a dedicated assay) and aPTT for dabigatran. Quantitative assays are the **chromogenic anti-factor Xa assay** (Xa inhibitors) and the **dilute thrombin time / ecarin clot time** (dabigatran).
- ▶ **Specific reversal agents:**
 - **Idarucizumab** — a humanised antibody fragment, **5 g IV bolus**, binds dabigatran with high affinity for emergency reversal.
 - **Andexanet alfa** — a recombinant catalytically-inactive factor Xa “decoy” that sequesters rivaroxaban and apixaban (low-dose 400 mg bolus + 4 mg/min; high-dose 800 mg bolus + 8 mg/min).
 - **Four-factor prothrombin complex concentrate (25–50 units/kg)** is the non-specific alternative; vitamin K is of **no benefit** for DOAC bleeding.
- ▶ **Bleeding** is the major adverse effect, but DOACs cause **less intracranial haemorrhage than warfarin**; higher-dose dabigatran, rivaroxaban and edoxaban cause **more GI bleeding**. **Dyspepsia** occurs in up to 10% with dabigatran.
- ▶ **Periprocedural:** hold for 1–2 days (longer if renal impairment) before procedures with moderate/high bleeding risk.
- ▶ **Contraindications:** pregnancy and breastfeeding (small molecules cross the placenta and enter breast milk), mechanical heart valves, severe rheumatic mitral stenosis, severe renal impairment (drug-specific), and severe active bleeding.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Coagulation cascade showing sites of action.** Labels: *Tissue factor + Factor VIIa* → *Factor X* → *Factor Xa* (block here labelled **Rivaroxaban / Apixaban / Edoxaban**; and

Fondaparinux → via Antithrombin → Prothrombin (II) → Thrombin (IIa) (block here labelled Dabigatran; also Argatroban / Bivalirudin) → Fibrinogen → Fibrin clot. Mark warfarin acting on synthesis of Factors II, VII, IX, X for contrast.

- ▶ **DOAC summary box:** four boxes — Dabigatran (anti-IIa, prodrug, 80% renal) vs Rivaroxaban / Apixaban / Edoxaban (anti-Xa) — with target, bioavailability and half-life beside each.

Clinical / Diagnostic significance

- ▶ DOACs are now **first-line over warfarin** for non-valvular AF and for most VTE because of fixed dosing, predictable pharmacokinetics, fewer food/drug interactions and lower intracranial bleeding.
- ▶ **Drug selection by patient factor:** apixaban (lowest renal clearance, lowest bleeding) in CKD/high bleeding risk; avoid dabigatran in severe renal impairment; check P-gp/CYP3A4 interactions before prescribing.
- ▶ DOACs are **contraindicated in mechanical valves and rheumatic mitral stenosis** — a high-yield safety point (the RE-ALIGN trial showed harm with dabigatran in mechanical valves).
- ▶ Availability of **idarucizumab** and **andexanet alfa** has largely removed the historical objection that DOACs “have no antidote.”

High-yield exam pointers

- ▶ **One sentence classification:** newer anticoagulants = fondaparinux (indirect Xa) + parenteral DTIs (argatroban, bivalirudin) + DOACs = oral IIa inhibitor *dabigatran* and oral Xa inhibitors *rivaroxaban*, *apixaban*, *edoxaban*.
- ▶ “-xa-ban” in the name = factor Xa inhibitor; “-gatan” = thrombin inhibitor.
- ▶ Dabigatran is the only DOAC that is a **prodrug**, has the **lowest bioavailability (6%)** and **highest renal excretion (80%)**.
- ▶ Apixaban = lowest renal clearance, lowest bleeding, taken **bid**; rivaroxaban must be taken **with food** at the 15/20 mg dose.
- ▶ **AF dose-reduction triggers:** apixaban = ABC (Age >80, BW <60 kg, Cr ≥1.5 mg/dL); edoxaban = CrCl 15–50, weight ≤60 kg, or P-gp inhibitor.
- ▶ VTE: dabigatran & edoxaban need a **5-day heparin lead-in**; rivaroxaban & apixaban are single-drug oral regimens.
- ▶ **Reversal:** *idarucizumab* → dabigatran; *andexanet alfa* → rivaroxaban/apixaban; 4F-PCC if unavailable; vitamin K useless.
- ▶ **Absolute “do-not-use”:** mechanical heart valves, severe rheumatic mitral stenosis, pregnancy/lactation.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Antiplatelet, Anticoagulant, and Fibrinolytic Drugs” (J.I. Weitz) — classification of antithrombotic drugs, DOAC mechanism/site of action, Table of pharmacologic properties, indications, dosing, monitoring and reversal.
- ▶ **CMDT 2026** — “Disorders of Hemostasis, Thrombosis, & Antithrombotic Therapy” — current DOAC indications (incl. VTE prophylaxis in acute medical illness), drug-interaction cautions and transitioning between anticoagulants.



Classify oral antifungal therapy and the mechanisms of action and indications for use

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Antifungal agents are drugs that selectively kill (fungicidal) or inhibit (fungistatic) fungi while sparing the eukaryotic human host. Because fungi, like human cells, are eukaryotes, the number of exploitable selective targets is small, so far fewer antifungal than antibacterial agents exist. **Orally bioavailable** agents are the backbone of outpatient and step-down therapy and act on one of four fungus-specific targets: the **cell-membrane sterol ergosterol** (azoles, allylamines, polyenes), the **cell-wall β -1,3-glucan** (triterpenoids/echinocandins), **nucleic-acid synthesis** (flucytosine) and the **mitotic spindle** (griseofulvin). Early appropriate therapy plus source control and immune reconstitution determine outcome.

Classification of antifungal agents by target (oral agents in bold)

Target site	Class	Agents	Oral availability
Cell membrane — ergosterol synthesis (inhibit lanosterol 14 α -demethylase)	Azoles (triazoles/tetrazole)	Fluconazole, Itraconazole, Voriconazole, Posaconazole, Isavuconazole, Oteseconazole (older imidazoles—ketoconazole, clotrimazole, miconazole—mainly topical)	Oral + IV (oteseconazole oral only)
Cell membrane — squalene epoxidase	Allylamine	Terbinafine (naftifine topical)	Oral + topical

Target site	Class	Agents	Oral availability
Cell membrane — bind/extract ergosterol	Polyene	Amphotericin B (IV); Nystatin (oral non-absorbed, topical)	AmB IV only; nystatin oral-luminal
Cell wall — β -1,3-glucan synthase	Triterpenoid	Ibrexafungerp	Oral
Cell wall — β -1,3-glucan synthase	Echinocandins	Caspofungin, anidulafungin, micafungin, rezafungin	IV only
Nucleic-acid (DNA/RNA) synthesis	Pyrimidine analogue	Flucytosine (5-FC)	Oral (+ IV)
Mitotic spindle / microtubules	—	Griseofulvin	Oral

Oral azoles — mechanism, spectrum and indications

- ▶ **Mechanism:** inhibit fungal cytochrome-P450 lanosterol 14 α -demethylase, blocking conversion of lanosterol to ergosterol; accumulation of toxic methylated sterol intermediates and ergosterol depletion arrest growth — azoles are **fungistatic**. Advantages over amphotericin B: oral + IV forms and absence of nephrotoxicity.
- ▶ **Fluconazole** — oral/IV, long half-life, excellent penetration of CSF, ocular fluid and urine; minimal toxicity (rare hepatotoxicity; high dose $\rightarrow$ alopecia, dry mouth, metallic taste; even low doses in pregnancy linked to miscarriage/stillbirth). *No activity against molds or most endemic dimorphic fungi*; weaker against *C. glabrata*/*C. krusei*. **Indications:** preferred for **coccidioidal meningitis**; consolidation/maintenance therapy of **cryptococcal meningitis**; **mucosal (oropharyngeal, oesophageal, vulvovaginal) candidiasis**; candidaemia in non-critically-ill, non-neutropenic patients; step-down once a susceptible *Candida* is identified; prophylaxis in high-risk liver and allogeneic marrow transplant.
- ▶ **Itraconazole** — oral capsule/suspension + IV; *broader than fluconazole* (molds, endemic dimorphic fungi). **Drug of choice for mild-moderate histoplasmosis and blastomycosis**; also sporotrichosis, chronic coccidioidomycosis, phaeohyphomycosis, tinea/onychomycosis. Limitations: poor CSF penetration, erratic capsule absorption (monitor levels), potent CYP3A4 inhibitor, hepatotoxicity and **negative inotropy** $\rightarrow$ **may precipitate CHF**. *SUBA-itraconazole* gives improved/predictable absorption.
- ▶ **Voriconazole** — oral/IV; far broader than fluconazole (covers *C. glabrata*/*C. krusei*, **Aspergillus**, *Scedosporium*, endemic dimorphs) **but NOT Mucorales**; penetrates CSF and ocular fluid. **Preferred agent for invasive aspergillosis**. Metabolised by CYP2C9/3A4/2C19 (genetic polymorphism $\rightarrow$ variable levels — *monitor*); toxicities: visual disturbances,

photosensitivity/skin-cancer risk, hepatotoxicity, and the azole-unique **fluorosis-associated periostitis**.

- ▶ **Posaconazole** — oral suspension/tablet + IV; *broader than voriconazole, includes Mucorales*. Antifungal prophylaxis in neutropenic leukaemia and allogeneic HSCT; **treatment of fluconazole/itraconazole-refractory oropharyngeal candidiasis; salvage for aspergillosis, mucormycosis, fusariosis**. Tablet > suspension absorption; may cause pseudohyperaldosteronism** (hypokalaemia, oedema, hypertension).
- ▶ **Isavuconazole** — oral/IV; broad spectrum like posaconazole. FDA-approved for **aspergillosis** (non-inferior to voriconazole) and **mucormycosis**; less hepatotoxic, fewer P450 interactions, no skin/bone/visual toxicity.
- ▶ **Oteseconazole** — newest azole (a **tetrazole**), oral only; potent anti-*Candida* (incl. azole-resistant) and endemic-dimorph activity; long half-life allows **once-weekly** dosing. Approved for **recurrent vulvovaginal candidiasis**; no hepatotoxicity/P450 interactions but **contraindicated in women of reproductive potential** (fetal ocular toxicity).

Other oral agents

- ▶ **Terbinafine (allylamine)**: inhibits **squalene epoxidase**, blocking ergosterol synthesis and causing toxic squalene accumulation (fungicidal). Penetrates poorly beyond skin/nails, so reserved for **onychomycosis and dermatophytosis (ringworm)** — as effective as itraconazole; usual dose **250 mg orally daily** (≈ 6 weeks fingernail, ≈ 12 weeks toenail). Risk of **hepatotoxicity** (and rare cutaneous reactions).
- ▶ **Flucytosine (5-fluorocytosine)**: taken up by fungal cytosine permease and **converted intracellularly to 5-fluorouracil**, which inhibits fungal DNA/RNA synthesis. Always used in **combination** (synergy + avoids resistance) — chiefly with **amphotericin B for induction of cryptococcal meningitis** (good CSF penetration, rapid CSF sterilisation) and for candidal meningitis/endocarditis. Toxicity: **bone-marrow suppression** and hepatotoxicity (worse when combined with AmB).
- ▶ **Ibrexafungerp (triterpenoid)**: oral **β -1,3-glucan synthase inhibitor** (cell-wall target) with potent anti-*Candida* activity that is retained at the low pH of the vaginal mucosa; approved for **acute and recurrent vulvovaginal candidiasis**; contraindicated in pregnancy/lactation.
- ▶ **Griseofulvin**: binds fungal microtubules and disrupts the mitotic spindle; deposited in keratin precursor cells, rendering new keratin resistant to dermatophyte invasion. Approved for **dermatophyte infection of skin, hair and nails** — particularly **tinea capitis** (given with selenium sulfide/ketoconazole shampoo; examine family members). Side-effects: GI upset, headache, urticaria, photosensitivity.
- ▶ **Nystatin (oral polyene)**: binds ergosterol; not absorbed from the gut, so the **oral suspension** (“swish-and-swallow”) acts luminally for **oropharyngeal candidiasis**; also topical for vaginal candidiasis.

Parenteral comparators (for completeness — no oral form)

- ▶ **Amphotericin B (polyene):** broadest-spectrum, **fungicidal** — forms extramembranous sponge-like aggregates that **extract ergosterol** from the fungal membrane. **No licensed oral formulation**; remains preferred for **mucormycosis, fusariosis**, and induction of cryptococcal meningitis and severe endemic mycoses. Limited by **nephrotoxicity** and infusion reactions (fever, chills); **lipid formulations** (liposomal AmB, AmB lipid complex) reduce toxicity.
- ▶ **Echinocandins (caspofungin, anidulafungin, micafungin, rezafungin):** **IV only**; inhibit **β -1,3-glucan synthase**; fungicidal for *Candida*, fungistatic for *Aspergillus*; no activity vs *Cryptococcus*, Mucorales or endemic dimorphs. **First-line for candidaemia/invasive candidiasis** (minimal toxicity and interactions, active vs all *Candida*). Rezafungin allows weekly dosing.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **“Antifungal targets on the fungal cell” schematic:** draw a fungal cell with labelled concentric layers — **Cell wall (β -1,3-glucan)** → arrow from *Echinocandins* and *Ibrexafungerp* (triterpenoid) labelled “inhibit β -1,3-glucan synthase”; **Cell membrane (ergosterol)** → *Azoles* labelled “inhibit lanosterol 14 α -demethylase / ergosterol synthesis”, *Terbinafine* labelled “inhibit squalene epoxidase”, *Amphotericin B* / *Nystatin* (*polyenes*) labelled “bind & extract ergosterol → pore”; **Nucleus/DNA** → *Flucytosine* labelled “5-FC → 5-FU, inhibits DNA/RNA”; **Microtubules/mitotic spindle** → *Griseofulvin*.
- ▶ **Ergosterol biosynthesis pathway bar:** Squalene → (squalene epoxidase, blocked by *terbinafine*) → Lanosterol → (14 α -demethylase, blocked by *azoles*) → Ergosterol → (bound/extracted by *amphotericin B*, *nystatin*). Labels: Squalene, Squalene epoxidase, Lanosterol, 14 α -demethylase, Ergosterol.

Clinical / Diagnostic significance

- ▶ **Route dictates use:** oral azoles, terbinafine, flucytosine, ibrexafungerp and griseofulvin enable outpatient and **step-down (“IV-to-oral switch”)** therapy after initial IV induction; AmB and echinocandins anchor severe/inpatient disease.
- ▶ **Spectrum gaps to remember:** fluconazole — *no molds*; voriconazole — *no Mucorales*; echinocandins — *no Cryptococcus/Mucorales/dimorphs*; **posaconazole and isavuconazole cover Mucorales** (the only azoles that do).
- ▶ **Therapeutic drug monitoring** is required for itraconazole (capsule), voriconazole (CYP2C19 polymorphism) and posaconazole suspension to ensure efficacy and limit toxicity.
- ▶ **Drug interactions:** azoles are CYP inhibitors (itraconazole/voriconazole/posaconazole — clinically major); echinocandins and oteseconazole have minimal interactions.

- ▶ **Resistance:** rising azole/echinocandin-resistant *C. glabrata* and *C. auris* and azole-resistant *A. fumigatus* — echinocandins are preferred empirically for candidaemia, de-escalated to fluconazole once susceptibility is known.

High-yield exam pointers

- ▶ **Four targets:** ergosterol membrane (azoles, allylamines, polyenes), glucan cell wall (echinocandins, triterpenoids), DNA (flucytosine), spindle (griseofulvin).
- ▶ **Azoles inhibit 14 α -demethylase** → fungistatic; **AmB extracts ergosterol** → fungicidal; **terbinafine inhibits squalene epoxidase**.
- ▶ **Itraconazole = DOC for mild–moderate histoplasmosis & blastomycosis; voriconazole = DOC for invasive aspergillosis; fluconazole = DOC for coccidioidal meningitis + cryptococcal consolidation.**
- ▶ **AmB + flucytosine = induction for cryptococcal meningitis** (synergy, CSF penetration).
- ▶ **Posaconazole/isavuconazole cover Mucorales; voriconazole does not.**
- ▶ **Terbinafine/griseofulvin = dermatophytes (onychomycosis, tinea capitis); nystatin oral = oral thrush.**
- ▶ **Signature toxicities:** voriconazole — visual disturbance + periostitis + photosensitivity; posaconazole — pseudohyperaldosteronism; itraconazole — CHF; flucytosine — marrow suppression; AmB — nephrotoxicity; terbinafine — hepatotoxicity.
- ▶ **Newer oral agents: ibrexafungerp & oteseconazole for (recurrent) vulvovaginal candidiasis.**

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Pathogenesis, Diagnosis, and Treatment of Fungal Infections” (antifungal drugs: amphotericin B, azoles, echinocandins, ibrexafungerp, flucytosine, terbinafine, topical agents) — primary source for mechanisms, spectra and indications.
- ▶ **Harrison's 22e** — “Fungal Skin Infections / Dermatophytes” (griseofulvin, terbinafine, itraconazole for skin–hair–nail dermatophytosis).
- ▶ **CMDT 2026** — “Mycotic Infections” and “Dermatologic Disorders” (oral dosing and use: terbinafine 250 mg/day, itraconazole 200 mg/day, griseofulvin for tinea capitis, fluconazole for tinea versicolor).

Coverage note: Harrison 22e does not list griseofulvin in its core antifungal-drug section; its dermatophyte use is taken from Harrison's fungal-skin material and CMDT, and griseofulvin's microtubule/mitotic-spindle mechanism is standard, universally accepted textbook pharmacology.



Clinical implications of bioavailability and protein binding of drugs

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — **Bioavailability (F)** is the *fraction of an administered dose that reaches the systemic circulation in an unchanged, active form* after a non-intravenous route; by definition an intravenous dose has $F = 1$ (100%). **Plasma protein binding** describes the reversible association of drug with circulating proteins (chiefly albumin and α_1 -acid glycoprotein); only the **unbound (free) fraction** can cross membranes, reach target receptors, undergo glomerular filtration and hepatic metabolism, and so determines pharmacological effect. Both parameters are key determinants of drug *disposition* (absorption, distribution, metabolism, excretion) and explain much of the inter-individual and disease-related variability in drug response that the clinician must anticipate.

Bioavailability — concept and determinants

- ▶ F integrates two events: (1) the *fraction absorbed* across the gut wall, and (2) the *fraction surviving presystemic (first-pass) elimination* in gut wall and liver.
- ▶ Bioavailability is <100% for two main reasons (Harrison): **incomplete absorption**, or **metabolism/elimination before entering the systemic circulation** (first-pass effect).
- ▶ Compared with the same intravenous dose, a non-IV dose shows a **later and lower peak plasma concentration** and a **smaller area under the time–concentration curve (AUC)**; F is estimated as the ratio $AUC(\text{oral})/AUC(\text{IV})$, dose-corrected.
- ▶ **Factors reducing absorption**: incomplete release from the dosage form, destruction at the site of administration, poor solubility/lipophilicity, GI transit and gastric pH, food, and gut efflux transporters.
- ▶ **P-glycoprotein** (product of the *ABCB1/MDR1* gene) on the apical enterocyte and canalicular hepatocyte pumps drug back into lumen/bile, limiting bioavailability (e.g. digoxin); it is also a key element of the blood–brain barrier.

Route	Bioavailability	First-pass effect	Comment
Intravenous	100% (reference)	Bypassed	Most rapid, fully predictable
Intramuscular / subcutaneous	High, usually ~75–100%	Bypassed	Depends on perfusion, solubility
Sublingual / buccal / transdermal	Variable–high	Bypassed	Route for high first-pass drugs (GTN)
Rectal	Partial bypass	Partial	Lower haemorrhoidal veins skip liver
Oral	Lowest / most variable	Maximal	Gut wall + portal–hepatic extraction

First-pass (presystemic) elimination — and its clinical exploitation

- ▶ An orally administered drug must traverse **enterocyte** → **portal vein** → **liver** before reaching the systemic circulation; metabolism or biliary/luminal excretion at any step constitutes **presystemic (first-pass) extraction** (Harrison).
- ▶ **Drugs unusable orally:** *Nitroglycerin* is almost completely extracted presystemically, so it is given by the **sublingual, transdermal or intravascular** routes that bypass the liver.
- ▶ **High first-pass drugs needing larger oral doses:** *verapamil* — typical IV dose 1–5 mg versus a usual single oral dose of 40–120 mg (Harrison) — also propranolol, morphine, lidocaine, nifedipine, midazolam.
- ▶ **First-pass exploited therapeutically:** *low-dose aspirin* irreversibly acetylates cyclo-oxygenase in platelets within the portal blood, yet is **deacylated on first pass through the liver**, giving platelet inhibition with relative systemic sparing.

Clinical implications of altered bioavailability

- ▶ **Liver disease (cirrhosis):** reduced first-pass metabolism (hepatocyte dysfunction, altered architecture, **porto-systemic shunts**) raises oral bioavailability — for high-extraction drugs such as **morphine, meperidine (pethidine), midazolam and nifedipine** the oral bioavailability is **almost doubled**, so oral doses must be reduced (Harrison).
- ▶ **Heart failure / shock:** gut hypoperfusion and mucosal oedema slow or reduce drug absorption, blunting the effect of oral therapy; parenteral routes are preferred in the unstable patient.
- ▶ **Formulation matters:** slow-/sustained-release products deliberately slow absorption to smooth peak–trough swings; altered dissolution explains why expired or degraded drug fails.
- ▶ **Bioequivalence & generic substitution:** two products are *bioequivalent* when their rate (C_{max} , T_{max}) and extent (AUC) of absorption are statistically comparable; for **narrow-therapeutic-index drugs** (warfarin, phenytoin, digoxin, levothyroxine, antiepileptics, immunosuppressants) even small bioavailability differences between brands/generics can cause sub-therapeutic failure or toxicity, so switching warrants monitoring.
- ▶ **Drug interactions affecting F:** antacids/cholestyramine bind drugs in the gut (↓ absorption); proton-pump inhibitors/H₂-blockers raise gastric pH and reduce dissolution of weak bases (e.g. ketoconazole); P-glycoprotein/CYP3A inducers (rifampin, St John's wort) lower bioavailability of substrates.

Plasma protein binding — principles

- ▶ Only **free (unbound) drug** is pharmacologically active and available for distribution, metabolism and renal filtration; **drug response correlates with free, not total, plasma concentration** (Harrison).
- ▶ Bound and free drug exist in rapid equilibrium; binding acts as a **circulating reservoir** that buffers fluctuations and prolongs duration of action.

Binding protein	Drugs bound	Behaviour in disease
Albumin	Acidic / neutral drugs — warfarin, phenytoin, NSAIDs/salicylates, sulfonamides, valproate, diazepam	Falls in nephrotic syndrome, cirrhosis, malnutrition, burns, pregnancy → ↑ free fraction
α1-acid glycoprotein (AAG)	Basic drugs — lidocaine, quinidine/quinine, propranolol, verapamil, tricyclics	Acute-phase reactant — rises in MI, infection, surgery, malaria, cancer → ↓ free fraction
Lipoproteins / globulins	Lipophilic drugs (e.g. cyclosporine)	Vary with lipid status

- ▶ *Corpus example:* in malaria, plasma **protein binding of quinine to α1-acid glycoprotein increases to ~90%**, reducing free drug — illustrating how an acute illness alters the active fraction (Harrison, antimalarials chapter).

Clinical implications of altered protein binding

- ▶ The “**highly bound drug**” rule: the smaller the free fraction, the greater the effect of any change — *a fall in binding from 99% to 98% doubles the free concentration (1% → 2%)* and can precipitate toxicity even though *total* level is unchanged (Harrison).
- ▶ **Hypoalbuminaemia / uraemia (CKD, cirrhosis, nephrosis):** reduced binding **increases free drug and drug effect**; uraemia additionally displaces phenytoin from albumin (uraemic toxins compete) — hence free drug should be monitored.
- ▶ **Acute-phase states (MI, sepsis, surgery, trauma):** transient rise in AAG **increases binding of basic drugs and may reduce efficacy** (Harrison).
- ▶ **Displacement (protein-binding) drug interactions** (*universally taught examples*): sulfonamides / phenylbutazone / NSAIDs displace **warfarin** (transient ↑ INR, bleeding); **valproate** displaces **phenytoin**; sulfonamides and ceftriaxone displace **bilirubin** from neonatal albumin, risking **kernicterus**. Clinically, displacement alone is usually transient because the liberated drug is rapidly redistributed and cleared — it becomes dangerous mainly when **clearance is simultaneously impaired** and the drug is narrow-index.
- ▶ **Therapeutic drug monitoring (TDM) caveat:** for highly bound drugs, total levels mislead when binding is abnormal. For **phenytoin** the usual total target is **10–20 mg/L**, but falls to **~5–10 mg/L in uraemia and severe hypoalbuminaemia**; the **free phenytoin** target is **0.5–2.0 mg/L** and should be measured (or a corrected/Sheiner–Tozer estimate used) in renal/hepatic disease and low albumin (CMDT, therapeutic drug monitoring).
- ▶ **Distribution & special compartments:** highly bound drugs have limited tissue and CNS penetration; binding influences volume of distribution and the success of removal by dialysis (poorly bound drugs are dialysable).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Plasma concentration–time curves (IV vs oral):** x-axis *Time*, y-axis *Plasma concentration*; overlay an **IV bolus curve** (high early peak, single exponential decline) and an **oral curve** (delayed lower C_{max} , later T_{max} , smaller AUC). Label: C_{max} , T_{max} , $AUC(IV)$, $AUC(oral)$, “ $F = AUC(oral)/AUC(IV)$ ”, and shade the area difference as “incomplete bioavailability”.
- ▶ **First-pass elimination schematic:** boxes/arrows *Gut lumen* → *Enterocyte* → *Portal vein* → *Liver* → *Systemic circulation*; label **P-glycoprotein efflux** (enterocyte apex), **CYP3A4 metabolism** (enterocyte + hepatocyte), **biliary excretion**, and the routes that *bypass* it: **sublingual / transdermal / IV / rectal (lower veins)**.

Clinical / Diagnostic significance

- ▶ Predicts when to **avoid the oral route** (GTN) or **escalate the oral dose** (verapamil, propranolol) for high first-pass drugs.
- ▶ Mandates **dose reduction of high-extraction oral drugs in cirrhosis** and a **switch to parenteral therapy in shock/heart failure**.
- ▶ Justifies **monitoring free (not total) drug** for phenytoin (and other highly bound, narrow-index drugs) in **renal failure, hepatic failure and hypoalbuminaemia**.
- ▶ Explains brand–generic non-equivalence concerns and the need for re-titration/monitoring after switching narrow-index drugs.
- ▶ Frames clinically important **drug interactions** at absorption (chelation, pH, P-gp/CYP induction) and at protein-binding/displacement levels.

High-yield exam pointers

- ▶ **F = fraction reaching systemic circulation in active form; $IV = 100\%$; $F = AUC(oral)/AUC(IV)$.**
- ▶ Two causes of low F : **incomplete absorption + presystemic (first-pass) elimination**.
- ▶ **GTN** — complete first-pass extraction → never oral; **verapamil** IV 1–5 mg vs oral 40–120 mg.
- ▶ **Cirrhosis doubles oral bioavailability** of morphine, pethidine, midazolam, nifedipine → reduce dose.
- ▶ **Only free drug is active**; for a 99%-bound drug a 1% fall in binding **doubles free concentration**.
- ▶ **Albumin** → **acidic drugs** (warfarin, phenytoin); **α_1 -acid glycoprotein** → **basic drugs** (lidocaine, quinidine) and **rises as an acute-phase reactant**.
- ▶ **Hypoalbuminaemia/uraemia** ↑ free phenytoin → **monitor free level (0.5–2.0 mg/L)**; total target falls to 5–10 mg/L.
- ▶ Classic displacement: **sulfonamides** → **warfarin** (bleeding); **sulfonamides** → **bilirubin** → **kernicterus** in neonates.

- ▶ **Narrow-therapeutic-index drugs** (warfarin, digoxin, phenytoin, levothyroxine, immunosuppressants) are most vulnerable to both bioavailability and protein-binding changes.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Principles of Clinical Pharmacology*” (absorption and bioavailability, first-pass/presystemic elimination, P-glycoprotein, clinical implications of altered protein binding and clearance, disease effects on drug disposition); and the antimalarial-agents chapter (quinine binding to α 1-acid glycoprotein in malaria; phenytoin/warfarin as highly protein-bound drugs).
- ▶ **CMDT 2026** — Appendix “*Therapeutic Drug Monitoring*” (phenytoin total vs free target ranges; protein binding reduced in uraemia/hypoalbuminaemia; free-level monitoring).
- ▶ *Coverage note*: the quantitative bioequivalence limits (FDA 80–125% AUC/C_{max}), the explicit albumin-vs-AAG drug lists, the Sheiner–Tozer corrected-phenytoin equation, and the classic displacement examples (warfarin–sulfonamide, valproate–phenytoin, bilirubin–kernicterus) are standard, universally accepted clinical pharmacology included to complete the answer; Harrison 22e states the underlying free-drug and altered-binding principles but does not tabulate these specific examples.



Cloning: Principle and Methods

Asked in: Paper I Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — *Cloning* is the production of multiple genetically **identical** copies of a biological entity — a defined segment of DNA (a gene), a cell, or a whole organism. In clinical molecular medicine the term usually means **molecular (gene/DNA) cloning**: the insertion of a defined DNA fragment of interest into a self-replicating DNA molecule (a **vector**), introduction of this **recombinant DNA** into a host cell (commonly *Escherichia coli*), and faithful amplification of the fragment as the host divides — yielding limitless identical copies for sequencing, expression or therapy. The technique exploits two universal properties of DNA emphasised in Harrison: its **double-stranded base-pair complementarity** (A–T, G–C) and its **faithful semiconservative replication**, which together permit a fragment to be copied with high fidelity. Recombinant DNA and RNA technology underpins the large-scale manufacture of peptide hormones, growth factors, cytokines, clotting factors and vaccines (e.g., recombinant insulin analogues, mRNA SARS-CoV-2 vaccines, siRNA therapeutics).

Types of cloning

Type	What is copied	Core method	Product/use
Molecular / gene (DNA) cloning	A DNA fragment / gene	Recombinant DNA technology — vector + host	Gene amplification, sequencing, recombinant proteins
Cellular cloning	A single cell	Clonal expansion in culture	Cell lines, hybridomas (monoclonal antibodies)
Reproductive (organism) cloning	A whole organism	Somatic cell nuclear transfer (SCNT)	<i>Dolly the sheep</i> (1996); identical animal
Therapeutic cloning	Patient-specific stem cells	SCNT into enucleated oocyte → blastocyst	Autologous embryonic stem cells / iPSC-type cells for regenerative therapy

Principle — recombinant DNA technology

- ▶ **Restriction–ligation principle:** sequence-specific bacterial enzymes cut DNA at defined sites; the same cut ends on insert and vector are **complementary**, so they can be re-joined by a ligase to create a single hybrid (**recombinant**) molecule.
- ▶ **Self-replication principle:** the vector carries an **origin of replication**, so once inside a dividing host cell it (and its insert) is copied many-fold — *amplification by biological cloning*.
- ▶ **Selection principle:** a marker (usually antibiotic resistance) on the vector lets only successfully transformed cells survive, so that each surviving colony is a **clone** descended from one cell carrying one recombinant molecule.
- ▶ **Complementarity** also allows the alternative *in vitro* amplification route — the **polymerase chain reaction (PCR)** — and the detection of clones by **hybridisation** with labelled probes.

Essential tools — enzymes and vectors

Tool	Function in cloning
Restriction endonucleases (Type II)	Cut double-stranded DNA at specific <i>palindromic</i> recognition sites (e.g., <i>EcoRI</i> = GAATTC), generating either staggered “sticky” (cohesive) ends or blunt ends
DNA ligase (T4)	Seals the phosphodiester backbone, covalently joining insert to vector → recombinant DNA
Reverse transcriptase	Synthesises complementary DNA (cDNA) from an mRNA template (intron-free copy of a gene)
DNA polymerase / thermostable Taq polymerase	Fills/extends strands; drives PCR-based amplification of the insert

Tool	Function in cloning
Alkaline phosphatase / terminal transferase, nucleases	Prevent vector self-ligation; tailor ends
Vectors	Carrier DNA that replicates in the host and carries the insert (see range below)

Vector hierarchy by insert capacity (choice depends on fragment size):

- ▶ **Plasmids** — small circular bacterial DNA; inserts up to ~10 kb; carry *ori* + selectable marker (e.g., ampicillin resistance) + a multiple-cloning site.
- ▶ **Bacteriophage λ** (~15–20 kb) and **cosmids** (~45 kb) — larger inserts, packaged into phage.
- ▶ **Bacterial artificial chromosomes (BACs)** — up to ~300 kb; **yeast artificial chromosomes (YACs)** — up to ~1 Mb; used for genomic libraries and genome mapping.
- ▶ **Expression vectors** — contain a promoter/enhancer so the cloned gene is *transcribed and translated* into protein in the host.
- ▶ **Viral vectors** (for mammalian cells / gene therapy) — retroviral, **lentiviral**, **adeno-associated viral (AAV)**, adenoviral, herpesviral; AAV cargo is limited to ~5 kb because the wild-type genome is only ~4.7 kb.

Steps of molecular cloning

- ▶ **Generate the DNA fragment (insert):** isolate genomic DNA and digest it with a restriction enzyme, **or** copy an expressed gene into intron-free **cDNA** using reverse transcriptase, **or** amplify the target by **PCR** with specific primers.
- ▶ **Cut the vector** with the *same* restriction enzyme so its ends are complementary to the insert's ends.
- ▶ **Ligation:** mix insert + linearised vector with **DNA ligase** → covalently sealed **recombinant DNA** molecules.
- ▶ **Introduce into a host cell** (**transformation** of *E. coli* by heat-shock/electroporation, **or** **transfection/transduction** of mammalian cells with a viral vector).
- ▶ **Selection and screening:** plate on antibiotic-containing medium so only vector-bearing cells grow; identify clones carrying the *insert* by **blue–white (α -complementation, X-gal/IPTG) screening**, **colony hybridisation** with a labelled probe, **colony PCR**, or restriction mapping.
- ▶ **Amplify and harvest:** grow a positive colony (a pure **clone**) to mass-produce identical copies of the fragment for sequencing, probe production, **or** — with an expression vector — recombinant protein.

Gene libraries and alternative methods

- ▶ **Genomic library** — clones representing the *entire* genome (introns + exons + regulatory + non-coding DNA), made from restriction fragments of total genomic DNA.

- ▶ **cDNA library** — clones of only the *expressed* genes of a tissue (made from its mRNA via reverse transcriptase); tissue-specific and intron-free.
- ▶ **PCR cloning** — rapid *in vitro* amplification of a defined sequence; can replace biological cloning for sequence analysis and enables genetic testing on minute DNA amounts (blood, buccal cells, archival tumour) — heavily used in molecular diagnostics.
- ▶ **Expression cloning** — selecting clones by the *function/protein* they produce.

Reproductive and therapeutic cloning (organism-level)

- ▶ **Somatic cell nuclear transfer (SCNT)**: the nucleus of an adult somatic (donor) cell is transferred into an **enucleated oocyte**; the reconstructed egg is activated to develop. Transferred to a surrogate it yields a genetically identical animal (**reproductive cloning** — *Dolly*, 1996).
- ▶ **Therapeutic cloning**: the SCNT blastocyst is used instead to derive **patient-specific pluripotent stem cells** for autologous regenerative therapy, avoiding immune rejection. (Human reproductive cloning is banned on ethical grounds.)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Plasmid gene-cloning workflow**: draw a circular **plasmid vector** labelling *origin of replication*, *selectable marker* (amp^R), and *multiple-cloning/restriction site*; show a **foreign DNA fragment** cut by the *same restriction enzyme*; arrows to **DNA ligase** → **recombinant plasmid** → **transformation into E. coli** → **selection on antibiotic plate** → **colony (clone) amplification**. Labels: *target DNA*, *restriction enzyme*, *sticky ends*, *vector*, *ligase*, *recombinant DNA*, *host cell*, *antibiotic selection*, *clone*.
- ▶ **Sticky-end ligation inset**: two complementary single-stranded overhangs (e.g., ...G / AATTC... of *EcoRI*) annealing and being sealed; label *5' overhang*, *complementary base pairing*, *phosphodiester bond*, *DNA ligase*.

Clinical / Diagnostic significance

- ▶ **Recombinant therapeutics (expression cloning)**: human insulin and insulin analogues with favourable kinetics, growth hormone, erythropoietin, clotting factor concentrates, GLP-1 agonists, recombinant hepatitis B (HBsAg) and **mRNA** vaccines, and **siRNA** drugs (e.g., for hypercholesterolaemia) — all enabled by cloning genes into expression systems.
- ▶ **Monoclonal antibodies** via cloned/hybridoma technology underpin much of modern targeted therapy.
- ▶ **Gene therapy (cloning into viral vectors)**: therapeutic genes are cloned as **cDNA** into **lentiviral** vectors (β -thalassaemia, sickle cell disease, X-linked SCID, adrenoleukodystrophy, metachromatic leukodystrophy) or **AAV** vectors (spinal muscular atrophy, RPE65 retinal dystrophy, haemophilia A/B with *factor IX Padua*, Duchenne microdystrophin). Vectors are

classed as **integrating** (retro-/lentiviral, risk of insertional mutagenesis/LMO-2 leukaemia) vs **non-integrating/episomal** (AAV, adenoviral, plasmid).

- ▶ **Genome editing** extends cloning: a **CRISPR–Cas9/guide-RNA** complex (e.g., disrupting *BCL11A* to re-activate fetal haemoglobin) is delivered for sickle cell disease/thalassaemia, with optional AAV-supplied repair templates via homology-directed repair.
- ▶ **Molecular diagnostics built on the same principles**: PCR/qPCR, RFLP, Southern blotting, FISH, microarray/DNA chips, MLPA, and next-generation (massively parallel) sequencing for inherited-disease, oncology and infectious-pathogen testing.

High-yield exam pointers

- ▶ **Recombinant DNA** = insert + vector joined by **ligase** after cutting with the same **restriction endonuclease**.
- ▶ **Restriction enzymes** recognise short **palindromes** and give **sticky** or **blunt** ends (Arber, Smith, Nathans — Nobel 1978).
- ▶ Cloning vectors in ascending capacity: **plasmid** < **phage λ** < **cosmid** < **BAC** < **YAC**; expression vectors add a promoter; viral vectors transduce mammalian cells.
- ▶ **cDNA** (reverse transcriptase) is **intron-free**; a **cDNA library** = expressed genes, a **genomic library** = whole genome.
- ▶ **Selection** by antibiotic resistance; **screening** by **blue–white (α-complementation)**, colony hybridisation or colony PCR.
- ▶ **PCR** = rapid cell-free amplification alternative; requires **primers** + **thermostable polymerase** (Mullis — Nobel 1993).
- ▶ **SCNT** produced **Dolly (1996)** — reproductive cloning; therapeutic cloning yields **patient-specific stem cells**.
- ▶ Cloning into **expression/viral vectors** delivers recombinant insulin, vaccines, clotting factors and **gene therapies** (lentiviral vs AAV; integrating vs episomal).

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Principles of Human Genetics” (DNA structure, base-pair complementarity, replication, recombinant DNA/RNA technology, PCR, recombinant therapeutics); “The Practice of Genetics in Clinical Medicine” (PCR, RFLP, Sanger vs massively-parallel/next-generation sequencing, FISH, Southern blotting, MLPA, DNA microarrays); “Gene and Cell-Based Therapy in Clinical Medicine” (cloning into retroviral/lentiviral/AAV/adenoviral vectors, cDNA inserts, integrating vs non-integrating vectors, CRISPR–Cas9 genome editing, insertional mutagenesis).
- ▶ **Coverage note (spec gap = true)**: Harrison 22e is a clinical-genetics text and does **not** detail the classical wet-lab molecular-cloning workflow (restriction-enzyme digestion,

sticky/blunt-end ligation, plasmid/cosmid/BAC/YAC vectors, bacterial transformation, antibiotic selection, blue–white screening, and genomic vs cDNA libraries) or somatic-cell nuclear transfer. These elements are supplied here from **universally accepted standard molecular biology** (consistent with Harrison’s stated principles of DNA complementarity, replication and recombinant DNA technology) and are flagged as such; every Harrison-grounded specific (PCR, RFLP, FISH, Southern blot, NGS, viral vectors, AAV ~5 kb cargo limit, CRISPR/BCL11A, factor IX Padua, recombinant insulin/mRNA/siRNA) has been verified against the chapters above.

♦ ♦ ♦

Complement Pathway, Functions and Regulation

Asked in: Paper I Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — The **complement system** is a tightly regulated cascade of more than 30 plasma and membrane proteins that forms a major effector arm of **innate immunity** and bridges it to **adaptive immunity**. Activation proceeds through three initiating routes — the **classical**, **lectin (mannose-binding)** and **alternative** pathways — that all converge on the cleavage of C3, feed into a common **terminal pathway**, and culminate in the lytic **membrane attack complex (MAC, C5b–9)**. Its central outputs are **opsonisation** of microbes, generation of **inflammatory anaphylatoxins**, **cytolysis** of pathogens, and **clearance of immune complexes and apoptotic cells**. Because uncontrolled activation injures host tissue, the system is restrained by a panel of soluble and membrane-bound **regulatory proteins** whose failure produces a distinct group of human diseases.

Activation pathways

Feature	Classical pathway	Lectin (MBL) pathway	Alternative pathway
Principal trigger	Antigen–antibody immune complexes (IgM, IgG1/2/3) binding C1q	Mannose / terminal sugars on microbial surfaces	Spontaneous C3 “tick-over” (C3(H ₂ O)); microbial, fungal, viral, tumour and “altered-self” surfaces — antibody-independent
Recognition / initiating proteins	C1 complex = C1q–C1r–C1s → C4, C2	MBL / ficolins + MASP-1, MASP-2 → C4, C2	C3, factor B, factor D, properdin (P)
C3 convertase	C4b2a	C4b2a	C3bBb (stabilised by properdin)
C5 convertase	C4b2a3b	C4b2a3b	C3bBbC3b

Feature	Classical pathway	Lectin (MBL) pathway	Alternative pathway
Immune link	Links innate + adaptive (specific antibody)	Innate pattern recognition	Innate amplification loop

- ▶ **Terminal (common) pathway:** all three converge on **C3 cleavage** → C3a + C3b, then C5 → C5a + C5b; C5b sequentially recruits C6, C7, C8 and **multiple C9** molecules to form the **MAC (poly-C9 pore)** that inserts into and lyses target membranes.
- ▶ An **amplification loop** (factor D, factor B, properdin generating C3bBb) means a small initial stimulus from *any* pathway is greatly magnified through the alternative pathway.

Biological functions

- ▶ **Opsonisation / phagocytosis:** surface-bound **C3b and iC3b** (and C4b) coat microbes and are recognised by complement receptors (CR1/CD35, CR3) on neutrophils and macrophages — the dominant antibacterial role; deficiency predisposes to **encapsulated pyogenic organisms** (*S. pneumoniae*, *H. influenzae*).
- ▶ **Inflammation (anaphylatoxins):** small cleavage fragments **C3a and C5a** trigger mast-cell/basophil mediator release, increase vascular permeability and smooth-muscle contraction; C5a is a powerful **neutrophil chemoattractant** and activator.
- ▶ **Cytolysis:** the MAC (C5b–9) lyses bacteria and cells; it is the **only effective defence against Neisseria**** (thick wall lysed only by MAC).
- ▶ **Immune-complex handling:** early components (C1q, C4, C3) **solubilise and clear circulating immune complexes**; C3b-coated complexes bind erythrocyte CR1 and are transported to liver/spleen — failure causes deposition and **vasculitis / glomerulonephritis**.
- ▶ **Clearance of apoptotic cells** and cellular debris (C1q, C3) — important in preventing autoimmunity.
- ▶ **Bridge to adaptive immunity:** C3d bound to antigen engages CR2 (CD21) on B cells, lowering the threshold for B-cell activation and antibody production.

Regulation of complement

Regulation is essential because activated C3b and the convertases would otherwise deposit indiscriminately on host cells. Control acts at three checkpoints — **initiation, the C3/C5 convertases, and MAC assembly** — by both **fluid-phase** and **membrane-bound** inhibitors. **Properdin** is the only *positive* regulator.

Regulator	Location / type	Action
C1 inhibitor (C1-INH; SERPING1)	Plasma serpin	Inactivates C1r/C1s and MASP-2; also inhibits kallikrein and factor XIIa (limits bradykinin)

Regulator	Location / type	Action
C4b-binding protein (C4BP)	Plasma	Decays the classical C3 convertase; cofactor for factor I cleavage of C4b
Factor H	Plasma	Decays the alternative C3 convertase; cofactor for factor I cleavage of C3b; discriminates host vs microbial surfaces
Factor I	Plasma serine protease	Cleaves/inactivates C3b and C4b (requires cofactors H, C4BP or MCP)
Decay-accelerating factor (CD55, DAF)	Membrane, GPI-anchored	Accelerates decay of C3 and C5 convertases
Membrane cofactor protein (MCP, CD46)	Membrane	Cofactor for factor I cleavage of surface-bound C3b/C4b
CD59 (protectin / MIRL)	Membrane, GPI-anchored	Blocks incorporation of C9 into C5b-8 → prevents MAC formation
Properdin (factor P)	Plasma — <i>stabiliser</i>	Stabilises the alternative-pathway C3 convertase (C3bBb)

- Two regulators — **CD55 and CD59** — are attached to the membrane through a **glycosylphosphatidylinositol (GPI) anchor**; their loss (PNH) removes host protection from autologous complement.

Diseases of complement deficiency and dysregulation

Defect	Disorder	Mechanism
Classical components C1q, C1r/s, C4, C2	SLE / lupus-like syndromes, immune-complex disease, pyogenic infection	Defective clearance of immune complexes & apoptotic cells (C1q deficiency = strongest genetic link to SLE)
C3, factor I, factor H	Pyogenic infections; factor H → haemolytic-uraemic syndrome	Loss of opsonisation; factor I/H deficiency causes secondary C3 consumption
Alternative pathway factor D, properdin	Recurrent **Neisseria (meningococcal)** infection	Failure of alternative-pathway amplification
Terminal C5, C6, C7, C8 (±C9)	Recurrent *Neisseria* infection	Cannot assemble MAC to lyse <i>Neisseria</i>
C1-INH deficiency (<i>SERPING1</i>)	Hereditary angioedema (HAE)	Unopposed C1/kallikrein activation → excess bradykinin ; ↓C4, ↓C2

Defect	Disorder	Mechanism
PIGA mutation → loss of CD55 + CD59	Paroxysmal nocturnal haemoglobinuria (PNH)	Complement-mediated intravascular haemolysis + thrombosis
Alternative-pathway dysregulation — CFH, CFI, CD46, C3, CFB, THBD	Atypical HUS (aHUS)	Endothelial complement injury → thrombotic microangiopathy + AKI
C3 nephritic factor / CFHR mutations	C3 glomerulopathy (dense-deposit disease, C3GN)	Persistent alternative-pathway activation; glomerular C3 deposition with low C3

- **Hereditary angioedema:** autosomal dominant, fully penetrant; **Type 1** (~85%) low C1-INH antigen, **Type 2** dysfunctional protein, **Type 3** normal complement (often factor XII mutation). Features — non-pruritic, non-urticarial angioedema, recurrent **GI colic**, **laryngeal oedema**; **chronically low C4** is the best screening clue. Treatment: acute — C1-INH concentrate, **icatibant** (B2-receptor antagonist), **ecallantide** (kallikrein inhibitor); prophylaxis — C1-INH, **lanadelumab**, **berotralstat**, attenuated androgens (danazol).
- **PNH:** somatic PIGA mutation in a haematopoietic clone → GPI-anchor deficiency → red cells lacking CD55/CD59 are exquisitely sensitive to complement; intravascular haemolysis, haemoglobinuria, **thrombosis**, and marrow failure (links with aplastic anaemia). Diagnosis — **flow cytometry** showing CD55/CD59-negative cells (Ham acidified-serum test historically).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — The three activation pathways converging on the terminal pathway.** Three vertical limbs: (left) **Classical** — labels *Immune complex* → *C1q-C1r-C1s* → *C4, C2* → *C4b2a* (*C3 convertase*); (middle) **Lectin** — labels *Mannose on microbe* → *MBL/ficolin* + *MASP-1/MASP-2* → *C4, C2*; (right) **Alternative** — labels *C3(H₂O) / microbial surface* → *factor B + factor D + properdin* → *C3bBb* (*C3 convertase*). All converge at a central box *C3* → *C3a* + *C3b*, then *C5* → *C5a* + *C5b*, then *C5b-6-7-8-9* (*MAC / poly-C9*) → **membrane lysis**. Side arrows label *C3a*, *C5a* = **anaphylatoxins** and *C3b* = **opsonin**.
- **Diagram 2 — Regulators superimposed on the cascade.** Mark inhibitory points: **C1-INH** on *C1r/C1s* & *MASP*; **C4BP + factor I** on *C4b*; **factor H + factor I** and **CD55 (DAF)** on the *C3 convertase*; **MCP/CD46** as *factor-I* cofactor; **CD59 (protectin)** blocking *C9/MAC*. Show **properdin** as a green “+” stabilising *C3bBb*.

Clinical / Diagnostic significance

- **Functional screening:** **CH50** assesses the *classical* + terminal pathway; **AP50 (AH50)** assesses the *alternative* + terminal pathway. A **low CH50 with normal AP50** localises the defect to early

classical components, and vice-versa; a profoundly low value prompts measurement of individual components.

- ▶ **C3 and C4 levels** are key serological clues: **low C3 + low C4** indicates **classical-pathway consumption** (active SLE, immune-complex disease); **low C3 with normal C4** indicates **alternative-pathway activation** (post-streptococcal GN, C3 glomerulopathy, aHUS).
- ▶ **Disease-specific tests**: **flow cytometry** for CD55/CD59-deficient clones (PNH); **C1-INH antigen + functional assay with C4 (HAE)**; **anti-factor H antibodies / complement gene panel** (aHUS); **C3 nephritic factor** (dense-deposit disease).
- ▶ **Therapeutics**: terminal-complement blockade with the **anti-C5 monoclonal antibody eculizumab** (and longer-acting **ravulizumab**) is transformative in PNH, aHUS, and C3 glomerulopathy. Because anti-C5 therapy abolishes MAC, patients are at high risk of *Neisseria* and **must receive meningococcal vaccination** ($\pm$ penicillin prophylaxis) before treatment.
- ▶ **Infection prophylaxis**: patients with classical-, alternative- or terminal-pathway deficiency need appropriate vaccination (**meningococcal, pneumococcal, Hib**) and often **oral penicillin** prophylaxis.

High-yield exam pointers

- ▶ Three activation pathways (classical, lectin, alternative) $\rightarrow$ **all cleave C3** $\rightarrow$ common terminal MAC (C5b-9).
- ▶ **C3 convertases**: classical/lectin = **C4b2a**; alternative = **C3bBb**. **C5 convertases**: **C4b2a3b** and **C3bBbC3b**.
- ▶ **C3a + C5a = anaphylatoxins** (C5a chemotactic); **C3b = opsonin**; **MAC = lysis**, the sole defence against *Neisseria*.
- ▶ **Early classical deficiency (C1q/C4/C2)** $\rightarrow$ **SLE & immune-complex disease**; **terminal/alternative deficiency $\rightarrow$ recurrent Neisseria****.
- ▶ **Regulators**: C1-INH (HAE), factor H/I & MCP (aHUS), CD55/CD59 GPI-anchored (PNH), C4BP, properdin (only positive regulator).
- ▶ **HAE = C1-INH deficiency**, bradykinin-mediated, **persistently low C4**, no urticaria/pruritus, treat with C1-INH/icatibant/ecallantide.
- ▶ **PNH = PIGA mutation**, loss of CD55/CD59, intravascular haemolysis + thrombosis, diagnosed by **flow cytometry**.
- ▶ **Eculizumab (anti-C5)** for PNH/aHUS/C3G — give **meningococcal vaccine first**.
- ▶ **CH50 (classical)** and **AP50 (alternative)** are the functional screening tests; combine with C3/C4 levels.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Introduction to the Immune System” (complement pathways, anaphylatoxins, opsonisation, MAC, Table 360-12 Complement Deficiencies and Associated Diseases); “Primary Immune Deficiency Diseases” (complement deficiency, CH50/AP50, *Neisseria* and SLE associations); “Hemolytic Anemias” (PNH — PIGA/GPI/CD55/CD59, aHUS — CFH/CFI/CD46/C3/CFB/THBD, eculizumab); “Urticaria, Angioedema, and Allergic Rhinitis” (hereditary angioedema, C1-INH/SERPING1, bradykinin, icatibant/ecallantide/lanadelumab/berotralstat); “Glomerular Diseases” (C3 glomerulopathy, dense-deposit disease, C3 nephritic factor, CFHR mutations).
- ▶ **Coverage note:** Harrison provides full pathway, function, deficiency and disease detail and uses the CD55/CD59/CD46 nomenclature; the synonymous regulator labels DAF, protectin/MIRL, MCP and C4b-binding protein, and the convertase composition diagram, are standard, universally accepted immunology added for completeness and are consistent with the cascade as depicted in Harrison's Fig. 360-5 and Fig. 105-10. No dedicated subspecialty immunology text was listed in the spec; grounding is Harrison-based and internally cross-verified.



Cytochrome P450 enzyme system and drug metabolism

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Drug metabolism* (biotransformation) is the enzymatic conversion of a drug into more polar, more readily excretable products, occurring predominantly in the liver but also in kidney, intestinal epithelium, lung and plasma. The **cytochrome P450 (CYP)** superfamily is a group of heme-containing **mono-oxygenase** enzymes (named for the 450-nm absorbance peak of their reduced carbon-monoxide complex) that catalyse most **Phase I** oxidative reactions and so determine the clearance, bioavailability and interaction profile of a large fraction of drugs in clinical use. Variability in CYP function — from genetic polymorphism, enzyme induction/inhibition or disease — is a principal source of the wide inter-individual variability seen in drug response and adverse drug reactions (ADRs).

Phases of drug metabolism (biotransformation)

- ▶ **Phase I (functionalisation):** chemical modification — *most often oxidation* — that introduces or unmasks a reactive group (–OH, –NH₂, –SH). This is accomplished chiefly by members of the **cytochrome P450 mono-oxygenase superfamily**; reactions also include reduction and hydrolysis. The product may be active, inactive or toxic.
- ▶ **Phase II (conjugation):** covalent attachment of an endogenous moiety to the drug or its Phase I metabolite, generating a highly polar, usually inactive conjugate. Enzymes include **glucuronyl-**

acetyl-, sulfo- and methyl-transferases (e.g., UGT1A1, N-acetyltransferase, thiopurine S-methyltransferase).

- ▶ **Net effect:** metabolites are *more polar and more readily excreted* than the parent drug (renally or in bile). Drug efflux/uptake **transporters** (e.g., the P-glycoprotein efflux pump, product of the *ABCB1/MDR1* gene, on the apical enterocyte and canalicular hepatocyte membranes) act in concert with metabolism to limit drug delivery to the systemic circulation.
- ▶ **First-pass (presystemic) elimination:** an orally administered drug must traverse the enterocyte, portal vein and hepatocyte before reaching the systemic circulation; CYP-mediated metabolism (especially intestinal/hepatic CYP3A) plus efflux at these sites reduces **bioavailability**.

The cytochrome P450 superfamily — organisation

- ▶ **Nomenclature:** root “CYP”, then a **family** number (e.g., 3), a **subfamily** letter (e.g., A) and an **individual gene** number (e.g., 4) → *CYP3A4*; families/subfamilies are grouped by amino-acid sequence homology.
- ▶ The families most important for human drug metabolism are **CYP1, CYP2 and CYP3**.
- ▶ **CYP3A (CYP3A4, CYP3A5)** metabolises the **greatest number of drugs in therapeutic use**; CYP3A4 activity varies up to an order of magnitude between individuals, largely from variation in *regulatory* regions rather than coding mutations.
- ▶ **CYP2D6** is *second to CYP3A4* in the number of commonly used drugs it handles, and is highly polymorphic.
- ▶ CYPs may **bioactivate** procarcinogens and generate **reactive electrophilic metabolites** that covalently bind tissue macromolecules (protein/DNA) close to the site of production (typically the liver), mediating certain ADRs.

Major drug-metabolising CYP isoforms — representative substrates and inhibitors

Isoform	Representative substrates	Representative inhibitors
CYP3A	Calcium-channel blockers; antiarrhythmics (lidocaine, quinidine, mexiletine); HMG-CoA reductase inhibitors (statins); erythromycin, clarithromycin; cyclosporine, tacrolimus; HIV protease inhibitors (indinavir, saquinavir, ritonavir)	Amiodarone; ketoconazole, itraconazole; ritonavir; gemfibrozil/fibrates
CYP2D6	β -blockers (timolol, metoprolol, carvedilol); propafenone, flecainide; tricyclic	Quinidine (even ultra-low doses); fluoxetine, paroxetine

Isoform	Representative substrates	Representative inhibitors
	antidepressants; bupropion; codeine, tamoxifen (prodrugs)	
CYP2C9	Warfarin; phenytoin; glipizide; losartan (prodrug)	Amiodarone; fluconazole; phenytoin
CYP2C19	Omeprazole; mephenytoin; clopidogrel (prodrug)	Omeprazole; ritonavir; fluoxetine, fluvoxamine
CYP2B6	Efavirenz	Ticlopidine

- ▶ **Non-CYP pathways also tested in exams:** thiopurine S-methyltransferase (6-mercaptopurine, azathioprine); N-acetyltransferase/NAT2 (isoniazid, procainamide, hydralazine, some sulfonamides); UGT1A1 (irinotecan); pseudocholinesterase (succinylcholine); xanthine oxidase (azathioprine/6-MP — inhibited by allopurinol). Transporters: P-glycoprotein (digoxin, HIV protease inhibitors) and SLCO1B1/OATP1B1 (simvastatin and some statins).

Enzyme induction and inhibition — basis of drug–drug interactions

- ▶ **Induction** (increased synthesis/activity → *reduced* drug levels and effect, or increased toxic-metabolite formation): classic inducers are **rifampin**, **carbamazepine**, **phenytoin**, **St John's wort** and **glutethimide**, plus *smoking*, *chlorinated insecticides* and *chronic alcohol ingestion*. Induction lowers concentrations of warfarin, quinidine, cyclosporine, losartan, **oral contraceptives** (→ contraceptive failure), methadone and dabigatran.
- ▶ **Inhibition** (→ *increased* drug levels and dose-related toxicity): **cimetidine** inhibits many CYPs (raises warfarin, theophylline, phenytoin); **amiodarone** inhibits multiple CYPs and P-glycoprotein (raises warfarin, digoxin, dabigatran); CYP3A inhibitors precipitate statin and colchicine toxicity; CYP2D6 inhibitors potentiate β -blockade.
- ▶ **Clinical sentinels:** prescribers must be especially alert when *starting or stopping* **CYP2D6**, **CYP3A** or **P-glycoprotein inhibitors** and **CYP3A/P-glycoprotein inducers**, e.g., a stable warfarin patient who bleeds after **amiodarone** is added (warfarin metabolism inhibited), not a direct amiodarone reaction.
- ▶ **Reactive-metabolite toxicity (acetaminophen/paracetamol):** CYP-generated reactive metabolite is normally detoxified by hepatic **glutathione**; once glutathione is depleted it binds hepatic protein → hepatocyte necrosis. Risk is *increased* by enzyme inducers (phenobarbital, phenytoin) and by ethanol (which exhausts glutathione stores). Antidote: **N-acetylcysteine** (IV 140 mg/kg loading, then 70 mg/kg every 4 h), which replenishes sulfhydryl/glutathione.

Pharmacogenomics of CYP — metaboliser phenotypes

- ▶ Polymorphism produces a **multimodal population distribution** of enzyme activity (classically demonstrated for CYP2D6):

- **Poor metabolisers (PM):** two loss-of-function alleles → slow clearance, higher steady-state levels, longer time to steady state.
 - **Intermediate metabolisers (IM):** one functional / reduced-function allele.
 - **Extensive (normal) metabolisers (EM):** one or two functional alleles.
 - **Ultra-rapid metabolisers (UM):** gene duplication (2–12 active copies) → very low parent-drug levels.
- ▶ **CYP2D6:** PM phenotype in 5–10% of European- and African-derived populations (few Asians); UMs frequent in East Africa, the Middle East and Oceania. **Codeine** is bioactivated to **morphine** by CYP2D6 — analgesia is *blunted in PMs* and *dangerous (respiratory depression) in UMs*; deaths in children after tonsillectomy led the FDA to a black-box warning and to **forbid codeine in children <12 years**. PMs show exaggerated β -blockade (metoprolol, carvedilol, timolol, propafenone).
 - ▶ **CYP2C19:** PM common (~20%) in Asians, ~2–3% in others, >50% in Oceania. Reduced bioactivation of **clopidogrel** → less antiplatelet effect and more stent thrombosis/ischaemic events; omeprazole both is a substrate and phenocopies the defect by inhibition.
 - ▶ **CYP2C9 + VKORC1:** together account for up to 50% of variability in stable **warfarin** dose; CYP2C9 variants also cause phenytoin neurotoxicity and glipizide hypoglycaemia, and impair bioactivation of the prodrug **losartan**.
 - ▶ **CYP3A5:** a splicing polymorphism (common in Europeans/Asians) reduces activity; African-origin “expressers” clear **tacrolimus** faster (reduced efficacy at standard dose).
 - ▶ **Implementation:** the **Clinical Pharmacogenetics Implementation Consortium (CPIC)** and the Dutch Pharmacogenetics Working Group publish drug–gene dosing guidance; “point-of-care” vs “pre-emptive” genotyping models are in use.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Two-phase hepatocyte metabolism schema:** *Lipophilic drug* → arrow into a box labelled “Phase I: CYP450 oxidation (–OH/–NH₂/–SH added)” → *intermediate metabolite* → arrow into a box labelled “Phase II: conjugation (glucuronyl-/sulfo-/acetyl-/methyl-transferase)” → *polar conjugate* → arrows to “Bile” and “Urine.” Side label: “P-glycoprotein (ABCB1) efflux.” Annotate the CYP box with “Inducers: rifampin, carbamazepine, phenytoin, St John’s wort” and “Inhibitors: amiodarone, ketoconazole, cimetidine, fluoxetine.”
- ▶ **Diagram 2 — Population distribution of CYP2D6 activity:** x-axis “enzyme activity (low → high)”, y-axis “population frequency”, with labelled peaks “Poor metaboliser (2 LOF alleles),” “Extensive/normal metaboliser,” “Ultra-rapid metaboliser (gene duplication)” and a vertical “antimode” line separating PMs.

Clinical / Diagnostic significance

- ▶ **Prodrugs requiring CYP bioactivation:** codeine (→morphine, CYP2D6), clopidogrel (CYP2C19), losartan (CYP2C9), tamoxifen (CYP2D6), many ACE inhibitors, irinotecan — failure of activation = therapeutic failure.
- ▶ **“High-risk pharmacokinetics”:** when an active drug depends on a *single* CYP pathway, any inhibitor (drug, gene or disease) causes large swings in concentration — dangerous for narrow-therapeutic-index drugs (warfarin, phenytoin, ciclosporin, theophylline, digoxin).
- ▶ **Therapeutic drug monitoring & genotyping:** anticonvulsants, antiarrhythmics, immunosuppressants and some antibiotics benefit from level monitoring; targeted CYP2C19/CYP2D6/CYP2C9 genotyping guides clopidogrel, codeine and warfarin use.
- ▶ **Disease modifiers:** in cirrhosis, oral bioavailability of high first-pass drugs (morphine, meperidine, midazolam, nifedipine) is nearly *doubled* — reduce oral doses. In the **porphyrias**, CYP inducers can precipitate acute attacks.
- ▶ **Special groups:** neonates have immature CYP pathways; the elderly on polypharmacy are prone to CYP-mediated interactions and ADRs.

High-yield exam pointers

- ▶ CYP = heme-thiolate **mono-oxygenase**; named for **450-nm** CO-complex absorbance; chiefly hepatic endoplasmic reticulum.
- ▶ **CYP3A4** metabolises the most drugs; **CYP2D6** is second and highly polymorphic.
- ▶ **Inducers** (Rifampin, Carbamazepine, Phenytoin, St John’s wort, chronic alcohol, smoking) ↓ drug levels → e.g., **OCP failure, warfarin resistance**.
- ▶ **Inhibitors** (amiodarone, azole antifungals, macrolides, cimetidine, grapefruit-type CYP3A inhibition, fluoxetine/paroxetine) ↑ drug levels → toxicity (statin myopathy, colchicine, warfarin bleeding).
- ▶ Metaboliser phenotypes: **PM / IM / EM / UM**; **UM + codeine = fatal respiratory depression** (FDA bans codeine <12 y after tonsillectomy).
- ▶ **Clopidogrel = CYP2C19** (loss-of-function → stent thrombosis); **warfarin = CYP2C9 + VKORC1** (≈50% of dose variance).
- ▶ **Paracetamol** reactive metabolite detoxified by **glutathione**; antidote **N-acetylcysteine**; alcohol/inducers raise risk.
- ▶ Phase II = **conjugation** (glucuronidation by UGT1A1 → Gilbert’s/irinotecan; acetylation by NAT2 → slow acetylators → INH hepatitis, drug-induced lupus).

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Principles of Clinical Pharmacology” (drug metabolism, Phase I/II, CYP substrate–inhibitor–inducer tables, first-pass effect,

high-risk pharmacokinetics, drug interactions, reactive-metabolite/acetaminophen toxicity) and “Pharmacogenomics” (CYP3A/2D6/2C19/2C9 polymorphisms, PM/IM/EM/UM phenotypes, codeine/clopidogrel/warfarin/tacrolimus pharmacogenetics, CPIC).

- ▶ **Harrison’s 22e** — “Toxic and Drug-Induced Hepatitis” (acetaminophen reactive-metabolite mechanism, glutathione, N-acetylcysteine dosing; CYP-inducer enhancement of toxicity).
- ▶ **Coverage note:** This is a pharmacology topic with no dedicated subspecialty textbook in the spec (specialty_books empty; CMDT not flagged); the answer is grounded entirely in the two Harrison clinical-pharmacology chapters plus the drug-induced hepatitis chapter. CYP nomenclature convention (family/subfamily/gene) and the 450-nm naming are stated as universally accepted standard pharmacology, as exact homology thresholds are not specified in the corpus.



Cytokines physiology and clinical implications

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — Cytokines are soluble, low-molecular-weight proteins produced by a wide variety of cell types that act through specific cell-surface receptors to regulate the **growth, development, and activation** of immune cells and to mediate the **inflammatory response**. They are pivotal to both **innate and adaptive immunity**, and their expression is perturbed in most immune, inflammatory, and infectious disease states. Functionally overlapping molecules that primarily attract and direct leukocyte movement are called **chemokines**. The cytokine system is the molecular target of an expanding class of “biologic” therapies, making its physiology directly relevant to internal-medicine practice.

General properties (physiology)

- ▶ **Mode of action** — cytokines act (1) in an **autocrine** manner when the target cell is the same cell that secreted it, (2) in a **paracrine** manner when the target is a nearby cell, and (3) in an **endocrine** manner when secreted into the circulation to act on distant tissue.
- ▶ **Pleiotropy** — a single cytokine acts on many different cell types, because receptors for it are expressed on multiple lineages.
- ▶ **Redundancy** — different cytokines exert similar (overlapping) biologic functions.
- ▶ **Synergy / antagonism and networks** — one cytokine commonly induces another, producing interlinked “**cytokine networks**”; effects may be additive (synergy) or opposing (antagonism).

- ▶ **Nomenclature** — cytokines thought primarily to target leukocytes were named **interleukins** (IL-1, IL-2, IL-3 ...); those described by an original function retained that name (e.g., **granulocyte colony-stimulating factor** [G-CSF], interferons, tumour necrosis factor).
- ▶ **Mechanism** — they alter **gene activation**, producing cellular activation, growth, differentiation, surface-molecule expression, and effector function. The **TH1/TH2/TH17** classification of helper T cells is itself defined by the *pattern of cytokines* the cell secretes (TH1 → cell-mediated immunity; TH2 → humoral immunity; TH17 → mucosal defence against extracellular bacteria/fungi).

Structural classification of cytokines and their receptors

- ▶ Cytokines fall into **three major structural families**: the **hematopoietin family**; the **TNF / IL-1 / PDGF / TGF- β family**; and the **CXC and C-C chemokine families** (chemokines have a distinctive 3-D structure and act via G-protein-coupled receptors).
- ▶ Cytokine receptors are grouped into **five families** by their conserved extracellular domains:

Receptor family	Representative members	Note
Immunoglobulin (Ig) superfamily	IL-1 receptors (type I, type II)	Extracellular Ig domains
Hematopoietic growth-factor (type I) receptor family	Receptors sharing the common γ chain (γ_c) — IL-2, IL-4, IL-7, IL-9, IL-15, IL-21; gp130-using receptors (IL-6, IL-11)	γ_c mutation causes X-linked SCID (X-SCID)
Interferon (type II) receptor family	Receptors for IFN- γ and IFN- β	Conserved cysteine-paired ~210-aa binding domain
TNF (type III) receptor family	TNF-R1 (p55), TNF-R2 (p75), CD40, Fas/Apo-1, CD27, CD30, NGF receptor	Cysteine-rich repeats; Fas triggers apoptosis
Seven-transmembrane (G-protein-coupled) family	Chemokine receptors (e.g., CXCR4, CCR5)	CXCR4 & CCR5 are the major HIV-1 co-receptors

Major cytokines and their physiological actions

Cytokine	Principal source	Key biologic action
IL-1 α/β	Monocytes-macrophages, endothelium	Upregulates adhesion molecules, fever, shock , hepatic acute-phase protein production, hematopoiesis
IL-2	T cells	T-cell activation & proliferation, B-cell growth, NK proliferation/activation

Cytokine	Principal source	Key biologic action
IL-4	T cells, mast cells, basophils	Drives TH2 differentiation; B-cell Ig class-switch to IgG1 and IgE; anti-inflammatory
IL-5	T cells, mast cells, eosinophils	Regulates eosinophil migration and activation
IL-6	Monocytes-macrophages, fibroblasts	Acute-phase protein induction, T/B differentiation, myeloma & osteoclast growth
IL-8 (CXCL8)	Monocytes, neutrophils, endothelium	Neutrophil chemotaxis and adhesion (via CXCR1/CXCR2)
IL-10	Monocytes-macrophages, T cells	Anti-inflammatory — inhibits macrophage proinflammatory cytokine production, downregulates MHC class II
IL-12	Activated macrophages, dendritic cells	Induces TH1 formation; ↑IFN-γ, ↓IL-17; ↑CD8 CTL activity
IL-17	CD4 ⁺ (TH17) T cells	Enhances cytokine/chemokine secretion; promotes delayed-type reactions
IL-23	Macrophages	Opposite of IL-12 — ↑IL-17, ↑IFN-γ; sustains TH17
IFN-α / IFN-β	All cells (type I IFN)	Antiviral; activate T cells/macrophages/NK; upregulate MHC class I; antitumour
IFN-γ	T cells, NK cells (type II)	Activates macrophages & NK; induces MHC class II; drives TH1
TNF-α	Monocytes-macrophages, mast cells	Fever, anorexia, shock, capillary-leak syndrome, proinflammatory cytokine induction
G-CSF / GM-CSF	Macrophages, fibroblasts, T cells	Regulate myelopoiesis; reverse chemotherapy-induced neutropenia; GM-CSF aids DC maturation
TGF-β	Most cell types	Immunosuppressive — downregulates T-cell/macrophage/granulocyte responses; stimulates matrix synthesis & angiogenesis

Cytokine signalling — the JAK-STAT pathway

- ▶ Hematopoietin-receptor signalling uses the Janus kinase (JAK) family — JAK1, JAK2, JAK3, and Tyk2, which preferentially associate with different receptor subunits.
- ▶ Cytokine binding **juxtaposes receptor subunits**, allowing paired JAKs to **transphosphorylate** and activate one another; JAKs then phosphorylate receptor tyrosines.
- ▶ STAT (signal transducer and activator of transcription) factors dock via **SH2 domains**, are phosphorylated by JAKs, dissociate, **translocate to the nucleus**, and bind specific DNA motifs to regulate gene transcription.
- ▶ **Clinical correlate** — JAK3 mutation produces an X-SCID-like phenotype (but affects both sexes, as JAK3 is on chromosome 19). **JAK inhibitors** (small molecules) are approved for rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, atopic dermatitis, and alopecia areata.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Modes of cytokine action.** Draw three cells with arrows: *Autocrine* (cytokine loops back to its own secreting cell), *Paracrine* (acts on an adjacent cell), *Endocrine* (enters a blood vessel to act on a distant cell). Labels: **Secreting cell, Cytokine, Receptor, Autocrine, Paracrine, Endocrine, Bloodstream, Distant target cell.**
- ▶ **Diagram 2 — JAK-STAT signalling.** Draw a transmembrane cytokine receptor dimer. Labels: **Cytokine (ligand), Receptor subunits, JAK1/JAK2/JAK3/Tyk2, Transphosphorylation, Tyrosine-P residues, STAT with SH2 domain, STAT phosphorylation, STAT dimer, Nucleus, DNA/gene transcription.**

Clinical / Diagnostic significance

- ▶ Anti-cytokine biologic therapy is a mainstay for autoimmune/inflammatory disease:

Target	Agent(s)	Main indication(s)
TNF- α	Adalimumab, infliximab, golimumab, certolizumab pegol (mAbs); etanercept (soluble Fc:TNF-receptor trap)	RA, psoriasis/psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis
IL-1	Anakinra (IL-1 receptor antagonist), canakinumab, rilonacept (IL-1 trap)	Cryopyrin-associated/auto-inflammatory syndromes, gouty arthritis, juvenile arthritis
IL-6 / IL-6R	Tocilizumab (anti-IL-6R); siltuximab (anti-IL-6)	RA, juvenile idiopathic arthritis; Castleman's disease
IL-12 / IL-23	Anti-IL-12/IL-23 (p40) mAb (e.g., ustekinumab)	Psoriasis, inflammatory bowel disease (block TH17 differentiation)

Target	Agent(s)	Main indication(s)
IL-17	Anti-IL-17 mAb (e.g., <i>secukinumab</i>)	Psoriasis, psoriatic arthritis
IL-4R α	Dupilumab	Atopic dermatitis, steroid-dependent asthma
IgE	Omalizumab	Allergic asthma
BAFF	Belimumab	Systemic lupus erythematosus
VEGF	Bevacizumab, ramucirumab, ranibizumab, aflibercept	Tumour angiogenesis; macular degeneration/diabetic macular edema

- ▶ **Therapeutic cytokines (replacement/augmentation):** IFN- α/β in viral and autoimmune disease; IFN- γ corrects the phagocyte defect of **chronic granulomatous disease**; G-CSF/GM-CSF reverse chemotherapy-induced neutropenia; IFN- β and IL-11 lower IL-1/TNF- α and are used as inhibitory agents in inflammation.
- ▶ **Cytokine excess (cytokine release syndrome, CRS):** uncontrolled cytokine release with systemic inflammation is the dose-limiting toxicity of CAR T-cell therapy; IL-6/IL-6R blockade (tocilizumab) is a key antidote — illustrating the “cytokine storm” concept.
- ▶ **Autoantibodies to cytokines** cause distinctive disease: anti-IFN- γ $\rightarrow$ disseminated mycobacterial/bacterial infection and VZV reactivation; anti-GM-CSF $\rightarrow$ **pulmonary alveolar proteinosis** and fungal infection; anti-IL-17A/IL-17F $\rightarrow$ **chronic mucocutaneous candidiasis**; anti-IL-6 $\rightarrow$ severe bacterial infections; anti-IL-1/TNF autoantibodies seen in RA, systemic sclerosis, SLE.
- ▶ **Diagnostic use:** acute-phase reactants (CRP, driven by IL-6) and the febrile/inflammatory response are downstream cytokine readouts; chemokine receptors CXCR4/CCR5 are exploited for HIV tropism testing and CCR5-antagonist therapy.

High-yield exam pointers

- ▶ Three cytokine actions: **autocrine, paracrine, endocrine**; two cardinal properties: **pleiotropy** and **redundancy**, forming cytokine networks.
- ▶ **Five cytokine-receptor families:** Ig superfamily, hematopoietic (type I), interferon (type II), TNF (type III), and 7-transmembrane (GPCR/chemokine).
- ▶ **Common γ -chain cytokines** = IL-2, -4, -7, -9, -15, -21; γ c or JAK3 mutation = SCID.
- ▶ **Pro-inflammatory triad:** IL-1, IL-6, TNF- α (fever, shock, acute-phase response). **Anti-inflammatory:** IL-10, TGF- β .
- ▶ **TH1** = IFN- γ /IL-2 (cell-mediated); **TH2** = IL-4/IL-5/IL-13 (humoral, IgE/eosinophils); **TH17** = IL-17/IL-23 axis (mucosal, psoriasis/IBD).

- ▶ IFN type I (α , β) $\rightarrow$ MHC class I & antiviral; IFN- γ (type II) $\rightarrow$ MHC class II & macrophage activation.
- ▶ Signalling = JAK-STAT; targeted by oral JAK inhibitors (RA, UC, atopic dermatitis, alopecia areata).
- ▶ Know the biologic targets: TNF (etanercept/infliximab), IL-1 (anakinra), IL-6R (tocilizumab), IL-17/IL-23 (psoriasis), IL-4R α (dupilumab), IgE (omalizumab), BAFF (belimumab).
- ▶ IFN- γ is therapeutic in **chronic granulomatous disease**; CRS is the cytokine-storm toxicity of CAR T-cell therapy.

SOURCE & COVERAGE

Harrison 22e — Ch 360 “Introduction to the Immune System” (cytokine biology, Table 360-7 Cytokines and Cytokine Receptors, Table 360-8 chemokine families, receptor families and JAK-STAT signalling) and Ch 361 “Mechanisms of Regulation and Dysregulation of the Immune System” (anti-cytokine biologics — Table 361-5, cytokine autoantibodies, cytokine release syndrome). **Coverage note:** Both chapters fully support the physiology and the biologic-target list. Brand/generic names *ustekinumab* and *secukinumab* are not spelled out in the provided text (which states only “anti-IL-12/IL-23” and “anti-IL-17” antibodies) — they are added as universally accepted standard internal medicine and flagged in italics. The term “cytokine storm” is standard terminology; the source explicitly describes **cytokine release syndrome** with CAR T-cell therapy.



Smoking-Related Health Hazards and Nicotine De-addiction Measures

Asked in: Paper IV May 2019 — RGUHS MD General Medicine

Definition / Introduction — *Nicotine addiction* is a chronic, relapsing disorder in which reversible binding of nicotine to **nicotinic acetylcholine receptors (nAChRs)** in brain reward circuits produces compulsive, repetitive use and a withdrawal syndrome on abstinence. While nicotine itself drives the dependence (and some pregnancy harm), the **vast majority of tobacco-attributable disease results from repeated exposure to the carcinogens and toxicants in combusted tobacco smoke**, not nicotine per se. Approximately **40% of cigarette smokers die prematurely** of smoking-related disease unless they quit, and globally tobacco accounts for ~13.6% of all deaths. Tobacco dependence is a treatable medical condition: structured counselling plus pharmacotherapy can roughly **triple** cessation success.

Mechanism of Nicotine Addiction (basis of de-addiction)

- ▶ Inhaled/absorbed nicotine reaches the brain within seconds and **reversibly attaches to nicotinic ACh receptors** active in networks subserving mood, reward, joy and excitement; chronic high exposure causes **upregulation of nicotinic receptors**.
- ▶ As blood nicotine falls between doses, nicotine detaches from receptors; the addicted user no longer feels “normal”, generating a **compulsive need for the next dose** — the diagnostic hallmark is *loss of control over the next use*.
- ▶ **Withdrawal symptoms** (irritability, craving, anxiety, restlessness) appear within a day of cessation and may persist **4–6 weeks**.
- ▶ Addictiveness is driven by **speed and arterial concentration** of nicotine reaching the brain. Mildly acidic aerosols (cigarettes, nicotine-salt vapes) reduce airway irritation, permitting deep inhalation; lung pH (~7.4) then converts nicotine to the rapidly absorbed **unprotonated (freebase)** form — explaining why cigarettes and nicotine-salt devices are the most addictive forms.
- ▶ **Genetic susceptibility** (genes reducing nicotine clearance or increasing dependence/depression risk) influences whether adolescent experimentation progresses to adult addiction.

Smoking-Related Health Hazards (system-wise)

- ▶ **Cardiovascular** — promotes both large-vessel atherosclerosis and small-vessel disease, and raises MI/sudden cardiac death risk by enhancing **platelet aggregation and vascular occlusion**. Attributable fractions: **~90% of peripheral vascular disease** (non-diabetic), **~50% of aortic aneurysms**, **~24% of coronary artery disease**, **~11% of ischaemic and haemorrhagic strokes**. There is a **multiplicative interaction** with hypertension and dyslipidaemia.
- ▶ **Cancer** — causes cancers of lung; lip, oral cavity, naso-/oro-/hypopharynx; nasal cavity/paranasal sinuses; larynx; oesophagus; stomach; pancreas; liver (HCC); colon and rectum; kidney and renal pelvis; ureter; urinary bladder; uterine cervix; and **acute myeloid leukaemia**. Risk rises **linearly with cigarettes/day** and **logarithmically with duration**. Synergy occurs with **alcohol** (oral cavity, oesophagus) and with **asbestos/radon** (lung).
- ▶ **Respiratory** — responsible for **~80% of COPD**; chronic mucous hyperplasia causes productive cough in up to 80% of smokers >60 yr; **~15–25%** develop clinically significant airflow obstruction (chronic bronchitis/emphysema).
- ▶ **Pregnancy** — premature rupture of membranes, abruptio placentae, placenta praevia, spontaneous abortion; offspring show preterm delivery, **small-for-gestational-age**, higher perinatal mortality, infant respiratory distress, **SIDS** and developmental lag.
- ▶ **Other** — delayed peptic-ulcer healing; periodontal disease; diabetes; active tuberculosis; rheumatoid arthritis; osteoporosis; senile cataract; macular degeneration; premature menopause; skin wrinkling; gallstones/cholecystitis (women); male impotence; and **poorer chemo-/radiotherapy outcomes**.

- ▶ **Environmental tobacco smoke (passive smoking)** — increases lung cancer and CAD in non-smokers; in children causes respiratory infections, chronic otitis media and asthma (incidence and exacerbation).
- ▶ **“Low-tar/low-nicotine” and filtered cigarettes confer no real benefit** — smokers compensate by deeper/more frequent puffing; design changes have driven the rise in **lung adenocarcinoma**.

Relative Risks for Current Smokers (Harrison Table 465-1)

Disease (current vs never smoker)	Male	Female
Lung cancer (age 45–64)	19.0	19.0
COPD (age 35–44)	29.7	38.9
Coronary heart disease (35–44)	3.9	5.0
Cerebrovascular disease (35–44)	2.2	2.3
Larynx cancer	14.6	13.0
Lip/oral cavity/pharynx	10.9	5.1
Oesophagus	6.8	7.8
Bladder	3.3	2.2

Relative risk for most cancers and COPD rises with age; for CVD the relative risk falls with age but the absolute excess death rate keeps rising (cumulative injury).

Benefits of Cessation (motivational pearls)

- ▶ Risk of a **second coronary event falls within 6–12 months**; rates of first MI and CHD death decline within 2–4 years.
- ▶ After **15 years** of abstinence, risk of stroke, MI and CHD death approaches that of a never-smoker.
- ▶ Cancer risk begins to fall after ~4 years, but a residual **3- to 4-fold lung cancer risk persists even 20 years** after quitting.
- ▶ Small-airway changes in young smokers reverse within 1–2 years; in established COPD, cessation mainly **slows the rate of decline** in lung function.

Nicotine De-addiction — Behavioural Framework (“5 A’s”)

- ▶ Cessation is typically **cyclical** — ~70–80% of smokers want to quit and >50% attempt yearly, but only ~6% remain abstinent at 6 months and ~3% at 2 years (CMTD: 5–10% unaided success). Repeated, structured intervention is therefore essential.
- ▶ **Ask** — systematically identify all tobacco/nicotine use at every visit (record cumulative daily episodes across *all* products — cigarettes, cigars, roll-your-own, vapes, oral nicotine).

- ▶ **Advise** — give a clear, strong, personalised message to quit; brief clinician advice at the time of an acute illness triggers a quit attempt in up to half of patients and makes quitting **1.6×** more likely.
- ▶ **Assess** — gauge readiness to change and intensity of addiction (uses/day, use within ~30 min of waking, prior quit history, craving on abstinence).
- ▶ **Assist** — negotiate a **quit date** (usually within a few weeks, not the visit day); offer pharmacotherapy to all who accept plus counselling; address anticipated **weight gain** (~80% gain, average ~2 kg; 10–15% gain >13 kg).
- ▶ **Arrange** — schedule follow-up contact around the quit date; system-wide tracking/outreach can raise 12-month abstinence to ~25%.
- ▶ *Counselling formats*: individual or group sessions (≥4–7 sessions of 20–30 min), telephone **quitlines** and text-messaging are all proven and highly cost-effective.

Pharmacotherapy for Nicotine De-addiction

Offer to all quit attempters **except** those with medical contraindications, pregnant/breastfeeding women and adolescents. Numbers in parentheses are the **multiple of cessation success vs no intervention** (Harrison Table 465-2).

Agent	Mechanism	Regimen	Efficacy (× vs none)
Nicotine patch	Transdermal NRT	7/14/21 mg per 24 h, 1 patch/day	1.9
Nicotine gum	Oral mucosal NRT	2 or 4 mg, 8–24 pieces/day	1.5
Nicotine lozenge	Oral mucosal NRT	2 mg (2.0) / 4 mg (2.8), up to 20/day	2.0–2.8
Nicotine nasal spray	Rapid NRT (Rx)	1–2 sprays, max 10/h	2.3
Nicotine oral inhaler	NRT (Rx)	4–16 cartridges/day	2.1
Bupropion SR	Dopamine–noradrenaline reuptake inhibitor	150 mg OD ×3 days → 150 mg BID; up to 6 months; start 1–2 wk before quit date	2.0
Varenicline	Partial agonist at nicotinic ACh receptor	0.5 mg OD ×3 days → 0.5 mg BID days 4–7 → 1 mg BID ; up to 6 months; start 1–2 wk pre-quit	3.1
Exclusive e-cigarette	Nicotine-salt aerosol (harm reduction)	Caution: avoid dual use	3.0

- ▶ NRT roughly **doubles** quit success; usual course **3–6 months**, higher doses for heavier smokers, with longer maintenance for those who relapse. Combining a **patch (basal) plus gum/lozenge (acute craving)** improves outcomes.
- ▶ **Bupropion** boosts dopamine/noradrenaline (mimicking nicotine), causes minimal weight gain, but is **contraindicated in seizure disorders**; especially useful where depression coexists.
- ▶ **Varenicline** is the single most effective monotherapy (partial agonism reduces craving while blunting reward); start 1–2 weeks before the quit date.
- ▶ **Combination therapy > single agent**. Pre-treatment (NRT, bupropion or varenicline) before the quit date improves results. The best outcomes (nearly **3-fold**) come from **advice + pharmacotherapy + counselling** together.
- ▶ **Harm reduction**: switching completely from combusted cigarettes to exclusive nicotine-salt e-cigarettes is at least as effective as FDA-approved drugs and markedly lowers toxicant biomarkers, but must avoid **dual use** (which negates benefit) — reserved chiefly for those failing or refusing approved therapy; never recommended to never-smokers.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Reward-pathway / addiction cycle**: Inhaled nicotine → arterial blood → brain → **nicotinic ACh receptor** binding on VTA dopaminergic neurons → dopamine release in **nucleus accumbens** (pleasure/reward) → receptor upregulation → falling nicotine → **withdrawal/craving** → next dose. Labels: *nicotine, nAChR, ventral tegmental area, nucleus accumbens, dopamine, reward, withdrawal/craving, compulsive use*.
- ▶ **Body-map of smoking hazards (whole-body schematic)**: label *brain/stroke; oral cavity–larynx–pharynx cancer; lung cancer & COPD; coronary artery disease; aortic aneurysm; peripheral vascular disease; oesophagus/stomach/pancreas/liver/colorectal cancer; kidney & bladder cancer; cervix & AML; pregnancy complications; passive-smoke effects in children*.

Clinical / Diagnostic significance

- ▶ **Diagnosis is clinical** — loss of control over next nicotine use; quantify via uses/day, time-to-first-use after waking, craving on abstinence and prior failed quits.
- ▶ Smoking **induces hepatic CYP450**, lowering levels of drugs such as **warfarin** (anticoagulation may destabilise on admission/discharge), increases first-pass clearance of **lidocaine/theophylline**, and blunts effects of **benzodiazepines and beta-blockers** — review doses when patients are hospitalised and abstinent.
- ▶ Continued smoking during cancer chemotherapy/radiotherapy worsens survival — cessation is part of oncologic care.
- ▶ Counsel about **screening** (low-dose CT lung-cancer screening for eligible heavy smokers) and aggressive control of co-existing CVD risk factors given multiplicative interaction.

High-yield exam pointers

- ▶ ~40% of smokers die prematurely; tobacco ≈ 13.6% of global deaths; ~480,000 US deaths/year.
- ▶ Top three killers: **cancer, cardiovascular disease, COPD** (~80% of COPD).
- ▶ Attributable fractions: **90% PVD, 50% aortic aneurysm, 24% CAD, 11% stroke**.
- ▶ Cancer risk: **linear** with cigarettes/day, **logarithmic** with duration; lung-adenocarcinoma rise linked to filter/design changes.
- ▶ Withdrawal lasts **4–6 weeks**; nicotine-salt/cigarette acidic aerosols → fast **freebase** absorption → high addictiveness.
- ▶ **5 A's**: Ask–Advise–Assess–Assist–Arrange; brief advice makes quitting **1.6×** more likely.
- ▶ **Varenicline** (partial nicotinic agonist) is most effective monotherapy (**3.1×**); **NRT doubles** success; **bupropion** contraindicated in seizures.
- ▶ Cessation benefits: coronary risk falls in **6–12 months**; risk approaches never-smoker by **15 years**; residual 3–4× lung-cancer risk persists.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Nicotine Addiction” (mechanism, relative-risk table, disease manifestations, environmental tobacco smoke, cessation framework, pharmacologic efficacy multipliers and dosing); “Promoting Good Health” (preventive context).
- ▶ **CMDT 2026** — “Disease Prevention & Health Promotion” (smoking-cessation counselling, Table 1–4 inquiries, Table 1–5 medication doses for NRT/bupropion/varenicline, weight gain, e-cigarette/EVALI caution).

Coverage note: The spec lists no dedicated subspecialty textbook (specialty = GENERAL); the answer is fully grounded in Harrison 22e and CMDT 2026. The “5 A's” labelling follows the standard AT/USPHS clinical-practice framework — Harrison's Table 465-2 lists the same actions (Ask, Advise, Identify-those-willing/Assess, Assist, Arrange).



Delayed (Type IV) Hypersensitivity Reactions

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — *Hypersensitivity* denotes an exaggerated or inappropriate adaptive immune response to an antigen that causes tissue injury. In the **Gell and Coombs classification** (Types I–IV), **Type IV (delayed, cell-mediated) hypersensitivity** is the only type that is *antibody-independent*: it is mediated by **antigen-specific T lymphocytes** (CD4⁺ T-helper and CD8⁺ cytotoxic T cells) and the macrophages/eosinophils/neutrophils they recruit. It is termed “delayed” because the reaction develops **48–72 hours** after antigen exposure in a sensitised host — the time required to recruit and activate

effector T cells — in contrast to the immediate (minutes) reaction of Type I. The classic prototypes are the tuberculin (Mantoux) skin reaction, allergic contact dermatitis, granuloma formation, and severe cutaneous adverse drug reactions (SJS/TEN, DRESS).

Gell and Coombs classification — placing Type IV in context

Type	Eponym / name	Principal mediator	Onset	Representative examples
I	Immediate / anaphylactic	IgE on mast cells & basophils (TH2/ILC2: IL-4, IL-5, IL-13)	Minutes	Anaphylaxis, urticaria, angioedema, allergic asthma/rhinitis
II	Cytotoxic (antibody-mediated)	IgG/IgM + complement; ADCC by NK cells/phagocytes	Variable	Autoimmune haemolytic anaemia, drug-induced cytopenias, Goodpasture, Graves
III	Immune-complex	Antigen–antibody (IgG/IgM) complexes → complement, neutrophils	Hours–days	Serum sickness, Arthus reaction, SLE, post-streptococcal glomerulonephritis, drug-induced vasculitis
IV	Delayed / cell-mediated	T cells (CD4 TH1/TH2/TH17, CD8 CTL) + macrophages/eosinophils/neutrophils	48–72 h	Tuberculin reaction, contact dermatitis, granulomas, SJS/TEN, DRESS, allograft rejection

- Types I–III are antibody (humoral)-mediated and transferable by serum; Type IV is cell-mediated and transferable only by sensitised T cells/lymphocytes, not by serum.

Mechanism — two sequential phases

1. Sensitisation (afferent/induction) phase — occurs on *first* contact, evolving over ~10–14 days, and is clinically silent:

- The antigen is often a **low-molecular-weight hapten** (e.g., nickel, urushiol of poison ivy, a drug or its metabolite) that must **covalently bind a self carrier-protein** to become immunogenic (*hapten–prohapten model*); some drugs bind **non-covalently** to the HLA molecule or T-cell receptor (the **pharmacological interaction “p-i” model**, e.g., abacavir within HLA-B*57:01).

- ▶ **Antigen-presenting cells** — cutaneous **Langerhans/dendritic cells** — process the antigen and migrate to regional lymph nodes, presenting peptide on MHC class II to naïve CD4⁺ T cells and on MHC class I to CD8⁺ T cells.
- ▶ Under IL-12/IFN- γ this drives **clonal expansion and differentiation into effector and memory TH1 (also TH2, TH17) and cytotoxic CD8⁺ T cells**.

2. Effector (elicitation) phase — occurs on *re-exposure*, peaking at 48–72 h:

- ▶ Sensitised CD4⁺ TH1 cells recognise antigen and secrete IFN- γ , TNF- α and IL-2, which **recruit and activate macrophages**, increasing their microbicidal and tissue-damaging capacity.
- ▶ CD8⁺ cytotoxic T cells kill target cells directly via **perforin, granzyme B and granulysin** (the dominant cytolytic mediator of keratinocyte death in SJS/TEN).
- ▶ Persistent, indigestible antigen $\rightarrow$ chronic macrophage activation $\rightarrow$ transformation into **epithelioid and multinucleate giant cells** $\rightarrow$ **granuloma** formation (e.g., tuberculosis, leprosy, sarcoidosis, fungal infection).

Subclassification of Type IV (Pichler) — by effector cell and cytokine

Harrison (adapted from Jutel *et al*, *Allergy* 2023) subdivides cell-mediated reactions by the dominant effector arm:

Subtype	Effector cells	Key cytokines/mediators	Final effector	Clinical correlate
IVa (T1)	TH1, ILC1, Tc1, NK	IFN- γ , TNF- α , granzyme B, perforin, granulysin	Macrophage activation $\rightarrow$ granuloma	Tuberculin reaction, granulomatous disease, allergic contact dermatitis
IVb (T2)	TH2, ILC2, Tc2, NK-T	IL-4, IL-5, IL-9, IL-13, IL-31	Eosinophil inflammation	DRESS/DIHS, maculopapular exanthem with eosinophilia
IVc (T3)	TH17, ILC3, Tc17	IL-17, IL-22, IL-23, CXCL8 (IL-8), GM-CSF	Neutrophil inflammation	AGEP, neutrophilic drug eruptions

- ▶ The *classic four-part Pichler scheme* additionally separates **Type IVc = CD8⁺ cytotoxic reactions** (SJS/TEN, fixed drug eruption) and **Type IVd = neutrophil-rich reactions** (AGEP) — both are universally taught and worth naming.

Clinical examples — organised by category

- ▶ Diagnostic skin tests (in-vivo DTH):

- **Tuberculin / Mantoux (TST):** intradermal PPD (purified protein derivative, standard PPD-S/RT23); reaction read at **48–72 h** as induration. Cellular basis = previously sensitised **CD4⁺ T cells** attracted to the skin site producing cytokines. CDC cut-offs: **≥5 mm** (HIV, recent TB contacts, organ-transplant/immunosuppressed, fibrotic CXR), **≥10 mm** (recent immigrants, injection drug users, lab/congregate-setting staff, children <5 y), **≥15 mm** (low-risk persons). Modern equivalents — **TBST** and **IGRAs** (QuantiFERON-TB Gold Plus, T-SPOT.TB) use TB-specific antigens **ESAT-6 and CFP-10**.
- **Lepromin test** (tuberculoid leprosy), **Candida**, **mumps**, **trichophyton** (anergy panel) — assess intact cell-mediated immunity; *anergy* indicates impaired DTH (HIV, sarcoid, malnutrition, overwhelming TB).
- ▶ **Infective / granulomatous DTH:** tuberculosis (caseating granuloma; the tissue damage and cavitation are largely DTH-mediated), tuberculoid leprosy, leishmaniasis, deep fungal infection, schistosome-egg granuloma.
- ▶ **Allergic contact dermatitis (prototype skin DTH):** sensitisers include **nickel**, **urushiol** (poison ivy/oak), **potassium dichromate**, **neomycin/bacitracin/polymyxin B**, **formaldehyde**, **paraphenylenediamine**, **adhesive tape**. *Allergic* contact dermatitis (a DTH, lag ~48 h on re-challenge) is distinguished from *irritant* dermatitis (non-immune, onset within hours); confirmed by **patch testing**. *Systemic contact dermatitis/SDRIFE* follows systemic exposure to a previously contact-sensitising drug.
- ▶ **Drug-induced delayed hypersensitivity (T-cell-mediated):** **morbilliform/maculopapular exanthem** (commonest), **fixed drug eruption** (sulfonamides, NSAIDs, tetracyclines), **DRESS/DIHS** (eosinophilia, facial oedema, hepatitis; aromatic anticonvulsants, allopurinol, vancomycin, sulfonamides), **AGEP** (sterile pustules), **SJS/TEN** (full-thickness epidermal necrosis; granulysin-mediated). Strong **HLA-restricted pharmacogenomic associations:** ***HLA-B57:01**–abacavir (**100% negative predictive value; PREDICT-1**), **HLA-B15:02**–*carbamazepine* **SJS/TEN** (*Han Chinese*), **HLA-B58:01**–allopurinol **DRESS/SJS-TEN**, **HLA-A32:01**–*vancomycin* **DRESS**, **HLA-B13:01**–dapson; **CYP2C93*** slow metabolism predisposes to phenytoin reactions.
- ▶ **Transplantation: acute cellular allograft rejection** and **graft-versus-host disease** are T-cell-mediated (Type IV).
- ▶ **Cell-mediated autoimmunity (DTH component):** type 1 diabetes mellitus, Hashimoto thyroiditis, multiple sclerosis, rheumatoid arthritis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Two-phase mechanism of Type IV hypersensitivity.** Labels: *Hapten + carrier protein; Langerhans/dendritic cell (APC); MHC II → naïve CD4⁺ T cell; MHC I → CD8⁺ T cell; regional lymph node — clonal expansion; Sensitisation phase (10–14 days); Memory/effector TH1 + cytotoxic CD8⁺ T cells; Re-exposure; Effector phase (48–72 h); IFN-*

γ , TNF- α $\rightarrow$ macrophage activation; Perforin/granzyme/granulysin $\rightarrow$ target-cell death; epithelioid & giant cells $\rightarrow$ granuloma.

- ▶ **Diagram 2 — Tuberculin (Mantoux) reaction.** Labels: Intradermal PPD (forearm); Read at 48–72 h; measure induration (not erythema) in mm; cut-offs ≥ 5 / ≥ 10 / ≥ 15 mm.

Clinical / Diagnostic significance

- ▶ **Diagnostic use:** DTH skin tests (tuberculin, lepromin, anergy panel) detect prior sensitisation and gauge intact cell-mediated immunity; *anergy* flags immunodeficiency.
- ▶ **Granuloma = protective yet pathogenic:** the same DTH that walls off intracellular organisms (*M. tuberculosis*, *M. leprae*) also causes the caseation, cavitation and tissue destruction of disease.
- ▶ **Management of contact dermatitis:** identify and remove the allergen; **patch testing** to confirm; topical (or short systemic) glucocorticoids; emollients.
- ▶ **Severe cutaneous adverse drug reactions (SCARs):** SJS/TEN, DRESS and AGEP are dermatological emergencies — **immediate withdrawal of the culprit drug**, supportive/burns-unit care, and monitoring for late autoimmune sequelae (thyroiditis, diabetes) in DRESS.
- ▶ **Pharmacogenomic screening prevents disease:** pre-prescription *HLA-B57:01 testing before **abacavir**, and HLA-B15:02 before **carbamazepine** (and HLA-B58:01** before **allopurinol** in at-risk groups) avert life-threatening reactions.
- ▶ DTH underlies the efficacy read-out of **BCG vaccination** and the immunology of **granulomatous diseases** (sarcoidosis, Crohn's, berylliosis).

High-yield exam pointers

- ▶ Type IV is the **only antibody-independent Gell–Coombs type** — T-cell mediated, transferable by lymphocytes, not serum.
- ▶ Reaction is “**delayed**” — **peaks at 48–72 h**; two phases: **sensitisation (10–14 d)** then **elicitation (48–72 h)**.
- ▶ Effector arms: CD4 TH1 $\rightarrow$ IFN- γ $\rightarrow$ macrophage activation/granuloma; CD8 CTL $\rightarrow$ perforin, granzyme, granulysin $\rightarrow$ cytotoxicity.
- ▶ **Tuberculin test** read at 48–72 h; measure **induration in mm** (not erythema); cut-offs 5/10/15 mm; modern IGRA uses **ESAT-6 & CFP-10**.
- ▶ **Allergic contact dermatitis** (nickel, poison ivy/urushiol, chromate, neomycin) — diagnosed by **patch test**; *irritant* type is non-immune and faster.
- ▶ **SCARs are Type IV:** SJS/TEN, DRESS, AGEP, morbilliform, fixed drug eruption — first step is **stop the drug**.
- ▶ **Memorise HLA links:** B57:01–**abacavir**, B15:02–**carbamazepine**, B58:01–**allopurinol**, A32:01–**vancomycin**, B*13:01–**dapsone**.

- ▶ Acute cellular allograft rejection and GVHD are clinically important Type IV reactions.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Introduction to the Immune System” (T-cell subsets, TH1/TH17, granuloma/macrophage activation); “Cutaneous Drug Reactions” (Revised immune-pathway classification Table 63-1 with Type IVa/IVb/IVc, HLA-pharmacogenomic associations, SJS/TEN/DRESS/AGEP); “Eczema, Psoriasis... (dermatitis)” (allergic vs irritant contact dermatitis, patch testing); “Tuberculosis” (skin-test reactivity as delayed-type hypersensitivity, PPD, TST cut-offs Table 183-5, IGRA/ESAT-6/CFP-10).
- ▶ **Coverage note:** The Gell–Coombs four-type framework is presented across the immunology, allergy/pulmonary-diagnostics and drug-reaction chapters rather than as a single dedicated table; the classic two-phase DTH mechanism, the 10–14-day sensitisation interval, the Pichler IVc/IVd cytotoxic-vs-neutrophil subdivision, and standard contact allergens/anergy-panel antigens are universally accepted textbook immunology used to complete the answer.



Nucleotide Repeat Expansion Disorders

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Nucleotide (most commonly *trinucleotide* / *triplet*) repeat expansion disorders are a distinct class of human genetic disease caused by **dynamic mutations** — tandemly repeated short DNA sequences that are intrinsically unstable and **expand beyond a critical threshold copy number**, with progressive lengthening of the repeat both across generations (germline) and within tissues (somatic). They were first recognised as the cause of *fragile X syndrome*, and now encompass several common neurological diseases (Huntington's disease, myotonic dystrophy, Friedreich's ataxia, spinocerebellar ataxias). Their hallmark clinical signature is **genetic anticipation** — earlier onset and greater severity in successive generations.

Molecular basis and key concepts

- ▶ **Mechanism of expansion** — repeats expand through **unequal recombination (crossing-over)** and **slipped-strand mispairing** during DNA replication; once an expansion is present the DNA fragment is unstable and tends to expand further during cell division.
- ▶ **Premutation → full mutation** — a *premutation* is a small increase in repeat copy number; the carrier may be phenotypically normal or mildly affected, but in subsequent generations the expanded repeat may increase further in length, producing an increasingly severe phenotype — the essence of a **dynamic mutation**.

- ▶ **Anticipation** — when repeat length increases from one generation to the next, disease manifests earlier and more severely. In Huntington's disease there is a direct correlation between age of onset and triplet-codon length; documented across many repeat disorders.
- ▶ **Repeat length–phenotype correlation** — larger expansions → younger onset and more aggressive disease (well shown in SCA1, SCA7, DRPLA, SBMA).
- ▶ **Somatic / tissue-specific instability** — repeat number can vary between tissues; e.g., in myotonic dystrophy the CTG repeat may be ~10-fold larger in muscle than in lymphocytes.
- ▶ **Parent-of-origin effect** — paternal transmission tends to cause greater expansion (HD, SCA7, DRPLA), whereas the severe **congenital form of myotonic dystrophy** occurs almost exclusively with maternal transmission.

Classification by repeat location and pathogenic mechanism

Repeat disorders are best grouped by *where* the repeat lies and *how* it injures the cell:

Group	Repeat / location	Pathogenic mechanism	Examples
Coding (exonic) CAG	CAG in coding exon → polyglutamine (polyQ) tract	Toxic gain-of-function of mutant protein; β -pleated aggregates form neuronal intranuclear inclusions	Huntington's disease, SBMA (Kennedy), SCA1/2/3/6/7/12/17, DRPLA
Non-coding — loss of function	CGG in 5'UTR; GAA in intron	Hypermethylation/gene silencing or reduced gene expression	Fragile X (FMR1), Friedrich's ataxia (frataxin)
Non-coding — RNA toxic gain	CTG/CCTG in untranslated region/intron	Mutant RNA forms nuclear foci that sequester splicing proteins	Myotonic dystrophy DM1 (DMPK), DM2 (CNBP)
Larger/other repeats (non-coding)	Hexanucleotide GGGGCC; pentanucleotide AAGGG; intronic GAA	RNA foci, dipeptide-repeat proteins, haploinsufficiency	C9orf72 ALS/FTD, RFC1-CANVAS, SCA27B (FGF14)

- ▶ **Polyglutamine (polyQ) diseases** share a unifying biology: expanded CAG encodes glutamine; ataxins/huntingtin with >~40 glutamines undergo conformational change to a β -pleated structure, accumulate in neuronal nuclei, bind and impair the TATA-binding protein and CREB-binding protein, overwhelm the **ubiquitin–proteasome system**, impair autophagy, and induce neuronal apoptosis.

Representative disorders (with genetic detail)

Selected trinucleotide repeat disorders (Harrison *Table 479-5*):

Disease	Locus	Repeat	Normal / Disease range	Inheritance	Gene product
Spinobulbar muscular atrophy (Kennedy, SBMA)	Xq12	CAG	11–34 / 40–62	XR	Androgen receptor
Fragile X (FRAXA)	Xq27.3	CGG	6–50 / 200–300	XR	FMR-1 protein (FMRP)
Fragile X (FRAXE)	Xq28	GCC	6–25 / >200	XR	FMR-2 protein
Myotonic dystrophy (DM1)	19q13.32	CTG	5–30 / 200–1000	AD	Myotonin protein kinase (DMPK)
Huntington's disease (HD)	4p16.3	CAG	6–34 / 37–180	AD	Huntingtin
SCA1	6p22.3	CAG	6–39 / 40–88	AD	Ataxin-1
SCA2	12q24.12	CAG	15–31 / 34–400	AD	Ataxin-2
SCA3 / Machado-Joseph disease	14q32.12	CAG	13–36 / 55–86	AD	Ataxin-3
SCA6	19p13	CAG	4–16 / 20–33	AD	$\alpha 1A$ voltage-gated Ca^{2+} channel (CACNA1A)
SCA7	3p14.1	CAG	4–19 / 37 to >300	AD	Ataxin-7
SCA12	5q32	CAG	6–26 / 66–78	AD	Protein phosphatase 2A
DRPLA	12p13.31	CAG	7–23 / 49–75	AD	Atrophin-1
Friedreich's ataxia (FRDA1)	9q21.11	GAA	7–22 / 200–900	AR	Frataxin

- **Huntington's disease** — AD, *huntingtin* on 4p16.3, CAG >40 fully penetrant (intermediate 36–39 with reduced penetrance). Onset 25–45 yr; chorea early, evolving to dystonia, rigidity, bradykinesia and myoclonus; behavioural disturbance, depression with suicidality, and dementia. The **Westphal variant** (akinetic-rigid) affects ~10%, usually juvenile-onset. MRI shows

caudate (head) and putamen atrophy with enlarged frontal horns; intranuclear ubiquitin + huntingtin inclusions. Expansion is greater with **paternal** transmission. Tetrabenazine, **deutetrabenazine** and valbenazine treat chorea; antisense oligonucleotide trials ongoing.

- ▶ **Myotonic dystrophy** — commonest adult muscular dystrophy. **DM1** = unstable CTG repeat in 3' untranslated region of *DMPK* (chr 19); “hatchet face”, frontal balding, grip/percussion myotonia, posterior subcapsular cataracts, cardiac conduction block (sudden death), insulin resistance, hypersomnia, testicular atrophy. **Congenital DM1** in ~25% of infants of affected mothers. **DM2 / PROMM** = CCTG repeat in intron 1 of *CNBP (ZNF9)*, predominantly proximal. Both act by an **RNA toxic gain-of-function** — mutant RNA forms intranuclear inclusions that sequester splicing proteins, causing mis-splicing of multiple transcripts. Mexiletine for myotonia; pacemaker/ICD for conduction disease.
- ▶ **Friedreich’s ataxia** — most common inherited ataxia (AR); homozygous **GAA** expansion in intron 1 of *frataxin* (chr 9) in >95%; **loss of frataxin expression**. Onset <25 yr: progressive gait ataxia, **areflexia with extensor plantar responses**, loss of vibration/position sense, dysarthria, pes cavus, scoliosis; **hypertrophic cardiomyopathy in 90%** and **diabetes in 20%**. Frataxin is a mitochondrial iron-homeostasis protein; its loss causes mitochondrial iron accumulation and oxidative injury. **Omaveloxolone** (NRF2 agonist) is the first FDA-approved drug.
- ▶ **Spinocerebellar ataxias** — polyQ “ataxins”; **SCA3/MJD** is the most common AD ataxia worldwide; **SCA7** is uniquely associated with **retinal pigmentary/macular degeneration** (blue-yellow colour blindness). Genotype is the diagnostic gold standard.
- ▶ **SBMA (Kennedy’s disease)** — XR, CAG in exon 1 of the **androgen receptor**; lower-motor-neuron bulbar and limb weakness with **androgen insensitivity** (gynaecomastia, reduced fertility); inverse correlation between repeat number and age of onset.
- ▶ **Fragile X syndrome** — commonest inherited cause of intellectual disability; CGG in 5'UTR of *FMRI*; **full mutation (>200)** triggers promoter **hypermethylation and gene silencing**, loss of FMRP.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Dynamic mutation and anticipation (pedigree):** A three-generation pedigree (I → II → III) with the repeat tract drawn beside each affected member showing increasing length. Labels: *Normal (stable allele) → Premutation → Full mutation; Slipped-strand mispairing / unequal crossing-over; Increasing CAG repeat number; Anticipation = earlier onset + increasing severity; Paternal vs maternal transmission bias.*
- ▶ **Diagram 2 — Classification tree by repeat location/mechanism:** Root “Repeat expansion disorders” branching to (a) *Coding CAG → polyglutamine → toxic protein gain-of-function* (HD, SCA1/2/3/6/7, SBMA, DRPLA — neuronal intranuclear inclusions); (b) *Non-coding loss-of-function* (CGG–FMR1 fragile X; GAA–frataxin Friedreich’s); (c) *Non-coding RNA*

toxic gain (CTG–DMPK DM1; CCTG–CNBP DM2 — RNA nuclear foci). Label each branch with repeat type, gene and mechanism.

Clinical / Diagnostic significance

- ▶ **Diagnosis** — repeat sizing by PCR (small alleles) and Southern blot (large expansions); genotype is the gold standard for SCAs and confirms HD, DM, FRDA. Triplet-repeat sizing also enables **prenatal diagnosis** (e.g., myotonic dystrophy).
- ▶ **Genetic counselling is mandatory** — presymptomatic/predictive HD testing must be done with trained counsellors because disclosure can precipitate depression and suicide; anticipation and parent-of-origin effects must be explained to families.
- ▶ **Phenotype prediction** — repeat length broadly predicts severity and age of onset and helps anticipate the more severe congenital DM1 in offspring of affected mothers.
- ▶ **Therapeutics** — symptomatic for most (tetrabenazine/deutetrabenazine for HD chorea; mexiletine + cardiac pacing for DM); **omaveloxolone** for Friedreich's ataxia; **antisense oligonucleotide / RNA-lowering and gene-editing (CRISPR)** strategies are in trials for HD and others.

High-yield exam pointers

- ▶ **Dynamic mutation** = unstable repeat expanding beyond a threshold; **first described in fragile X**.
- ▶ **Anticipation** = earlier onset + worse disease in successive generations with longer repeats — the defining clue.
- ▶ **CAG = polyglutamine diseases** (HD, SCA1/2/3/6/7/17, SBMA, DRPLA) → **toxic gain-of-function**, neuronal **intranuclear inclusions**, threshold ~**40 glutamines**.
- ▶ **HD**: chr 4p16.3, CAG >40 (36–39 reduced penetrance); caudate atrophy; Westphal variant; paternal anticipation.
- ▶ **Myotonic dystrophy**: DM1 = CTG in DMPK 3'UTR (chr 19); DM2 = CCTG in CNBP/ZNF9; **RNA gain-of-function**; congenital form via affected mother.
- ▶ **Friedreich's ataxia**: GAA in intron 1 of frataxin, AR, **loss of function**; areflexia + upgoing plantars, HCM, diabetes; omaveloxolone.
- ▶ **Fragile X** (CGG, FMR1) and **Friedreich's** (GAA) = **loss-of-function**; remember they are the non-coding exceptions to the polyQ rule.
- ▶ **SCA7** = ataxia + **retinal degeneration**; **SCA3/MJD** = commonest AD ataxia.
- ▶ Newer **non-triplet repeats**: C9orf72 GGGGCC hexanucleotide (commonest familial ALS/FTD), RFC1 AAGGG (CANVAS), FGF14 GAA (SCA27B).

SOURCE & COVERAGE

- ▶ Harrison's *Principles of Internal Medicine*, 22e — “Principles of Human Genetics” (Jameson & Kopp; unstable DNA sequences, dynamic mutation, anticipation, *Table 479-5* Selected Trinucleotide Repeat Disorders); “Ataxic Disorders” (SCAs, Machado-Joseph, Friedreich's ataxia, DRPLA, polyglutamine biology); “Tremor, Chorea, and Other Movement Disorders” (Huntington's disease genetics, MRI, treatment, HDL disorders); “Muscular Dystrophies and Other Muscle Diseases” (myotonic dystrophy DM1/DM2, DMPK/CNBP, RNA toxicity); plus the motor neuron disease chapter (Kennedy's/SBMA) and the ALS/frontotemporal dementia chapters (C9orf72 GGGGCC hexanucleotide expansion).
- ▶ Coverage note: The corpus covers this topic well. Fragile X is detailed mainly through *Table 479-5* genetics (gene, locus, repeat ranges, loss-of-function silencing) rather than a dedicated clinical fragile-X chapter; FXTAS (the premutation-associated tremor/ataxia syndrome) is not separately described in the searched chapters, so it is not emphasised here.



Problems in Old Age and Their Management (Geriatric Syndromes)

Asked in: Paper IV Jun 2024 — RGUHS MD General Medicine

Definition / Introduction — *Geriatric medicine* addresses the health of older adults (conventionally ≥ 65 years), in whom illness is shaped less by single organ disease than by *multimorbidity*, diminished physiologic reserve and impaired function. Ageing itself is not a disease: normal ageing changes do not cause symptoms but increase susceptibility to disease. The characteristic clinical problems of old age — the *geriatric syndromes* (falls, incontinence, delirium/dementia, frailty, polypharmacy) — are multifactorial, often atypical in presentation, under-diagnosed and frequently reversible. Their management is *person-centred*: function, comfort, quality of life and what “matters most” to the patient supersede cure.

Principles of care — the “5 M's” and comprehensive geriatric assessment

- ▶ The modern framework for caring for older adults is the 5 M's of geriatrics: **Mentation** (cognition, mood, delirium), **Mobility** (gait, falls), **Medication** (polypharmacy, deprescribing), **Multicomplexity** (multimorbidity, geriatric syndromes) and **Matters Most** (goals of care). This reframes care from a disease-driven to a person-centred paradigm.
- ▶ **Comprehensive Geriatric Assessment (CGA)** is the cornerstone — a multidimensional, interdisciplinary evaluation of medical conditions, functional status (basic and instrumental

Activities of Daily Living), cognition/affect, social support, nutrition and a “geriatric review of systems” using validated screens.

- ▶ Key principles: conditions are multiple and multifactorial; iatrogenic illness (adverse drug reactions, immobility, deconditioning) is common; many treatable problems (fall risk, incontinence, elder abuse) are missed; and care is mostly delivered outside hospital with vulnerable *care transitions*.

Falls and immobility

- ▶ **Epidemiology:** about *one in three* community-dwelling older people and *one in two* long-term-care residents fall annually; complications (hip/wrist fracture, subdural haematoma) are a leading cause of injury death after 65.
- ▶ **Causes are multifactorial** — intrinsic (postural hypotension, arrhythmia, aortic stenosis, Parkinson’s disease, neuropathy, visual impairment, cognitive impairment, muscle weakness, foot disorders) and extrinsic (sedatives, antihypertensives, environmental hazards). Up to half of “unexplained falls” in dementia are due to near-syncope from postural hypotension. Always exclude *syncope* and *seizure*.
- ▶ **Screen** every older person: “Have you fallen in the past year?”, “Are you afraid of falling?”, “Trouble rising from a chair?” Assess with the **Get Up and Go test**.
- ▶ **Management** is multifactorial: physical therapy for strength and balance, ***Tai Chi** (*proven in trials*), medication review/*withdrawal*, treat postural hypotension and arrhythmia, correct vision, podiatry/footwear, home-hazard modification, fall-alert system and hip protectors in selected patients. Vitamin D ≥ 800 IU/day is reasonable, but high-dose vitamin D (60,000 IU monthly) increases falls and should be avoided. Patients fracturing after a fall must be evaluated and treated for osteoporosis*.
- ▶ *Immobility* and hospital bed-rest cause deconditioning, muscle loss, pressure injury, venous thromboembolism and functional decline — early mobilisation is preventive.

Polypharmacy and prescribing

- ▶ **Polypharmacy** (commonly ≥ 5 simultaneous drugs): ~40% of those ≥ 65 take 5–9 drugs and ~20% take ≥ 10 . It magnifies adverse drug events ($>100,000$ hospitalisations/year), chiefly from *warfarin/antiplatelets*, *insulin/hypoglycaemics* and cardiovascular drugs.
- ▶ **Evaluation:** medication reconciliation at every visit and especially at care transitions; match each drug to an indication; watch for the **prescribing cascade** (e.g. treating amlodipine-induced oedema with a diuretic).
- ▶ **Deprescribing tools:** the AGS *Beers criteria* (potentially inappropriate medications) and the STOPP** (Screening Tool of Older Persons’ Prescriptions) criteria. Common deprescribing targets: benzodiazepines/hypnotics, anticholinergics, PPIs without indication, hypoglycaemics causing tight control, and statins near end of life.

- **Safe geriatric prescribing:** “start low, go slow”; minimise drug number; estimate renal function (Cockcroft–Gault, which safely under-estimates clearance) and adjust renally-cleared drugs; simplify regimens and use adherence aids.

Cognitive disorders — delirium and dementia

Feature	Delirium	Dementia
Onset	Acute, <i>fluctuating</i>	Insidious, progressive
Attention	Impaired (hallmark)	Preserved early
Course	Usually reversible	Chronic, often irreversible
Consciousness	Often altered	Clear until late

- **Delirium** occurs in up to **40% of hospitalised** older patients; it is a *medical emergency* signalling underlying illness. Diagnose with the **Confusion Assessment Method (CAM)**: acute onset + fluctuating course **and** inattention **plus** disorganised thinking *or* altered consciousness. Identify precipitants (drugs, infection, electrolytes, hypoxia, pain, retention, impaction). Manage by treating the cause, reorientation, sensory aids, mobilisation, sleep hygiene; reserve low-dose **risperidone (0.25–0.5 mg)** or **quetiapine (12.5–50 mg)** for danger or psychosis. Avoid benzodiazepines (except alcohol withdrawal).
- **Dementia:** by age 85, **30–40%** have dementia; **>20%** of those over 70 have mild cognitive impairment (MCI), **15–20%/year** of whom progress. Alzheimer’s and vascular dementia (often coexisting) predominate; *dementia with Lewy bodies* (~25%) features early parkinsonism, fluctuating attention and visual hallucinations. Screen with the **Mini-Cog** (3-item recall + clock draw); confirm with MoCA/MMSE plus neuroimaging and reversible-cause labs (B12, TSH, metabolic). Manage with non-pharmacological measures, cholinesterase inhibitors/memantine (modest benefit, GI and bradycardia effects), treat depression, and avoid antipsychotics for behavioural symptoms unless dangerous.

Urinary incontinence, sleep, frailty and other syndromes

- **Urinary incontinence/overactive bladder:** affects ~1 in 3 older women and 15–20% of men; precipitates falls, social isolation and institutionalisation. Types: **stress, urge, mixed, overflow, functional**; distinguish with the **3 Incontinence Questions (3IQ)**. Exclude reversible causes (UTI, atrophic vaginitis, drugs, impaction, hyperglycaemia, CHF). Check **post-void residual** (>200 mL abnormal). Treat with pelvic-floor (*Kegel*) and behavioural therapy, **antimuscarinics** or **β3-agonists** for urge, α-blockers ± 5α-reductase inhibitor in men.
- **Sleep disorders:** insomnia (~30%), obstructive sleep apnoea (~10%), restless legs (5–10%) and periodic limb movements. Treat with sleep hygiene/stimulus-control first; if needed use **melatonin** or **low-dose trazodone** — avoid chronic benzodiazepine hypnotics (hangover, falls).

- ▶ **Frailty:** a syndrome of reduced physiologic reserve. The **Fried phenotype** requires ≥ 3 of five criteria — *unintentional weight loss, weakness (grip), exhaustion, slowness (gait speed), low physical activity*; the **Rockwood Frailty Index** is a deficit-accumulation measure. Prevalence $\sim 10\text{--}14\%$ in the community, rising with age. Manage with structured **exercise (resistance + aerobic)**, protein/nutritional supplementation, polypharmacy reduction and treatment of comorbidity.
- ▶ **Pressure injuries, malnutrition/weight loss, sensory (vision, hearing) impairment and chronic pain** (commonly osteoarthritis) round out the syndromes. For pain, prefer **acetaminophen 1 g 2–3 times daily**, topical NSAIDs/lidocaine, and *duloxetine*; avoid systemic NSAIDs (GI bleed, renal, CHF) in the multimorbid.
- ▶ **Elder abuse and neglect** (incidence $\geq 8\text{--}10\%$ /year, under-reported): physical, psychological, financial, sexual and neglect/self-neglect. Screen privately (“Do you feel unsafe?”, “Has anyone taken your money?”); treat injuries and report to adult protective services.

Management of common chronic diseases — geriatric tailoring

- ▶ **Hypertension:** treat to individualised targets; *HYVET* (≥ 80 years, target ≤ 150 mmHg) reduced stroke, heart failure and mortality; *SPRINT* supported lower systolic targets in selected fit elderly — but beware postural hypotension, falls and syncope.
- ▶ **Diabetes:** relax control — **HbA1c target** $\sim 7.5\%$ in most older adults; **metformin** first line; *avoid glyburide* (hypoglycaemia); avoid sliding-scale insulin. SGLT2 inhibitors aid heart-failure/renal outcomes.
- ▶ **Prevention:** individualise cancer screening to life expectancy; vaccinate against **influenza, pneumococcus, herpes zoster, COVID-19 and RSV**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **The 5 M’s of geriatrics** — a central hub “Matters Most” with four spokes labelled *Mentation, Mobility, Medication, Multicomplexity*.
- ▶ **Multifactorial falls model** — a circle “FALL” with arrows from labelled risk factors: *Postural hypotension, Medications (sedatives/antihypertensives), Visual impairment, Gait/balance & muscle weakness, Cognitive impairment, Foot/footwear problems, Environmental hazards* → leading to outcomes *Hip/wrist fracture, Subdural haematoma, Fear of falling, Loss of function*.

Clinical / Diagnostic significance

- ▶ Atypical disease presentation is the rule — infection may present as delirium or a fall rather than fever; myocardial infarction may be painless.
- ▶ A new **fall, delirium or incontinence** should trigger a search for acute illness, not be dismissed as “ageing”.

- ▶ CGA-based, interdisciplinary models — **Acute Care for the Elderly (ACE) units**, co-management (e.g. ortho-geriatric hip-fracture care) and structured **care-transition programmes** — reduce complications, length of stay and readmission.
- ▶ End-of-life planning matters: **CPR survival is <20%** in hospitalised patients ≥ 65 and near-zero in nursing-home residents; advance directives (living will, POLST, durable power of attorney) and avoidance of feeding tubes in advanced dementia are person-centred standards.

High-yield exam pointers

- ▶ **Geriatric giants/syndromes**: Falls, Incontinence, Delirium/Dementia, Frailty, Polypharmacy (plus immobility, pressure injury, malnutrition, sensory loss).
- ▶ **5 M's**: Mentation, Mobility, Medication, Multicomplexity, Matters Most.
- ▶ **CAM** = acute/fluctuating + inattention + (disorganised thinking *or* altered consciousness).
- ▶ **Fried frailty phenotype** = weight loss, weakness, exhaustion, slowness, low activity (≥ 3 of 5).
- ▶ **Beers and STOPP** criteria identify potentially inappropriate medications; use **Cockcroft–Gault** for renal dosing.
- ▶ Falls: screen (“fallen in past year?”), **Get-Up-and-Go**, Tai Chi, vitamin D 800 IU (avoid high-dose monthly).
- ▶ Older-adult targets: **HbA1c** $\sim 7.5\%$, metformin first line, avoid glyburide; HTN — HYVET/SPRINT.
- ▶ Avoid benzodiazepines for insomnia/delirium; prefer melatonin or low-dose trazodone.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Caring for the Geriatric Patient” (5 M's, CGA, falls, polypharmacy/Beers–STOPP, delirium and dementia, incontinence, sleep, frailty, elder abuse, hypertension/diabetes/pain in older adults, models of care) and “Biology of Aging” (hallmarks of ageing — genomic instability, telomere attrition, cellular senescence, stem-cell exhaustion).
- ▶ **CMDT 2026** — “Geriatric Disorders” (functional screening, delirium work-up, falls risk-factor table and targeted interventions, immobility).



Thermoregulation

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Thermoregulation is the homeostatic process by which the body maintains its **core temperature within a narrow range of 36.5–37.5°C (97.7–99.5°F)** despite wide swings in environmental temperature and in metabolic heat production. It is a classic negative-feedback control system with a central integrator (the **hypothalamic thermoregulatory centre**), afferent thermosensors,

and efferent autonomic, somatic, endocrine and behavioural effectors that continuously balance heat production/gain against heat loss. In a thermoneutral environment the resting metabolic rate generates *more* heat than is needed to hold the core temperature, so the system is biased toward controlled heat dissipation. Disturbance of this loop underlies fever, hyperthermia/heatstroke and hypothermia.

The thermoregulatory control loop — afferent, central, efferent

- ▶ **Central integrator (the “thermostat”):** the **preoptic anterior hypothalamus (POAH)** is the central thermostat; the posterior hypothalamus also participates. Neurons here receive **two kinds of input** which they integrate against a regulated **set point** ($\sim 37^{\circ}\text{C}$):
 - signals from **peripheral warmth/cold receptors in the skin** (cutaneous thermoreception), carried by peripheral nerves; and
 - the temperature of the **blood bathing the hypothalamus** itself (central/core thermoreception).
- ▶ **Comparator action:** if integrated temperature exceeds the set point, heat-loss effectors are driven; if it falls below, heat-conservation and heat-production effectors are driven — until blood temperature again matches the set point.
- ▶ **Efferent (output) limbs:**
 - **Autonomic (immediate defence):** sympathetic control of **cutaneous vasomotor tone** (vasoconstriction to conserve / vasodilation to dissipate heat), **sudomotor (sweating)** activity, and release of **norepinephrine** with increased muscle tone. The autonomic limb is the rapid first responder.
 - **Somatic:** **shivering** thermogenesis via skeletal muscle.
 - **Endocrine (delayed defence):** prolonged cold stimulates the **thyroid axis**, raising basal metabolic rate; antidiuretic hormone and aldosterone also rise with heat stress.
 - **Behavioural:** adding/removing clothing, seeking shade or warmth, altering posture and activity — quantitatively the most powerful and the cheapest defence.

Heat production (thermogenesis) and heat gain

- ▶ **Obligatory (basal) heat:** generated continuously by metabolism in **muscle and liver**; even at rest this exceeds the heat needed to maintain core temperature.
- ▶ **Shivering thermogenesis:** rhythmic involuntary skeletal-muscle contraction; the principal acute mechanism to raise core temperature in cold.
- ▶ **Non-shivering thermogenesis:** heat from the **liver** and metabolic tissues, augmented by sympathetic/thyroid drive, contributing to the rise in core temperature without shivering.
- ▶ **Exercise / exertion:** strenuous exercise can increase heat generation up to **twentyfold**, making exertional heat illness possible even in cool conditions.

- ▶ **Exogenous heat gain:** by **radiation** (a major source of gain in hot climates) and by conduction/convection when ambient temperature exceeds skin temperature.

Heat loss (dissipation) — the four/five physical mechanisms

The skin surface acts as the **radiator** and is the principal site of heat loss; cutaneous **skin blood flow** can increase 25–30 times above basal rate to deliver core heat to the surface, with **compensatory vasoconstriction of the splanchnic and renal beds** to support blood pressure.

Mechanism	Definition	Key quantitative / clinical points
Radiation	Emission of infrared electromagnetic energy to surroundings	~55–65% of heat loss at rest; <i>reverses</i> to become a major heat gain in hot climates
Conduction	Direct transfer of heat to a cooler contacting object	~10–15%; greatly increased in cold water (thermal conductivity of water is 25× that of air); ineffective once ambient > skin temperature
Convection	Loss of heat to moving air currents	Increased in wind ; ineffective once ambient > skin temperature
Evaporation	Latent heat lost as sweat/skin moisture vaporises	The single most efficient mechanism in heat; becomes progressively ineffective when relative humidity > 70%
Respiration	Heat lost in expired air (and respiratory water)	Listed as a fifth mechanism in cold-injury physiology; depends on ambient temperature and humidity

- ▶ The **wet-bulb globe temperature (WBGT)** integrates air temperature, humidity, radiant heat and wind speed, and is superior to the simple “heat index” for assessing environmental heat load.

Normal core temperature and its physiological variation

- ▶ **Mean oral temperature** ≈ 36.6°C (95% CI 35.7–37.3°C); a temperature >37.7°C (99.9°F) — the 99th percentile of healthy individuals — defines fever.
- ▶ **Diurnal rhythm:** lowest around **8 a.m.**, highest around **4 p.m.**; seasonal variation (lower in summer, higher in winter).
- ▶ **Site differences:** rectal temperature is ~0.4°C (0.7°F) **higher** than oral; **lower-oesophageal** temperature best reflects core; unadjusted-mode **tympanic** readings run ~0.8°C (1.6°F) **lower than rectal**.
- ▶ **Menstrual cycle:** at ovulation temperature **rises by ~0.6°C (1°F)** and stays elevated through the luteal phase (progesterone effect).

- **Modifiers:** temperature falls slightly with age ($\sim 0.02^{\circ}\text{C}$ lower per decade), and varies with demographics and comorbidity (e.g., higher in cancer, lower in hypothyroidism).

Integrated responses to cold and heat stress; acclimatisation

Stimulus	Heat conservation/production response	Heat dissipation response
Cold exposure	Cutaneous reflex vasoconstriction (conserves heat); shivering + raised muscle tone; norepinephrine release and non-shivering thermogenesis; delayed thyroid-axis activation; behavioural warming	Suppressed
Heat exposure	Suppressed	Cutaneous vasodilation (skin blood flow up 25–30 $\times$) + diaphoresis/evaporation; splanchnic–renal vasoconstriction to defend BP; behavioural cooling

- **Heat acclimatisation** is a set of adaptations developing over 1 to several weeks of work in the heat: the sweating threshold is lowered, sweat volume increases with a lower salt concentration, plasma volume expands (better cutaneous flow), and the heart rate falls with a higher stroke volume. Sweating rates reach 1–2 L/h in acclimatised individuals. Acclimatisation is lost (“de-acclimatisation”) within weeks of leaving the hot environment.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Thermoregulatory negative-feedback loop (block diagram).** Labels: *Cutaneous warmth/cold receptors* and *temperature of blood* → afferent input → **Preoptic anterior hypothalamus** (set point / comparator) → efferent limbs: (1) Sympathetic — cutaneous vasoconstriction/vasodilation; (2) Sudomotor — sweating; (3) Somatic — shivering; (4) Endocrine — thyroid axis / norepinephrine; (5) Behavioural responses → effectors alter *Heat production vs Heat loss (radiation, conduction, convection, evaporation, respiration)* → **Core temperature** → feedback arrow back to hypothalamus.
- **Set-point diagram — fever vs hyperthermia.** Draw a horizontal “thermostat” line at 37°C . *Fever*: set point raised (e.g., $37 \rightarrow 39^{\circ}\text{C}$) by PGE₂ → body actively conserves/produces heat to reach it (vasoconstriction, shivering, “feels cold”). *Hyperthermia/heatstroke*: set point unchanged at 37°C but core temperature overshoots because heat load exceeds dissipation. Label the OVLT/PGE₂ input on the fever side.

Clinical / Diagnostic significance

- **Fever vs hyperthermia (a must-distinguish):**

Feature	Fever	Hyperthermia (e.g., heatstroke)
Hypothalamic set point	Raised (PGE2-mediated)	Normal / unchanged
Mechanism	Pyrogens → IL-1, IL-6, TNF, IFN → PGE2 (via EP-3 receptor, near the OVLT — organum vasculosum of lamina terminalis) → cAMP → raised set point	Heat load (exogenous + endogenous) overwhelms dissipation; no pyrogens
Skin	Often cold (vasoconstriction), shivering	Hot, dry (classic heatstroke) or sweaty (exertional)
Response to antipyretics	Responds (aspirin/acetaminophen/NSAID lower set point by ↓brain PGE2)	No response — dangerous; needs rapid physical cooling

- **Pyrogen pathway (fever):** exogenous pyrogens (e.g., lipopolysaccharide/endotoxin) → myeloid/endothelial cells release **pyrogenic cytokines** (IL-1, IL-6, TNF) → hypothalamic endothelial PGE2 → glial cAMP → set point reset upward; antipyretics (cyclooxygenase inhibitors) reverse this.
- **Hyperthermia/heatstroke:** core >40.5°C with CNS dysfunction; above 42°C thermosensitive enzymes fail and there is **uncoupling of oxidative phosphorylation**, endothelial injury, heat-shock-protein/cytokine-mediated SIRS, DIC and multiorgan failure. Antipyretics are useless and potentially harmful; treat by rapid cooling (evaporative/immersion) to ~38–39°C.
- **Hypothermia (core <35°C):** failure of heat conservation; the **autonomic** limb (vasoconstriction, shivering) is the immediate defence and the **endocrine** (thyroid) limb the delayed one. The **Osborn (J) wave**, cold diuresis, coagulopathy and “paradoxical undressing” are classic; rewarming risks **core-temperature afterdrop**.
- **Drugs/conditions that impair thermoregulation:** anticholinergics, phenothiazines, tricyclics (impair sweating, depress POAH dopamine), **beta-blockers**, **calcium-channel blockers** and **stimulants** (reduce cutaneous perfusion), and ethanol/anaesthetics (block shivering, cause vasodilation) — all raise heat- or cold-illness risk. Useful differentials of disordered thermoregulation: **malignant hyperthermia**, **neuroleptic malignant syndrome**, **serotonin syndrome**, **thyroid storm**.
- **Metabolic cost of temperature change:** oxygen consumption rises ~13% for every 1°C above 37°C, explaining why fever stresses cardiac/pulmonary/CNS-compromised patients.

High-yield exam pointers

- Central thermostat = **preoptic anterior hypothalamus**; integrates **skin thermoreceptor** input + **blood temperature**; regulated **set point** ~37°C.

- ▶ Normal core 36.5–37.5°C; mean oral 36.6°C; fever defined as >37.7°C (99th percentile).
- ▶ Four/five heat-loss routes: radiation (55–65%), conduction (10–15%), convection, evaporation (most efficient, fails if humidity >70%), respiration.
- ▶ Skin blood flow can rise 25–30×; evaporative sweating up to 1–2 L/h when acclimatised; water conducts heat 25× faster than air.
- ▶ Fever = raised set point (pyrogen→PGE2→EP-3, near OVLT); hyperthermia = normal set point overwhelmed — only fever responds to antipyretics.
- ▶ Efferent limbs: autonomic (immediate) + endocrine/thyroid (delayed) + somatic shivering + behavioural.
- ▶ Acclimatisation (1–several weeks): lower sweat threshold, more sweat with less salt, plasma-volume expansion, lower HR.
- ▶ O2 consumption ↑13% per 1°C rise; ovulation raises core by ~0.6°C; rectal is 0.4°C > oral.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Fever” (Dinarelllo & Surana; thermoregulatory centre, set point, normal temperatures and variation, fever vs hyperthermia, pyrogen/PGE2 pathway, antipyretic mechanism); “Heat-Related Illnesses” (Danzl; thermoregulation, heat-dissipation mechanisms, skin blood flow, acclimatisation, heatstroke); “Hypothermia and Peripheral Cold Injuries” (Danzl; five heat-loss mechanisms with percentages, autonomic vs endocrine defence of thermoneutrality).
- ▶ **Coverage note:** This is a basic-physiology (anatomy/physiology) question; the RGUHS spec lists **no dedicated specialty textbook**, and Harrison covers thermoregulation only as it is embedded within the Fever, Heat-Related-Illness and Hypothermia chapters (spec flagged as a thin/”gap” topic). The answer therefore synthesises these three chapters; the underlying control-loop framework (afferent–integrator–efferent limbs, shivering/non-shivering thermogenesis, behavioural responses) is universally accepted standard physiology and is stated only where consistent with the cited Harrison text. Cell-physiology depth (e.g., brown-adipose-tissue UCP-1 mechanism, TRP-channel thermoreceptors) is not elaborated in this corpus and has been omitted rather than fabricated.



DNA replication

Asked in: Paper I Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — DNA replication is the enzymatically catalysed, **semiconservative** process by which a cell duplicates its entire double-stranded genome so that each daughter cell receives an identical copy during division. It exploits the strict **base-pair complementarity** of the double helix (A–

T, G–C): the two parental strands separate and each acts as a **template** for synthesis of a new complementary strand, so every daughter duplex contains one old (parental) and one newly made strand. In humans, ~3 billion base pairs per haploid genome are copied with extraordinary fidelity during the **S phase** of the cell cycle, the accuracy of which is essential to prevent mutation, cancer and inherited disease.

Structure of DNA — the template that makes replication possible

- ▶ DNA is a **double-stranded right-handed helix** of four bases — **adenine (A)**, **thymine (T)**, **guanine (G)**, **cytosine (C)** — with **A pairing T** (2 hydrogen bonds) and **G pairing C** (3 hydrogen bonds) across the helix.
- ▶ The two strands are **antiparallel**: one runs 5'→3', its partner 3'→5'; the sugar–phosphate (deoxyribose–phosphodiester) backbone is on the outside, bases inside.
- ▶ This **complementarity and double-stranded nature permit faithful replication during cell division** and underlie the flow of information DNA → RNA → protein.
- ▶ In the eukaryotic nucleus DNA is packaged with **histones** into **nucleosomes** (core octamer of H2A, H2B, H3, H4; H1 is the linker histone), coiled into **solenoid** fibres and **supercoiled chromatin**, ending in **centromeres** and **telomeres** — all of which must be transiently unpacked and re-assembled as the replication fork passes.

Key enzymes and proteins of the replication machinery

Protein / enzyme	Function
DNA helicase	Unwinds and separates the parental duplex at the fork (ATP-dependent)
Topoisomerase / DNA gyrase	Relieves torsional strain (positive supercoils) ahead of the fork
Single-strand binding (SSB) proteins	Coat and stabilise unwound single strands; prevent re-annealing
Primase (an RNA polymerase)	Synthesises short RNA primers providing a free 3'-OH to start synthesis
DNA polymerase	Adds dNTPs to the 3'-OH; synthesises only 5'→3', reads template 3'→5'; has 3'→5' exonuclease proofreading
Sliding clamp / clamp loader	Tethers polymerase to template for high processivity
DNA ligase	Seals nicks (phosphodiester bonds) between adjacent fragments
Telomerase	Reverse transcriptase that extends 3' chromosome ends (germ/stem/cancer cells)

- ▶ **Polymerase specialisation:** in bacteria, **Pol III** is the main replicase and **Pol I** removes RNA primers and fills the gaps; in eukaryotes, **Pol α /primase** initiates, **Pol δ** extends the lagging strand and **Pol ϵ** the leading strand, while **Pol γ** replicates mitochondrial DNA.

Stages of replication — initiation, elongation, termination

- ▶ **Initiation:** Begins at specific **origins of replication** — a single *oriC* in bacteria but **thousands of origins** along the large eukaryotic chromosomes (permitting timely S-phase completion). Origins are “licensed” once per cycle by the **origin recognition complex (ORC)** and loading of the **MCM helicase**, ensuring DNA is copied **exactly once** per cell cycle. Helicase opens the duplex to form two **replication forks** moving in opposite directions (a **replication bubble**).
- ▶ **Elongation:** Helicase unwinds; SSB and topoisomerase keep the template open and untangled. Primase lays an RNA primer; DNA polymerase extends it 5'→3', incorporating the correct complementary dNTP. Because the two template strands are antiparallel and polymerase works in only one direction, the two new strands are made differently (see below).
- ▶ **Termination:** Forks converge; in eukaryotes adjacent **replicons** merge, RNA primers are excised and replaced with DNA, and ligase joins all fragments into two continuous daughter duplexes. Histones reassemble nucleosomes on the new DNA.

Leading vs lagging strand and Okazaki fragments

Feature	Leading strand	Lagging strand
Direction relative to fork	Same as fork movement	Opposite to fork movement
Synthesis	Continuous	Discontinuous
Primers needed	One (single)	Many (one per fragment)
Product	One long strand	Short Okazaki fragments later ligated
Eukaryotic polymerase	Pol ϵ	Pol δ

- ▶ The lagging strand is built as short segments called **Okazaki fragments** (~100–200 nucleotides in eukaryotes; ~1000–2000 in bacteria), each begun with its own RNA primer; primers are then removed, gaps filled and nicks sealed by **DNA ligase**.

Fidelity, proofreading and DNA repair

- ▶ Replication is remarkably accurate (~1 error per 10^9 – 10^{10} bp) because of (1) correct base selection, (2) 3'→5' **exonuclease proofreading** by polymerase, and (3) post-replication **mismatch repair**.
- ▶ Certain sites are mutation “hot spots”: adjacent pyrimidines (T-T, C-C) form **UV-induced photoadducts/pyrimidine dimers**; methylated CpG cytosines deaminate to thymine causing recurrent C→T (G→A) transitions.

- Repair pathways correcting replication/damage errors — and the diseases caused by their failure:

Repair pathway	Corrects	Disease if defective
Nucleotide excision repair (NER)	Bulky lesions / pyrimidine dimers	Xeroderma pigmentosum
Mismatch repair (MMR) — <i>MutS/MSH2, MLH1</i>	Base mismatches & slippage from replication	HNPCC / Lynch syndrome (colon, endometrial, ovarian cancer)
Homologous recombination — <i>BRCA1/2, Fanconi pathway</i>	Double-strand breaks, inter-strand crosslinks	Hereditary breast/ovarian cancer; Fanconi anaemia

Telomeres, telomerase and the “end-replication problem”

- Because lagging-strand synthesis needs a primer, the extreme 3' end of a linear chromosome cannot be fully copied, so chromosomes **shorten with each division** (telomere attrition) — a marker of replicative ageing/senescence.
- **Telomerase**, a ribonucleoprotein **reverse transcriptase** carrying its own RNA template, adds tandem **TTAGGG** repeats to chromosome ends, counteracting shortening.
- Telomerase is active in germline, stem and most **cancer** cells (conferring replicative immortality) but largely silent in mature somatic tissue — a key link between replication biology and oncogenesis and ageing.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled replication fork:** show parental duplex opened into a “Y”. Label — *parental DNA (3' and 5' template strands), helicase (at fork), single-strand binding proteins, topoisomerase/gyrase (ahead of fork), RNA primer, primase, leading strand (continuous, 5'→3'), lagging strand with Okazaki fragments, DNA polymerase, DNA ligase, direction of fork movement.*
- **Semiconservative replication (Meselson–Stahl) schematic:** one parental double helix → two daughter duplexes, each with one *old (parental)* strand (shaded) and one *new* strand. Label *parental strand, newly synthesised strand, origin of replication, replication bubble/two forks.*

Clinical / Diagnostic significance

- **Cancer:** loss of replication fidelity / repair drives carcinogenesis — MMR defects produce **microsatellite instability** in Lynch syndrome; **BRCA1/2** and Fanconi-pathway defects give breast/ovarian cancer; reactivated **telomerase** sustains tumour growth.
- **Pharmacology:** replication is the target of cytotoxic and antimicrobial drugs — antimetabolites and **fluoropyrimidines/cytarabine/gemcitabine** (block dNTP supply/incorporation), **topoisomerase inhibitors** (irinotecan, etoposide), **alkylating agents** and **fluoroquinolones**

(inhibit bacterial gyrase/topoisomerase) and antiretroviral/antiviral **reverse-transcriptase and polymerase inhibitors**.

- ▶ **Inherited disease:** replication-slippage at unstable repeats causes **trinucleotide-repeat expansion disorders** (e.g., Huntington, fragile X, myotonic dystrophy); unequal crossing-over of tandem repeats causes **CMT1A** (PMP22 duplication).
- ▶ **Diagnostics:** the same complementarity and polymerase chemistry underpin **PCR, next-generation sequencing** and molecular cytogenetics used across modern internal medicine.

High-yield exam pointers

- ▶ DNA replication is **semiconservative** — proven by **Meselson & Stahl**; each daughter duplex = one old + one new strand.
- ▶ DNA polymerase synthesises only **5'→3'** and **needs an RNA primer** made by primase (cannot start de novo).
- ▶ **Leading strand = continuous; lagging strand = discontinuous (Okazaki fragments)** later joined by DNA ligase.
- ▶ Fork proteins: **helicase** (unwinds), **SSB** (stabilises), **topoisomerase/gyrase** (relieves supercoils), **primase, polymerase, ligase**.
- ▶ **Bacteria = one origin (oriC); eukaryotes = many origins**; replication confined to **S phase** and licensed (**ORC/MCM**) to occur **once per cycle**.
- ▶ Fidelity = base selection + **3'→5' proofreading** + **mismatch repair**; MMR failure → **Lynch syndrome / microsatellite instability**.
- ▶ **NER defect** → **xeroderma pigmentosum**; **BRCA/Fanconi defect** → **breast/ovarian cancer, Fanconi anaemia**.
- ▶ **Telomerase** (RNP reverse transcriptase) adds **TTAGGG** repeats, solves the end-replication problem; reactivated in cancers.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — "*Principles of Human Genetics*" (DNA double-helix structure and base-pair complementarity, faithful semiconservative replication, chromatin/nucleosome/telomere organisation, the cell cycle and replication of chromosomes at mitosis, replication-error mutational hot spots, and the DNA-repair pathways with their disease correlations — nucleotide excision repair/xeroderma pigmentosum, mismatch repair/HNPCC–Lynch, BRCA1 and the Fanconi pathway, and trinucleotide-repeat expansion).

Coverage note: Harrison 22e (and the cited chapter) treat DNA structure, chromatin, the cell cycle, replication fidelity and DNA-repair/cancer correlations, but do **not** detail the enzymatic replication-fork machinery. The mechanistic specifics in this answer —

helicase/topoisomerase/SSB/primase/polymerase/ligase, leading- versus lagging-strand synthesis, Okazaki fragments, polymerase subtypes, origin licensing (ORC/MCM) and telomerase chemistry — are drawn from universally-accepted standard molecular biology and are stated to satisfy the full scope of the question; they are not unique claims of the corpus.

♦ ♦ ♦

Down Syndrome (Trisomy 21): Genetic Mechanism, Risk Factors and Clinical Features

Asked in: Paper I Nov 2019 — RGUHS MD General Medicine

Definition / Introduction — Down syndrome is the commonest **autosomal chromosomal (aneuploidy) disorder** compatible with survival and the leading genetic cause of **intellectual disability**. It results from the presence of **three copies of chromosome 21 (trisomy 21)**, or of a rearrangement that produces three copies of the critical long-arm segment of chromosome 21. Nearly **0.5% of all human conceptions are trisomic for chromosome 21**; because of high fetal loss the birth incidence is about **1 in 700**, varying from ~1 in 1000 in young mothers to more than three-fold higher with advanced maternal age. The phenotype reflects a *gene-dosage effect* — over-expression of the genes on the supernumerary chromosome 21.

Cytogenetic basis — three genetic mechanisms

Chromosomal disorders are caused by **numerical (aneuploidy) or structural (translocation, deletion, duplication) aberrations**; such disorders occur in ~1% of the general population, ~8% of stillbirths and close to **50% of spontaneously aborted fetuses** (Harrison). Trisomy 21 arises by three distinct mechanisms:

Mechanism	Karyotype	Approx. share	Origin / key point
Free (standard) trisomy 21	47,XX,+21 or 47,XY,+21	~95%	Meiotic non-disjunction, predominantly in maternal meiosis I; <i>strongly maternal-age dependent</i> ; recurrence risk low (~1%)
Robertsonian translocation	e.g. 46,XX,der(14;21) or der(21;21) — <i>translocation Down syndrome</i>	~4%	Fusion of long arms of an acrocentric chromosome (commonly 14, or 21;21) with chromosome 21; <i>not</i> age-related; ~ $\frac{1}{3}$

Mechanism	Karyotype	Approx. share	Origin / key point
			inherited from a phenotypically normal balanced-translocation carrier parent , giving a substantial recurrence risk
Mosaicism	46,N/47,+21	~1–2%	Post-zygotic non-disjunction at an early mitotic division → two cell lines; phenotype usually milder and variable

- ▶ *Cytogenomic (karyotype/chromosomal microarray) analysis should always be performed* — even though most patients have simple trisomy — to detect **unbalanced translocations**, because such a child may have a parent carrying a **balanced translocation** with a high recurrence risk in future offspring and in that parent's relatives (CMDT).

Mechanism of non-disjunction and gene dosage

- ▶ **Non-disjunction** = failure of paired homologous chromosomes (meiosis I) or sister chromatids (meiosis II) to segregate, so one gamete receives **two copies of chromosome 21** and, after fertilisation by a normal gamete, the zygote is trisomic.
- ▶ The error occurs most often in the **maternal oocyte at meiosis I**; the oocyte pool is arrested from fetal life and only completes meiosis at ovulation, so prolonged arrest predisposes to mis-segregation — the biological basis of the maternal-age effect (rates of **aneuploidy are increased in the female germline**; by contrast new *point* mutations increase with paternal age).
- ▶ **Mosaic trisomy** reflects **mitotic non-disjunction** in the early embryo, producing a normal and a trisomic cell line.
- ▶ The phenotype is a **gene-dosage (over-expression) effect** of the *Down syndrome critical region* on the distal long arm (**21q22**); triplication of genes here (including *APP*) accounts for the major features and for the near-universal Alzheimer pathology.

Risk factors

- ▶ **Advanced maternal age** — the single most important factor. The risk rises *exponentially* and accelerates markedly after **age 35**; by **age 45 the risk is as high as ~1 in 40**, because older oocytes are predisposed to non-disjunction during meiosis (CMDT).
- ▶ **Previous child with trisomy 21** — recurrence in free trisomy is ~1% (age-related risk plus a small increment).

- ▶ **Parental balanced (Robertsonian) translocation carrier** — confers the highest recurrence risk: a *der(21;21)* carrier parent has an effectively ~100% risk, and a *der(14;21)* carrier mother ~10–15% (lower if the father is the carrier).
- ▶ **Parental germline mosaicism** for trisomy 21.
- ▶ *Paternal age does NOT increase the risk of trisomy 21 (CMDT)* — a high-yield discriminator.

Clinical features (multisystem)

Diagnosis is usually made at **birth** on the basis of typical craniofacial features, **hypotonia** and a **single transverse palmar crease (CMDT)**.

System	Features
Craniofacial / dysmorphic	Brachycephaly with flat occiput , up-slanting palpebral fissures with epicanthal folds , <i>Brushfield spots</i> (speckled iris), small ears, flat nasal bridge, large/protruding tongue (relative macroglossia), short neck
Musculoskeletal / limbs	Hypotonia , single transverse palmar (simian) crease, clinodactyly of the 5th finger , wide “sandal gap” between 1st–2nd toes, joint laxity, atlanto-axial instability
Neurodevelopment	Intellectual disability of variable degree; developmental delay; early-onset Alzheimer-type dementia in the 4th–5th decade
Cardiac	Congenital heart disease in ~50% , classically atrioventricular (endocardial) canal / AV septal defect , also VSD, ASD, tetralogy
Gastrointestinal	Duodenal atresia , Hirschsprung disease, celiac disease (immune-related)
Haematologic	Transient abnormal myelopoiesis (transient neonatal leukaemia) that usually resolves with conservative care; increased childhood acute lymphoblastic and especially myeloid leukaemia (ML-DS)
Endocrine / immune	Hypothyroidism , diabetes mellitus, immune deficiency with frequent infections

- ▶ **Leukaemia** in Down syndrome typically responds to *reduced-dose chemotherapy*, but relapse carries a poor outcome (CMDT).
- ▶ **Alzheimer disease**: adults with trisomy 21 *consistently* develop the neuropathologic hallmarks of AD if they survive beyond ~40 years; the **extra dose of the APP gene on chromosome 21 is the initiating cause, producing excess cerebral amyloid (Harrison)*. Average life expectancy of those surviving childhood who develop dementia is ~55 years*.

Diagnosis and screening

- ▶ **Prenatal screening (first/early-second trimester):** maternal serum **multiple-marker screen** (α -fetoprotein and other biomarkers), increased **nuchal translucency/thickness** and **under-development of the nasal bone** on ultrasonography.
- ▶ **Cell-free fetal DNA (cffDNA / NIPT)** in maternal blood gives high-sensitivity, high-specificity non-invasive detection.
- ▶ **Confirmatory diagnosis:** fetal **karyotype/cytogenomic analysis** by **chorionic villus sampling** or **amniocentesis** prenatally, and **postnatal karyotype** — mandatory to define the mechanism (free trisomy vs translocation) for **recurrence-risk counselling**.
- ▶ *Indications for cytogenetic analysis* (Harrison Table 479-4) include advanced maternal age, abnormal ultrasound, a positive maternal serum screen, multiple congenital anomalies, intellectual disability and developmental delay.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Non-disjunction in meiosis:** normal vs abnormal segregation of chromosome 21. Label: *homologous pair of chromosome 21, meiosis I — failure of homologue separation (non-disjunction), meiosis II, gametes — one with 2 copies of 21 and one with 0, fertilisation by normal gamete $\rightarrow$ 47,+21 trisomic zygote.*
- ▶ **Robertsonian translocation karyogram:** label *acrocentric chromosomes 14 and 21, fusion at centromere $\rightarrow$ der(14;21), balanced carrier parent (45 chromosomes, normal phenotype), unbalanced offspring with translocation Down syndrome (46 chromosomes, 3 copies of 21q).*

Clinical / Diagnostic significance

- ▶ **Always karyotype** the child (and parents if a translocation is found) — distinguishes the ~95% sporadic free trisomy (low recurrence) from translocation Down syndrome (potentially very high familial recurrence).
- ▶ **Multisystem surveillance** at diagnosis: echocardiography for AV canal/CHD, evaluation for duodenal atresia, baseline blood count for transient myelopoiesis/leukaemia, **thyroid function**, screening for **celiac disease**, hearing/vision, and caution regarding **atlanto-axial instability** (cervical-spine assessment before anaesthesia or sport).
- ▶ **Management is largely supportive:** surgical correction of duodenal atresia and congenital heart disease as in any patient; no medical therapy alters the neurodevelopmental or neurodegenerative course, and **antioxidant supplementation has shown no benefit** (CMDT).
- ▶ **Genetic counselling** for parents on recurrence risk and prenatal options in future pregnancies is essential.

High-yield exam pointers

- ▶ Commonest **autosomal aneuploidy**; birth incidence $\sim 1/700$; $\sim 0.5\%$ of conceptions are trisomic for 21.
- ▶ Three mechanisms: **free trisomy** $\sim 95\%$ (**meiotic non-disjunction**, **maternal age-dependent**), **Robertsonian translocation** $\sim 4\%$ (**familial**, **age-independent**), **mosaic** $\sim 1-2\%$.
- ▶ **Advanced maternal age** is the key risk factor; by age 45 ≈ 1 in 40; **paternal age does not increase risk**.
- ▶ **CHD** in $\sim 50\%$, classically **AV (endocardial) canal defect**; **GI: duodenal atresia** (“double-bubble”).
- ▶ **Haematology: transient abnormal myelopoiesis** in neonates; increased **ALL and AML (ML-DS)** in childhood.
- ▶ Classic signs: hypotonia, **single palmar crease**, epicanthal folds, Brushfield spots, protruding tongue, clinodactyly, sandal gap.
- ▶ **Triplicated APP gene (chromosome 21) $\rightarrow$ early Alzheimer dementia** by the 4th–5th decade; life expectancy ~ 55 years.
- ▶ **Cytogenomic/karyotype analysis is mandatory** to detect unbalanced translocation and guide recurrence-risk counselling.
- ▶ Prenatal: **multiple-marker serum screen + nuchal translucency + nasal bone**, confirmed by **cffDNA (NIPT)** and **amniocentesis/CVS karyotype**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Principles of Human Genetics” (chromosomal/cytogenetic disorders: aneuploidy, non-disjunction, Robertsonian translocation, mosaicism, indications for cytogenetic analysis); “The Integration of Inherited Genetics into Clinical Practice”; “Alzheimer’s Disease and Other Dementias” (*APP*/chromosome-21 mechanism); “Myelodysplastic Syndromes” (Down syndrome predisposition).
- ▶ **CMDT 2026** — “Genetic & Genomic Disorders: Down Syndrome” (incidence, maternal-age risk, screening, clinical features, leukaemia, dementia, karyotype/counselling, management).

Coverage note: Harrison 22e treats chromosomal-syndrome clinical detail sparingly (chromosome-disorder specifics are condensed from earlier editions), so the clinical and screening depth here is drawn mainly from CMDT 2026. The exact mechanism percentages ($\sim 95\%$ free trisomy / $\sim 4\%$ translocation / $\sim 1-2\%$ mosaic), the specific translocation recurrence-risk figures, the “21q22 Down syndrome critical region”, and several classic dysmorphic eponyms (Brushfield spots, clinodactyly, sandal gap) are universally accepted standard genetics not all stated verbatim in the available corpus; CMDT confirms the translocation/recurrence principle,

the single palmar crease, flat occiput, epicanthal folds, large tongue and 50% CHD/AV-canal figure.



Effects of Disease on Drug Concentration and Response

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — The response to a drug is the product of two linked processes: **pharmacokinetics** (the relationship between dose and plasma/tissue concentration, governed by absorption, distribution, metabolism and excretion — ADME) and **pharmacodynamics** (the relationship between concentration and effect at the molecular target). Concurrent disease can perturb *either* arm, shifting the position of the dose–response curve relative to the **therapeutic window** and thereby causing toxicity or loss of efficacy at conventional doses. A useful unifying idea is that disease modulates drug action by altering the **expression or function of the genes whose products determine PK and PD** — the same framework underlying pharmacogenomics. The clinically dominant disease states are **renal failure, hepatic disease, heart failure/shock, altered protein-binding (acute illness)**, and the physiologically “disease-like” extremes of **age**.

Conceptual framework — why disease matters

- ▶ **The therapeutic ratio (index/window)**: the separation between the dose–concentration curve for the *desired* effect and that for *toxicity* (Fig. 71-1). Disease that raises free drug concentration or sensitises the target effectively *narrows* this window; the danger is greatest for drugs with an intrinsically **narrow therapeutic index** (digoxin, phenytoin, aminoglycosides, vancomycin, warfarin, lithium, antiarrhythmics).
- ▶ **“High-risk pharmacokinetics”**: when active drug concentration depends on a **single** elimination pathway, any disease (or genetic/drug-interaction) inhibiting that pathway produces large, often dangerous swings in concentration. Drugs cleared by **multiple** pathways are relatively protected.
- ▶ **Free vs total drug**: only **unbound** drug is pharmacologically active. Because response tracks free concentration, disease-induced changes in protein binding can dissociate the *total* (measured) level from the *active* level — pivotal for highly bound drugs.
- ▶ **Both PK and PD shift**: disease may change concentration (PK) *and* independently alter target sensitivity (PD), e.g. receptor up-/down-regulation, ion-channel modulation by ischaemia/electrolytes.

Disease → mechanism → consequence (master table)

Disease state	Dominant PK/PD change	Net effect on drug	Illustrative drugs
Renal failure	↓ renal excretion of drug/active metabolite; altered binding in uraemia	↑ levels, accumulation, ADR	Digoxin; dofetilide, sotalol (QT/arrhythmia); normeperidine (seizures); edoxaban
Hepatic disease (cirrhosis)	↓ first-pass metabolism, portacaval shunting, ↓ hepatocyte function; ↓ albumin	↑ oral bioavailability; ↑ free drug	Morphine, meperidine, midazolam, nifedipine (bioavailability ~doubled)
Heart failure / shock	Redistribution of CO; ↓ Vd; ↓ hepatic & renal perfusion; ↓ gut perfusion	↑ plasma & CNS/cardiac levels; ↓ clearance; ↓ oral absorption	Lidocaine, digoxin; orally administered drugs (reduced effect)
Acute illness (MI, infection, surgery)	↑ acute-phase reactant binding (transient)	↓ free drug → ↓ efficacy	Drugs bound to α1-acid glycoprotein
Chronic kidney/liver disease	↓ albumin → ↓ binding	↑ free drug → ↑ effect/toxicity	Phenytoin (monitor <i>free</i> level)
Elderly / children	Altered organ maturity/decline, body-compartment size, polypharmacy	Variable; ↑ ADRs	Long- $t_{1/2}$ benzodiazepines (falls/hip fracture)

Renal disease

- ▶ If a drug or its active metabolite is mainly renally excreted and high levels cause ADRs (“high-risk pharmacokinetics”), the **dose or dosing interval must be reduced** in renal dysfunction to avoid toxicity.
- ▶ **Digoxin** is the classic example. **Dofetilide** and **sotalol** undergo predominant renal excretion and risk **QT prolongation and torsades** if not dose-reduced.
- ▶ **Active/toxic metabolites accumulate** even when the parent is hepatically cleared: **meperidine** (**pethidine**) is largely metabolised by the liver, but its metabolite **normeperidine** is renally excreted and accumulates in renal failure, producing **CNS excitation** — **irritability, twitching, seizures**.
- ▶ **Anticoagulants**: at approved doses **edoxaban** appears *more* effective in mild renal dysfunction, possibly reflecting higher drug levels — a caution against assuming “lower function is always safer.”
- ▶ **Binding**: **uraemia** alters **protein binding** of some drugs (e.g. **phenytoin**), so measuring the **free concentration** is preferable.

- ▶ **Practical dose adjustment** is based on the severity of dysfunction indexed by **creatinine clearance** (estimated in standard practice by the *Cockcroft–Gault* equation); published dose/interval tables give only a **first approximation** that must be refined with plasma-level data (where available) and clinical observation.

Hepatic disease

- ▶ **Standard liver-function tests do NOT predict** the need for dose adjustment in hepatitis or cirrhosis (a key exam point) — there is no hepatic equivalent of creatinine clearance; severity tools such as the *Child–Pugh* score are used clinically but no test reliably quantifies metabolic capacity.
- ▶ **Loss of first-pass (presystemic) metabolism** is the central effect: disrupted hepatocyte function, altered liver architecture and portacaval shunts mean orally administered drug bypasses hepatic extraction.
- ▶ For **high first-pass drugs** — morphine, meperidine, midazolam, nifedipine — **oral bioavailability is almost doubled** in cirrhosis versus normal liver. Therefore the **oral dose should be reduced**.
- ▶ Reduced albumin synthesis further **lowers protein binding**, raising free drug.

Heart failure and shock (circulatory failure)

- ▶ With **reduced tissue perfusion**, cardiac output is **redistributed** to protect heart and brain at the expense of other tissues.
- ▶ Consequences: drug distributes into a **smaller volume of distribution** → **higher plasma concentrations**, and the well-perfused **brain and heart are exposed to these higher levels** → exaggerated CNS or cardiac effects (e.g. lidocaine, digoxin toxicity).
- ▶ **Reduced renal and hepatic perfusion impairs clearance**; **reduced gut perfusion impairs absorption**, so orally administered drugs may have **reduced or absent effect** — favour the IV route in shock.

Altered protein binding and acute-phase states

- ▶ Many drugs circulate **partly bound to plasma proteins**; only free drug acts.
- ▶ In **chronic kidney or liver disease**, binding falls and **drug action increases**; in MI, infection or surgery, acute-phase reactants **transiently increase binding and decrease efficacy**.
- ▶ The effect is greatest for **highly bound drugs**: a fall in binding from **99% to 98% doubles the free fraction** (1% → 2%) — a quantitative pearl. Hence for **phenytoin**, monitor **free** rather than total concentration.

Disease-modified pharmacodynamics (same concentration, different effect)

- ▶ A drug may produce **no action or a different spectrum** in disease versus health, and disease can confound interpretation of ADRs (e.g. worsening dyspnoea on **amiodarone** in chronic lung disease may be drug, disease, or intercurrent illness — favour alternative antiarrhythmics).
- ▶ The drug–receptor interaction sits in a **dynamic biologic milieu**: **ion-channel blockade** (anticonvulsant/antiarrhythmic) is modulated by **membrane potential**, itself altered by **extracellular potassium and local ischaemia**.
- ▶ **Receptors are up-/down-regulated** by disease or by the drug: chronic **β -blockade up-regulates β -receptor density**, so abrupt withdrawal can precipitate rebound hypertension/tachycardia.

Extremes of age (physiologically “disease-like”)

- ▶ **Elderly**: multiple pathologies, **polypharmacy**, and decline of disposition organs → more interactions and ADRs. **Start below the usual adult dose and titrate slowly**; minimise drug number and doses/day. Long- $t_{1/2}$ **benzodiazepines** are linked to **hip fractures** (falls from sedation plus osteoporosis).
- ▶ **Children**: metabolism and response pathways **mature at different rates**; body-compartment sizes change. With limited evidence, doses are scaled to **weight or body surface area** as a first approximation unless age-specific data exist.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Therapeutic-ratio dose–response curves** (Fig. 71-1): two panels, x-axis *Dose or concentration*, y-axis *Probability of drug response (0–100%)*; plot a *Desired effect* curve and an *Adverse effect* curve. Label **Top = wide therapeutic ratio** (well-separated curves) and **Bottom = narrow therapeutic ratio** (overlapping curves); annotate the gap as the **therapeutic window**, and show how disease “shifts the adverse curve left.”
- ▶ **Presystemic (first-pass) elimination schematic** (Fig. 71-3): *Orally administered drug* → *Intestinal lumen* → *Enterocyte* (with **P-glycoprotein efflux** back to lumen and **metabolite** formation) → *Portal vein* → *Hepatocyte* (with **biliary canaliculus/bile** excretion and **metabolism**) → *Systemic circulation*. Annotate “**cirrhosis/portacaval shunt** → **first-pass lost** → **↑ oral bioavailability**.”

Clinical / Diagnostic significance

- ▶ **Therapeutic drug monitoring (TDM)** is the practical tool when disease distorts PK — useful for **anticonvulsants, antiarrhythmics, antirejection agents, aminoglycosides/vancomycin, digoxin, lithium**; measure **trough** for efficacy/toxicity (e.g. vancomycin nephrotoxicity) and **peak** (1–2 h) when targeting a peak effect (e.g. QT on sotalol/dofetilide).
- ▶ Prefer **free-drug levels** in hypoalbuminaemia/uraemia (phenytoin).

- ▶ Recognise **reactive-metabolite toxicity** amplified by disease/co-medication: **acetaminophen** hepatotoxicity follows glutathione depletion — risk ↑ with **enzyme inducers** (**phenobarbital**, **phenytoin**) and **ethanol**; treat with **N-acetylcysteine**.
- ▶ **Classify the ADR:** *Type A* (dose-dependent extension of pharmacology — bleeding on anticoagulants) versus *Type B* (dose-independent, often immunologic — SJS/TEN, DRESS, anaphylaxis).
- ▶ In shock/HF, **give drugs IV**, reduce loading where Vd is contracted, and re-check renal/hepatic function as perfusion changes.

High-yield exam pointers

- ▶ Response tracks **free, not total drug**; **99%→98% binding doubles free drug**.
- ▶ **Renal disease:** dose-reduce renally cleared, narrow-window drugs — **digoxin**, **dofetilide**, **sotalol**; beware **normeperidine** seizures.
- ▶ **Liver disease:** LFTs don't guide dosing; first-pass falls, so oral bioavailability of **morphine/meperidine/midazolam/nifedipine ~doubles** → cut the oral dose.
- ▶ **Heart failure/shock:** ↓ Vd + ↓ clearance → **higher plasma & CNS/cardiac levels**; gut hypoperfusion blunts oral absorption.
- ▶ **Acute-phase states** (MI, infection, surgery) transiently ↑ **binding** → ↓ efficacy.
- ▶ “**High-risk pharmacokinetics**” = single-pathway elimination + narrow window = dramatic disease-related toxicity.
- ▶ **β-blocker withdrawal** rebound reflects disease/drug **receptor up-regulation** (a PD effect).
- ▶ **Elderly:** “start low, go slow”, minimise polypharmacy; long-t_{1/2} benzodiazepines → hip fractures.
- ▶ Adjust by **creatinine clearance (Cockcroft–Gault)**, then confirm with TDM and clinical response.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Principles of Clinical Pharmacology*” (sections: Effects of Disease on Drug Concentration and Response — Renal disease, Liver disease, Heart failure and shock, Drug use in the elderly/children; Principles of Pharmacokinetics — protein binding, clearance, half-life, high-risk pharmacokinetics; Principles of Pharmacodynamics; Adverse Drug Reactions; Tables 71-1 and 71-2) and adjacent “*Pharmacogenomics*” for the gene-function framework.
- ▶ **Coverage note:** This is a single-chapter clinical-pharmacology topic and is covered well by Harrison 22e; the spec lists no dedicated subspecialty text and no CMDT chapter. *Cockcroft–Gault* (for creatinine-clearance estimation) and *Child–Pugh* (as the clinical hepatic-severity tool) are added as universally accepted standard internal medicine —

Harrison here specifies “creatinine clearance”-based renal dose adjustment and explicitly states that standard liver-function tests do **not** guide hepatic dose adjustment.



ELISA principle, methods and applications

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — The **Enzyme-Linked Immunosorbent Assay (ELISA)** is a *solid-phase immunoassay* that detects and quantifies an antigen or antibody by exploiting the highly specific antigen–antibody reaction, using an **enzyme-labelled reagent (conjugate)** that converts a colourless **chromogenic substrate** into a coloured product. The intensity of colour, read as **optical density (OD)** in a spectrophotometer, is proportional to the quantity of analyte. First described by *Engvall and Perlmann* and independently by *Van Weemen and Schuurs* (1971), ELISA replaced radioimmunoassay (RIA) because it gives comparable sensitivity without radioactive hazard. It is the workhorse screening and quantitative assay of clinical immunology, serology and endocrinology.

Immunological basis (the principle)

- ▶ ELISA depends entirely on the **specificity of the antibody–antigen bond**. Each B cell makes a **single antibody specificity**, and the **variable regions (VL and VH) form the antigen-binding (Fab) site**; within these are *hypervariable regions* that constitute the unique antigen-combining site (the *idiotype*) — this is what confers assay specificity.
- ▶ An antigen presents distinct **antigenic determinants (epitopes)**; an antibody is directed against one such epitope. *Sandwich* assays require an antigen large enough to carry **≥2 epitopes** so that capture and detector antibodies bind simultaneously.
- ▶ High assay sensitivity reflects **high-affinity antibodies** generated in vivo by *somatic hypermutation and affinity maturation*; reagent antibodies are often **monoclonal antibodies** (hybridoma technology), which provide a single, reproducible, well-defined specificity.
- ▶ The **enzyme label amplifies the signal**: one bound enzyme molecule turns over many substrate molecules, magnifying a small number of antigen–antibody complexes into a visible/measurable colour.

Components / reagents

- ▶ **Solid phase** — 96-well polystyrene microtitre plate (also beads, membranes) that adsorbs protein.
- ▶ **Capture reagent** — antigen (to detect antibody) or antibody (to detect antigen) coated on the well.
- ▶ **Enzyme conjugate** — antibody covalently linked to an enzyme.

- ▶ **Substrate / chromogen** — converted by the enzyme into a coloured product.
- ▶ **Blocking agent** — bovine serum albumin (BSA), casein or non-fat milk to saturate free sites and prevent non-specific binding.
- ▶ **Wash buffer** — phosphate-buffered saline with Tween-20 (PBS-T) to remove unbound reagents between steps.
- ▶ **Stop solution** — e.g., dilute sulphuric acid to halt the colour reaction.
- ▶ **Read-out** — ELISA plate reader (spectrophotometer) measuring OD at a defined wavelength.

Enzyme label	Common substrate / chromogen	Colour & read wavelength
Horseradish peroxidase (HRP)	TMB (tetramethylbenzidine); OPD; ABTS	blue → yellow on acid stop, read ~450 nm
Alkaline phosphatase (ALP)	p-nitrophenyl phosphate (pNPP)	yellow, read ~405 nm
β-galactosidase	ONPG / fluorogenic substrates	yellow / fluorescent

Types of ELISA

Type	What is coated	Detection step	Main use / notes
Direct	Antigen	Enzyme-labelled <i>primary</i> antibody binds antigen directly	Fewest steps, low cross-reactivity; less sensitive, each antibody must be labelled
Indirect	Antigen	Unlabelled primary (test) antibody, then enzyme-labelled anti-Ig secondary	Detects/quantifies antibody in serum (e.g., HIV, viral serology); signal amplified, one conjugate serves many tests
Sandwich (capture)	Capture antibody	Antigen bound, then enzyme-labelled detector antibody to a second epitope	Quantifies antigen ; needs multivalent antigen (≥2 epitopes); high sensitivity & specificity
Competitive / inhibition	Antibody (or antigen)	Sample analyte competes with labelled analyte for limited binding sites	For small antigens/haptens (single epitope: drugs, steroid hormones); signal is inversely proportional to analyte

- ▶ **Related variant** — ELISPOT: detects individual cytokine-secreting cells (e.g., IFN-γ-releasing T cells); the basis of some interferon-gamma release assays for tuberculosis.

Methodology (sandwich ELISA, stepwise)

- ▶ 1. **Coating** — adsorb capture antibody onto wells; incubate.
- ▶ 2. **Wash** — remove unbound antibody.
- ▶ 3. **Block** — add BSA to saturate remaining binding sites.
- ▶ 4. **Add sample** — patient serum/plasma; target antigen is captured; incubate, then wash off unbound material.
- ▶ 5. **Add conjugate** — enzyme-labelled detector antibody binds a second epitope of the captured antigen; incubate, wash.
- ▶ 6. **Add substrate/chromogen** — enzyme generates a coloured product over a timed interval.
- ▶ 7. **Stop** — add acid stop solution.
- ▶ 8. **Read & interpret** — measure OD in a plate reader; **quantitative** assays read against a *standard curve*; **qualitative** assays compare OD against a pre-set *cut-off* (positive vs negative). Each run includes positive, negative and blank controls.

Applications

- ▶ **Infectious-disease serology / screening:** HIV (modern *4th-generation combo* assays detect **p24 antigen + anti-HIV antibody**), hepatitis B (HBsAg, anti-HBc, anti-HBs), hepatitis C antibody, dengue (NS1 antigen, IgM/IgG), leptospirosis, syphilis, *H. pylori*, SARS-CoV-2 antibody.
- ▶ **Acute vs past infection:** IgM-capture (MAC-) ELISA detects recent infection because **IgM is the first antibody of the primary response**; IgG reflects past infection or immunity (*secondary antibody response*).
- ▶ **Endocrine / hormone assays:** hCG (pregnancy test), TSH, insulin, cortisol, thyroid hormones.
- ▶ **Tumour markers:** PSA, CEA, AFP, CA-125.
- ▶ **Autoantibodies:** ANA, anti-dsDNA, anti-CCP, ANCA, anti-TPO.
- ▶ **Allergy:** allergen-specific IgE.
- ▶ **Others:** cytokines, cardiac troponin, D-dimer, therapeutic-drug and toxicology monitoring, food/veterinary testing.

Advantages and limitations

- ▶ **Advantages:** high sensitivity and specificity; **safe** (no radioisotopes, unlike RIA); inexpensive and rapid; **high-throughput and automatable** (96-well plates, plate readers); both **qualitative and quantitative**; stable reagents and long enzyme-conjugate shelf life.
- ▶ **Limitations:** **false positives** from cross-reactivity/non-specific binding (mandating confirmatory testing); **false negatives** in the pre-seroconversion *window period*; the **hook/prozone effect** in sandwich assays; sensitive to technical error (inadequate washing, pipetting, incubation timing); a positive antibody result indicates exposure but **does not by itself distinguish active from past infection** (resolved by IgM-capture format or antigen/NAT testing).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Sandwich ELISA schematic** — labels: *microtitre well (solid phase), capture antibody, antigen (analyte), enzyme-labelled detector antibody, enzyme, chromogenic substrate, coloured product, read OD in plate reader.*
- ▶ **Indirect ELISA schematic** — labels: *well coated with antigen, patient serum antibody (primary), enzyme-conjugated anti-human Ig (secondary), substrate → colour; alongside a small bar of the 4 ELISA types (direct, indirect, sandwich, competitive).*

Clinical / Diagnostic significance

- ▶ **Screening tool:** because of its **high sensitivity**, ELISA is the first-line *screening* test (e.g., HIV); reactive results are confirmed by a more specific assay (Western blot / line immunoassay / NAT) to exclude false positives.
- ▶ **Window period:** antibody-based ELISA can be falsely negative early in infection before seroconversion; **antigen detection** (HIV p24, dengue NS1) or nucleic-acid testing covers this gap — the rationale for combined Ag/Ab assays.
- ▶ **Quantitation & monitoring:** quantitative ELISA against a standard curve allows titres/levels to be followed (hormones, tumour markers, antibody titres).
- ▶ **Hook (prozone) effect:** in sandwich assays a *very high* antigen concentration can paradoxically lower the signal and give a falsely low/negative result — suspect when the clinical picture mismatches the result; re-test with dilution.
- ▶ **Confirmation principle:** a sensitive screen (ELISA) followed by a specific confirmatory test minimises both false negatives (missed disease) and false positives (mislabelling).

High-yield exam pointers

- ▶ **ELISA = Enzyme-Linked Immunosorbent Assay**, a *solid-phase immunoassay*; Engvall & Perlmann, 1971; replaced RIA (no radioactivity).
- ▶ Principle: **antigen-antibody specificity + enzyme-amplified colorimetric read-out** ($OD \propto \text{analyte}$).
- ▶ Four types: **direct, indirect, sandwich, competitive** — *indirect = detect antibody, sandwich = detect/quantify antigen, competitive = small haptens (signal inversely proportional).*
- ▶ Common enzymes: **HRP** (substrate **TMB**, read 450 nm) and **ALP** (substrate **pNPP**, read 405 nm).
- ▶ Sandwich ELISA needs an antigen with ≥ 2 **epitopes**; reagent antibodies are often **monoclonal**.
- ▶ Classic use: **HIV screening** (4th-gen combo = p24 Ag + Ab), confirmed by Western blot.
- ▶ **IgM-capture ELISA = acute/recent infection** (IgM is the first antibody); **IgG = past/immune**.
- ▶ Pitfalls: false negative in **window period**; **hook/prozone effect** at very high antigen.

- Advantages: sensitive, specific, safe, cheap, rapid, **high-throughput/automatable**; ELISPOT detects single cytokine-secreting cells.

SOURCE & COVERAGE

Harrison 22e — Ch 360 “Introduction to the Immune System” (immunological basis: antibody–antigen specificity, Fab/variable-region antigen binding, idiotype, affinity maturation, monoclonal antibody technology, Ig structure, IgM primary vs IgG secondary antibody response). **Coverage note (gap):** Harrison Ch 360 does **not** describe the ELISA technique itself — assay formats (direct/indirect/sandwich/competitive), enzyme–substrate systems (HRP/TMB, ALP/pNPP), the stepwise methodology, the hook effect, and named clinical applications (HIV/HBV/HCV/dengue serology, hormone and tumour-marker assays) are drawn from standard, universally accepted laboratory/clinical-immunology knowledge and are not citable to the provided chapter. Only the underlying immunology is source-grounded.



Epigenetics

Asked in: Paper I Nov 2021 · Paper I May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — The term *epigenetics* (Greek *epi-* = “over, around”), coined by *Conrad Waddington* in 1942, denotes the heritable and reversible mechanisms by which **gene expression and phenotype are altered without any change in the underlying DNA nucleotide sequence**. The *epigenome* is the constellation of covalent modifications of DNA and histones — plus non-coding RNAs — that determine chromatin structure and hence the cell’s transcriptome and proteome. Although all somatic cells carry an essentially identical genome, sex-, tissue- and environment-dependent epigenetic marks generate cell-type specificity, and their dysregulation underlies imprinting disorders, cancer, ageing and neuropsychiatric disease.

Biochemical basis — the three core mechanisms

Fundamental to epigenetic regulation is packaging of the genome into **chromatin**. The basic unit is the **nucleosome** — 147 base pairs of DNA wrapped around an octamer of 8 histones (two copies each of the core histones **H2A, H2B, H3, H4**). Compaction governs accessibility to transcription factors and repair machinery: *euchromatin* (open) is transcriptionally active, *heterochromatin* (compacted) is repressed. Three processes regulate compaction:

Mechanism	Key players	Functional output
DNA methylation	Cytosine methylation of CpG dinucleotides (5-mC); written de novo by DNMT3A/3B, maintained after replication by	Promoter CpG-island methylation → gene silencing ; CpG islands normally

Mechanism	Key players	Functional output
	DNMT1; reversed via TET1–3 oxidation (5-mC→5-hmC→5-fC→5-caC)	unmethylated to permit transcription
Histone post-translational modifications (hPTMs)	≥60 covalent marks added by writers , removed by erasers , recognised by readers	Acetylation (KATs/HATs add; HDACs + NAD ⁺ -dependent sirtuins remove) loosens chromatin → activation; lysine methylation (KMTs) gives context-specific output
Nucleosome remodelling	ATP-dependent SWI/SNF, ISWI, INO80 families; histone variants H2AZ (start sites), H3.3 (gene bodies)	Reposition/evict nucleosomes; activate or repress transcription

- ▶ **Acetylation** of H3K9ac and H3K27ac → transcriptional activation (neutralises lysine positive charge, creating a reader-binding surface); dynamic and rapidly reversed by HDACs.
- ▶ **Lysine methylation** gives a “histone code”: *activating* marks = **H3K4me3**, **H3K36me3**, **H3K79me3**; *repressive* = **H3K27me3**; *repeat/centromeric silencing* = **H3K9me3**. Methylation is more stable than acetylation and its output depends purely on effector (reader) binding.
- ▶ Other marks: phosphorylation of **H2A at Ser139 (γH2A.X)** flags DNA double-strand breaks; ubiquitination, SUMOylation (repression) and PARP-mediated ADP-ribosylation also signal on chromatin.
- ▶ **RNA epigenetics (epitranscriptomics)**: reversible **m6A** methylation of mRNA by writers METTL3/METTL14 and demethylases ALKBH5/FTO controls mRNA fate (degradation vs translation).

Physiological epigenetic phenomena

- ▶ **X-chromosome inactivation (Lyonisation)**: dosage compensation silencing one of the two X chromosomes in females, mediated by the **Xist** long non-coding RNA; the inactive X is highly methylated with low histone acetylation. Choice of X is random but then stably transmitted through cell division; ~15% of X genes escape inactivation.
- ▶ **Genomic imprinting**: monoallelic, parent-of-origin-specific expression of a small subset of autosomal genes, mediated by allele-specific DNA methylation. The imprint is **reset in the germline** in a sex-specific manner and maintained lifelong.
- ▶ **Bivalent chromatin** in embryonic stem cells: developmental genes carry both activating **H3K4me3** and repressive **H3K27me3** (“poised”), resolving to one mark on differentiation. **H3K9me3** heterochromatin (via SUV39H1) is an epigenetic barrier to reprogramming into iPSCs.

- ▶ **Environmental integration:** diet alters chromatin — acetyl-CoA (from ACLY/ACSS2/PDH) is the best predictor of histone acetylation; **S-adenosylmethionine (SAM)** is the universal methyl donor for DNA/histone methylation, linking folate/methionine status to the epigenome.

Epigenetics in disease

- ▶ **Cancer — a combined genetic + epigenetic disease.** The first epigenetic driver, the remodeller **SMARCB1**, was identified in malignant rhabdoid tumours (1998); TCGA shows **25–30% of cancer driver mutations occur in chromatin-regulatory proteins** (e.g. **MLL3/MLL4**, **EP300/CBP**, **SMARCA4**, **ARID1A** — mostly loss-of-function). **EZH2** (H3K27me3 writer) is an oncogene over-expressed in breast/prostate/melanoma. “**Oncohistones**” — **H3.3 K27M** in paediatric high-grade glioma and **K36M** in chondroblastoma. **MLL1 (KMT2A)** translocations drive AML and ~80% of infant ALL. Metabolic mutations in **IDH1/2**, **FH**, **SDH** generate 2-hydroxyglutarate/fumarate/succinate that inhibit α -KG-dependent demethylases → hypermethylation. Cancer epigenomes show global hypomethylation (genomic instability) with focal CpG-island hypermethylation silencing tumour-suppressors.
- ▶ **Imprinting / uniparental-disomy (UPD) disorders:** **Prader-Willi** (loss of paternal 15q11-13 — deletion, maternal UPD, or imprinting defect) vs **Angelman** (loss of maternal 15q11-13); **Beckwith-Wiedemann syndrome** (overactive **IGF2** / loss of **CDKN1C**; paternal UPD chr 11; overgrowth + Wilms’ tumour risk); **GNAS1** imprinting → pseudohypoparathyroidism Ia (maternal) vs pseudopseudohypoparathyroidism (paternal, *Albright hereditary osteodystrophy*). Hydatidiform mole = exclusively paternal genome; ovarian teratoma = maternal.
- ▶ **Neurodevelopmental / neuropsychiatric:** **Rett syndrome** (X-linked, **MECP2** methyl-CpG-binding protein); **Kabuki syndrome** (**MLL4/KMT2D** or **UTX/KDM6A**); **Rubinstein-Taybi syndrome** (**CBP/CREBBP** acetyltransferase); **Fragile-X** (**FMR1/FMR2** promoter hypermethylation). Hypomethylation of **SNCA** (Parkinson’s) and **APP** (Alzheimer’s), and altered histone acetylation, feature in neurodegeneration; **BDNF** and **REST** are epigenetically regulated in depression/schizophrenia.
- ▶ **Ageing:** progressive heterochromatin loss (reduced **H3K9me3/H3K27me3**), seen severely in **Hutchinson-Gilford progeria** and **Werner syndrome**; the DNA-methylation “clock” predicts chronological age better than telomere length. **NAD⁺-dependent sirtuins** (class III HDACs, e.g. **SIRT1/SIRT6**) mediate caloric-restriction longevity.
- ▶ **Immunity/inflammation:** corticosteroids recruit **HDAC2** to NF- κ B-driven inflammatory promoters in asthma; **FOXP3** and **CTLA4** hypermethylation impairs regulatory T cells in rheumatoid arthritis; “trained immunity” / inflammatory memory is epigenetically encoded.

Tools for studying the epigenome

- ▶ **ChIP-seq** — chromatin immunoprecipitation + sequencing maps genome-wide histone marks and protein-DNA binding.

- ▶ **ATAC-seq** — Tn5 transposase inserts adapters into open chromatin to map accessibility, even single-cell.
- ▶ **CUT&RUN / CUT&Tag** — antibody-tethered MNase or Tn5; fewer cells, lower background, single-cell capable.
- ▶ **Hi-C / 3C and Hi-ChIP** — 3-D genome architecture, enhancer-promoter loops and topologically associated domains (TADs).
- ▶ **CRISPR epigenome editing** — catalytically dead dCas9 fused to a writer/eraser to activate or repress a target gene without cutting DNA.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Nucleosome & chromatin modifications:** DNA double helix wound around the histone octamer (label H2A, H2B, H3, H4, “147 bp”), with N-terminal **histone tails** carrying **acetylation** (Ac, H3K27ac → active) and **methylation** (Me, H3K27me3 → repressed); mark CpG DNA methylation (5-mC); show transition **euchromatin** (open, active) ↔ **heterochromatin** (compact, silent); annotate **Writers / Erasers / Readers** and DNMT1/3A/3B, TET, HATs/HDACs, KMTs/KDMs.
- ▶ **Imprint-reset schematic** (Fig 479-8 style): maternal germline X both alleles unmethylated, paternal germline methylated → reset each generation; label **Prader-Willi** (paternal loss) vs **Angelman** (maternal loss) at 15q11-13.

Clinical / Diagnostic significance

- ▶ **Diagnosis:** methylation-specific PCR / MS-MLPA for Prader-Willi, Angelman, Beckwith-Wiedemann and Fragile-X; epigenomic “cell-of-origin” profiling identifies cancers of unknown primary better than mutation sequencing; DNA-methylation age as a biomarker of biological ageing.
- ▶ **Therapeutics (epigenetic drugs):** DNMT inhibitors *azacitidine* and *decitabine* (global hypomethylation reactivating tumour-suppressors) for MDS and AML; HDAC inhibitors (vorinostat, romidepsin, panobinostat) for cutaneous T-cell lymphoma and multiple myeloma; EZH2 inhibitors (B-cell lymphoma, sarcoma); IDH inhibitors (IDH-mutant AML/glioma); LSD1, DOT1L and MLL1 inhibitors in leukaemias; BET (bromodomain) inhibitors suppress MYC. Reversibility of epigenetic marks is the key therapeutic rationale.
- ▶ **Pearl:** epigenetic therapy is increasingly combinatorial — re-expressing tumour antigens and IFN responses to potentiate chemotherapy and immunotherapy.

High-yield exam pointers

- ▶ Epigenetics = heritable change in gene expression **without** DNA-sequence change; coined by Waddington (1942).

- ▶ Three mechanisms: DNA methylation (CpG/5-mC), histone PTMs (acetylation/methylation), nucleosome remodelling; plus RNA m6A.
- ▶ DNMT1 = maintenance; DNMT3A/3B = de novo; TET enzymes erase methylation.
- ▶ Active marks: H3K4me3, H3K36me3, acetylation; repressive: H3K27me3, H3K9me3, DNA-CpG methylation.
- ▶ X-inactivation via Xist lncRNA; imprinting reset in germline — Prader-Willi (paternal), Angelman (maternal), Beckwith-Wiedemann (IGF2).
- ▶ Cancer: 25–30% of driver mutations in chromatin regulators; EZH2 oncogene; oncohistones H3K27M/H3K36M; IDH/FH/SDH → hypermethylation.
- ▶ Epigenetic drugs: azacitidine/decitabine (DNMTi), vorinostat/romidepsin (HDACi), EZH2/IDH/BET inhibitors — exploit reversibility.
- ▶ Disease links: Rett (MECP2), Fragile-X (FMR1), Rubinstein-Taybi (CREBBP), Kabuki (KMT2D/KDM6A), ageing methylation clock, progeria H3K9me3 loss.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "The Role of Epigenetics in Disease and Treatment" (biochemical bases, writers/erasers/readers, tools, cancer/ageing/brain/immunity epigenetics, epigenetic drugs).
- ▶ Harrison's Principles of Internal Medicine, 22e — "Principles of Human Genetics" (X-inactivation/Xist, genomic imprinting, imprint reset, uniparental disomy, Prader-Willi/Angelman/Beckwith-Wiedemann, GNAS1, Rett, cancer methylation).

Coverage note: This topic has no dedicated subspecialty textbook in the corpus and is not a CMDT topic; grounding is the two Harrison chapters above, which cover the ask comprehensively. Specific drug indications and disease-gene associations are taken verbatim from those chapters.



Extraocular muscles and their movements. Write a note on Superior orbital fissure syndrome

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — Each eye is moved by **six extraocular muscles (EOMs)** — four recti (superior, inferior, medial, lateral) and two obliques (superior, inferior) — supplied by the **oculomotor (III), trochlear (IV) and abducens (VI)** cranial nerves arising from their brainstem nuclei. Their coordinated action keeps the image of a target on the fovea (*foveation*) and maintains binocular single vision. The **superior orbital fissure (SOF)** is the cleft between the greater and lesser wings of the sphenoid through which III, IV, VI and the ophthalmic division (V1) of the trigeminal nerve enter the

orbit; its compromise produces a characteristic **painful ophthalmoplegia** with **V1 sensory loss** but **preserved vision** — the *superior orbital fissure syndrome*.

Extraocular muscles — innervation and actions

Muscle	Cranial nerve	Primary action	Secondary actions
Medial rectus	III (inferior division)	Adduction	—
Lateral rectus	VI	Abduction	—
Superior rectus	III (superior division)	Elevation (in abduction)	Adduction, intorsion
Inferior rectus	III (inferior division)	Depression (in abduction)	Adduction, extorsion
Superior oblique	IV	Intorsion; depression (in adduction)	Abduction
Inferior oblique	III (inferior division)	Extorsion; elevation (in adduction)	Abduction

- ▶ Mnemonic for innervation: **LR6 SO4, rest 3** — Lateral Rectus by VI, Superior Oblique by IV, the remaining four EOMs (plus levator palpebrae superioris and the pupillary sphincter/ciliary muscle) by III.
- ▶ The **oculomotor nerve** also supplies the **levator palpebrae superioris** (lid elevation) and, via its parasympathetic component, the **iris sphincter** and **ciliary muscle** (pupil constriction, accommodation).
- ▶ The **vertical recti** act best as pure elevators/depressors when the eye is **abducted**; the **obliques** act best when the eye is **adducted** (superior oblique = main depressor in adduction; inferior oblique = main elevator in adduction). This underlies the *cardinal positions* used to isolate weak muscles.

Movements of the eye and their neural control

- ▶ **Terminology:** *ductions* are monocular movements; *versions* are conjugate (both eyes same direction); *vergences* are disjunctive (convergence/divergence). The clinician tests the six **cardinal positions of gaze** to identify a paretic muscle, aided by yoke-muscle pairing (e.g., right lateral rectus pairs with left medial rectus on right gaze).
- ▶ **Classes of movement** (Harrison): **saccades** (rapid refixation), **smooth pursuit** (tracking a moving target), and **gaze stabilization / optokinetic reflexes** during head and body movement. These are coordinated by pontine–midbrain centres under descending **supranuclear** input from frontal and parieto-occipital cortex.
- ▶ **Horizontal gaze:** the **paramedian pontine reticular formation (PPRF)** drives the ipsilateral abducens nucleus; abducens interneurons cross via the **medial longitudinal fasciculus (MLF)** to the contralateral medial rectus subnucleus, yoking abduction of one eye with adduction of the other.

- ▶ **Internuclear ophthalmoplegia (INO):** an MLF lesion causes **failure of adduction** of the ipsilateral eye on lateral gaze with nystagmus of the abducting eye; **multiple sclerosis** is the commonest cause. The **frontal eye field** generates contralateral saccades.

Ocular motor nerve palsies — clinical correlation

- ▶ **Oculomotor (III) palsy:** ptosis, a **dilated pupil**, and the eye resting “**down and out**” (unopposed lateral rectus + superior oblique). A **pupil-involving, painful III palsy** suggests a **compressive lesion (posterior communicating artery aneurysm/tumour)** — demands urgent CT/MR angiography. A **pupil-sparing III palsy** is usually **microvascular** (diabetes, hypertension) and recovers spontaneously. *Aberrant regeneration* (lid elevation/pupil constriction on adduction or downgaze) follows trauma/compression, never microvascular infarct.
- ▶ **Trochlear (IV) palsy:** **vertical diplopia** worse on reading/downgaze, with **hypertropia and excyclotorsion**; the **Bielschowsky head-tilt test** (diplopia worse on tilting toward the affected side) is the cardinal sign. The IV nerve is uniquely vulnerable to **closed head trauma**.
- ▶ **Abducens (VI) palsy:** **horizontal diplopia** worse on gaze toward the lesion (failure of abduction). A **classic false-localising sign of raised intracranial pressure**; at the petrous apex, mastoiditis causes deafness, pain and VI palsy (**Gradenigo’s syndrome**).
- ▶ **Localising clue:** multiple ocular-motor palsies should never be ascribed to chance microvascular events — neuroimaging must target the **cavernous sinus, superior orbital fissure and orbital apex**, where III, IV, V1 and VI lie in close proximity.

Superior orbital fissure syndrome — anatomy, features and causes

- ▶ **Structures traversing the SOF:** oculomotor nerve (superior and inferior divisions), trochlear (IV), abducens (VI), the three branches of the **ophthalmic division (V1)** — lacrimal, frontal and nasociliary — the **superior ophthalmic vein**, and **sympathetic fibres**. *Crucially, the optic nerve (II) and ophthalmic artery pass through the separate optic canal, not the SOF**.*
- ▶ **Clinical features (Harrison Table 452-2 — “Sphenoid fissure / superior orbital”):** involvement of III, IV, VI and first division of V (V1) producing:
 - **Total external ophthalmoplegia** — globe fixed in central position with diplopia.
 - **Ptosis** (III → levator palpebrae) and a **fixed, dilated, unreactive pupil** (parasympathetic III involvement = internal ophthalmoplegia).
 - **Proptosis** (orbital congestion / superior ophthalmic vein obstruction).
 - **V1 sensory loss** over forehead, upper eyelid and cornea with an **absent corneal reflex**; periorbital pain is common.
 - **Vision is preserved** because the optic nerve is spared — the key sign distinguishing SOF syndrome from **orbital apex syndrome**.

- **Causes (Harrison):** invasive tumours of the sphenoid bone and aneurysms. Other standard causes: trauma (sphenoid/orbital fractures), neoplasms (meningioma, nasopharyngeal carcinoma, metastases), infections (including mucormycosis in diabetics), and idiopathic **granulomatous inflammation (Tolosa-Hunt syndrome)** — the latter is a painful ophthalmoplegia that is dramatically responsive to glucocorticoids.

Superior orbital fissure vs orbital apex vs cavernous sinus syndromes

Feature	SOF syndrome	Orbital apex syndrome	Cavernous sinus syndrome
Nerves involved	III, IV, V1, VI	III, IV, V1, VI + II	III, IV, VI, V1 (± V2)
Optic nerve / vision	Spared (vision intact)	Involved → visual loss	Usually spared
Pupil / sympathetics	Fixed dilated (III)	Fixed dilated (III)	III palsy ± Horner's (oculosympathetic)
Proptosis / chemosis	Proptosis ±	Proptosis ±	Prominent (venous occlusion), may be bilateral
Typical causes (Harrison)	Sphenoid tumours; aneurysms	Invasive fungal infection, amyloidosis, granuloma	Thrombosis (orbital cellulitis/ <i>S. aureus</i> , sinusitis, mucormycosis), aneurysm, carotid-cavernous fistula, tumour, Tolosa-Hunt

- The **orbital apex syndrome** is essentially “SOF syndrome **plus optic neuropathy**” — vision loss is the discriminator.
- **Cavernous sinus syndrome** adds V2 involvement, possible **postganglionic Horner's** (sympathetic plexus on the carotid), prominent **chemosis/orbital swelling**, and may become **bilateral** via intercavernous channels; a **carotid-cavernous fistula** produces a pulsatile, bruit-positive proptosis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1** — Actions of the six EOMs (right eye, “flower” diagram): central circle for the eye with eight radiating arrows labelled Superior rectus (up & out), Inferior rectus (down & out), Medial rectus (in/adduction), Lateral rectus (out/abduction), Superior oblique (down in adduction), Inferior oblique (up in adduction); annotate innervation III / IV / VI beside each.
- **Diagram 2** — Coronal section through the superior orbital fissure / cavernous sinus: label Oculomotor (III), Trochlear (IV), Ophthalmic (V1), Maxillary (V2), Abducens (VI), Internal carotid artery, Superior ophthalmic vein, Optic nerve (II) in optic canal

(separate), Annulus of Zinn. Mark that VI and ICA lie within the sinus while III, IV, V1, V2 lie in the lateral wall.

Clinical / Diagnostic significance

- ▶ **Examination:** test the six cardinal positions, **corneal light reflex (Hirschberg)** and the **cover test** (detects deviations as small as 1°); the **red-glass / diplopia chart** localises the paretic muscle. Always check the **pupil, lid and corneal sensation** in any ophthalmoplegia.
- ▶ A **painful ophthalmoplegia with V1 numbness and intact vision** = **SOF syndrome until proven otherwise** — obtain **contrast MRI/MRA of the orbital apex, SOF and cavernous sinus**; add CT for bony sphenoid lesions/fractures and **angiography** if aneurysm/fistula suspected.
- ▶ **Emergencies to exclude:** posterior communicating artery **aneurysm** (pupil-involving III palsy), **cavernous sinus thrombosis** (fever, bilateral signs, sepsis source) and **rhino-orbital mucormycosis** in a diabetic/immunocompromised host (urgent biopsy, antifungals, surgical debridement).
- ▶ **Management** is cause-directed: glucocorticoids for **Tolosa-Hunt**, antibiotics/anticoagulation for septic cavernous sinus thrombosis, surgery/embolisation for tumour or fistula. Symptomatic diplopia relief uses **occlusion, prisms (Fresnel), or eye-muscle surgery** once the deficit stabilises.

High-yield exam pointers

- ▶ **6 EOMs; innervation** = LR6 SO4, rest III. III also supplies levator, iris sphincter and ciliary muscle.
- ▶ **III palsy** = “down and out” + ptosis + **dilated pupil**; pupil-involving + pain → **aneurysm** (emergency); pupil-sparing → **microvascular**.
- ▶ **IV palsy** = **vertical diplopia, head-tilt test positive**; commonest nerve injured in head trauma.
- ▶ **VI palsy** = **horizontal diplopia**; false-localising sign of raised ICP; Gradenigo’s at petrous apex.
- ▶ **SOF contents** = III, IV, VI, V1, superior ophthalmic vein, sympathetics — **NOT the optic nerve (optic canal)**.
- ▶ **SOF syndrome:** ophthalmoplegia + ptosis + dilated pupil + V1 loss + **vision preserved**; **orbital apex** = SOF + optic neuropathy; **cavernous sinus** = adds V2 ± Horner’s + chemosis, may be bilateral.
- ▶ **Tolosa-Hunt** = **idiopathic granulomatous painful ophthalmoplegia, steroid-responsive** (diagnosis of exclusion).
- ▶ Multiple ocular-motor palsies together → image the **cavernous sinus / SOF / orbital apex**, not “diabetic coincidence.”

SOURCE & COVERAGE

Harrison 22e — Ch 34 “Disorders of the Eye” (EOM innervation, eye-movement classes/control, III/IV/VI palsies, INO; Horton) and Ch 452 “Trigeminal Neuralgia, Bell’s Palsy, and Other Cranial Nerve Disorders” (Table 452-2 cranial-nerve syndromes — superior orbital fissure, orbital apex, cavernous sinus; cavernous sinus syndrome text). **Coverage note:** Harrison covers SOF/orbital-apex/cavernous-sinus syndromes only briefly (Table 452-2) and does not tabulate the detailed primary/secondary actions of individual EOMs or the cardinal-position testing scheme; these, the muscle-action table, the *LR6SO4* mnemonic, the precise SOF contents (superior ophthalmic vein, sympathetics) and the optic-canal-vs-SOF distinction are supplied from universally accepted standard anatomy/neuro-ophthalmology (consistent with Brazis, *Localization in Clinical Neurology*, cited in the spec but not provided as text here). The *Rochon-Duvigneaud* eponym for SOF syndrome is standard but not in the provided Harrison text.



Fabry’s disease

Asked in: Paper IV Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Fabry disease (*angiokeratoma corporis diffusum universale*) is an **X-linked lysosomal storage disease** caused by deficient activity of the lysosomal hydrolase **α -galactosidase A**, encoded by the **GLA** gene. The enzyme defect leads to progressive intralysosomal accumulation of the neutral glycosphingolipid **globotriaosylceramide (Gb3, also called ceramide trihexoside)**, predominantly within **vascular endothelium**, and in renal, cardiac, neural, corneal and cutaneous cells. It is a multisystem vasculopathy and is regarded as **likely the most prevalent lysosomal storage disease (LSD)**, with manifestations spanning a spectrum from classic early-onset disease in hemizygous males to attenuated, organ-limited late-onset variants.

Etiology, genetics and pathogenesis

- ▶ **Enzyme/substrate:** deficiency of **α -galactosidase A** (a neutral glycosphingolipidosis) → failure to cleave the terminal galactose from **globotriaosylceramide (Gb3)**, causing its lysosomal accumulation. Substrate is in part delivered to lysosomes by **LDL-receptor-mediated uptake**.
- ▶ **Gene/inheritance:** mutations in the **GLA** gene on the X chromosome (Xq22). Inheritance is **X-linked**; Harrison’s neuropathy chapter terms it *X-linked dominant* because **heterozygous females can be clinically affected** owing to **Lyonization** (random X-inactivation).
- ▶ **Epidemiology:** estimated prevalence of **hemizygous males 1 in 40,000 to 1 in 3,500** in selected populations. **Females have a higher prevalence of mutations but far more variable expression; up to 70% of heterozygous females show clinical manifestations.**

- ▶ **Threshold concept:** disease appears when residual enzyme activity falls below a tissue-specific threshold; small differences in residual activity (and substrate flux) explain the broad phenotypic spectrum, including organ-restricted variants.
- ▶ **Pathology:** progressive Gb3 deposition in **endothelial and smooth-muscle cells of small vessels** produces a generalised vasculopathy with ischaemia/infarction in kidney, heart and brain; deposition in **dorsal-root ganglia/small nerve fibres** produces a painful small-fibre neuropathy.

Clinical features (multisystem)

The **classic triad/quartet** of early disease comprises **acroparesthesias, angiokeratomas, hypohidrosis and corneal opacity**, with later renal, cardiac and cerebrovascular failure.

System	Key manifestations (faithful to source)
Skin	Angiokeratomas — punctate, dark red to blue-black, flat or slightly raised, telangiectatic lesions that do not blanch with pressure ; densest between the umbilicus and knees (“bathing-suit area”), also umbilicus, scrotum, inguinal region, perineum. Easily overlooked.
Sweat glands	Hypohidrosis (heat/exercise intolerance).
Peripheral nerve	Acroparesthesia — debilitating episodic burning/lancinating pain of the hands and feet , lasting minutes to days, precipitated by temperature change, exercise, fatigue or fever ; begins in childhood/early adult life (small-fibre neuropathy).
Eye	Corneal and lenticular opacities on slit-lamp (classic whorl-like <i>cornea verticillata</i> ; Fabry cataract) — useful diagnostic clue; usually asymptomatic.
GI	Abdominal pain (may mimic appendicitis or renal colic) and recurrent diarrhoea , often from childhood.
Kidney	Proteinuria, isosthenuria and progressive renal dysfunction in the 2nd–4th decades → end-stage renal disease. ~5% of males with “ idiopathic renal failure ” carry GLA mutations.
Heart	Hypertension, left ventricular hypertrophy, anginal chest pain and congestive heart failure in the 3rd–4th decades; a restrictive / hypertrophic cardiomyopathy picture. ~1–3% of “ idiopathic hypertrophic cardiomyopathy ” is Fabry.
CNS / vasculature	Premature cerebrovascular disease / stroke and TIA (a noninflammatory vasculopathy); ~2–5% of

System	Key manifestations (faithful to source)
	“idiopathic stroke” at 35–50 years carry GLA mutations.
Other	Leg lymphedema without hypoproteinemia.

Phenotypic variants and sex differences

- ▶ **Classic male (hemizygous) phenotype:** earliest and most severe — childhood acroparesthesias, angiokeratomas, hypohidrosis, GI pain → renal, cardiac and cerebrovascular disease; untreated, death often by the fifth decade from cardiovascular, renal or cerebrovascular disease.
- ▶ **Later-onset / residual-activity variants:** patients with some residual α -galactosidase A activity develop late, often organ-restricted disease — predominantly cardiac (mimicking hypertrophic cardiomyopathy / “cardiac variant”), or predominantly renal or CNS; some present primarily with a dilated cardiomyopathy.
- ▶ **Heterozygous females:** highly variable, from asymptomatic carrier to full classic disease; here heart disease is the most common life-threatening manifestation.
- ▶ **Cause of death / organ hierarchy:** in males, renal disease followed by cardiovascular disease; in females, cardiac disease predominates.

Investigations / Diagnosis

- ▶ **Enzyme assay (males):** markedly reduced or absent α -galactosidase A activity in plasma/leukocytes (dried blood spot) is diagnostic in hemizygous males.
- ▶ **GLA gene sequencing:** required in females, in whom enzyme activity may be normal (Lyonization), and to confirm amenable mutations for chaperone therapy.
- ▶ **Biomarkers:** elevated Gb3 (plasma/urine) and its deacylated form lyso-Gb3 (globotriaosylsphingosine) support diagnosis and monitor treatment (standard practice).
- ▶ **Slit-lamp examination:** corneal/lenticular opacities aid diagnosis.
- ▶ **Tissue biopsy:** renal/cardiac/skin biopsy shows lipid-laden cells; electron microscopy reveals characteristic lamellar (“zebra-body”/myelin-figure) lysosomal inclusions (standard).
- ▶ **Organ surveillance:** urinalysis/proteinuria and eGFR; ECG/echocardiography/cardiac MRI (LVH, late gadolinium enhancement); MRI brain for white-matter/vascular lesions.

Management / Treatment

- ▶ **Disease-specific:**
 - **Enzyme replacement therapy (ERT)** — intravenous α -galactosidase A (agalsidase) clears stored lipid from many cell types; instituted early to slow progression.
 - **Pharmacologic chaperone** — oral migalastat — stabilises and enhances the patient’s residual mutant enzyme; an oral option only for patients with “amenable” GLA mutations.

- ▶ Symptomatic / supportive:
 - Neuropathic pain (acroparesthesia): gabapentin and carbamazepine reduce chronic and episodic pain; avoid known triggers (heat, exertion, fever).
 - Renal failure: chronic haemodialysis or kidney transplantation can be life-saving.
 - Cardiac/cerebrovascular: standard heart-failure/arrhythmia care, antihypertensives, and stroke prophylaxis (antiplatelet/risk-factor control).
- ▶ Key principle: renal insufficiency, cardiac fibrosis and stroke are irreversible — therefore early institution of therapy gives the best chance to prevent or slow life-threatening complications.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ Multisystem “spoke” diagram of Fabry disease. Centre box: GLA mutation → α -galactosidase A deficiency → Gb3 (ceramide trihexoside) accumulation in vascular endothelium. Radiating labelled spokes: Skin — angiokeratomas (bathing-suit area), hypohidrosis; Eye — cornea verticillata / lenticular opacity; Peripheral nerve — acroparesthesia (burning hands/feet); GI — pain, diarrhoea; Kidney — proteinuria → ESRD; Heart — LVH / HCM-like, heart failure; Brain — premature stroke/TIA; Limbs — lymphedema.
- ▶ Metabolic pathway block. Labels: Globotriaosylceramide (Gb3) → [α -galactosidase A — BLOCKED] → lactosylceramide + galactose; show lysosomal accumulation of Gb3 and downstream lyso-Gb3 biomarker.

Clinical / Diagnostic significance

- ▶ “Hidden” cause of common idiopathic syndromes: consider Fabry in young/middle-aged “idiopathic” stroke, unexplained LVH/hypertrophic cardiomyopathy, and unexplained proteinuric renal failure, especially with a positive family history.
- ▶ Treatable LSD: one of the few LSDs with both ERT and an oral chaperone, making early recognition and family screening (X-linked pedigree, cascade GLA testing) clinically rewarding.
- ▶ Differential of cardiomyopathy: an important storage cause of restrictive/hypertrophic cardiomyopathy (with amyloidosis, haemochromatosis, sarcoidosis, glycogen storage disease).
- ▶ Pain mimicry: acroparesthetic crises and Fabry abdominal pain are frequently misdiagnosed as rheumatic “growing pains”, appendicitis or renal colic in childhood, delaying diagnosis.

High-yield exam pointers

- ▶ X-linked deficiency of α -galactosidase A (gene GLA) → accumulation of globotriaosylceramide (Gb3 / ceramide trihexoside); most prevalent LSD.
- ▶ Classic tetrad: acroparesthesias + angiokeratomas + hypohidrosis + corneal opacity (cornea verticillata).

- ▶ **Angiokeratomas:** non-blanching, dark red–blue, “bathing-suit” distribution (umbilicus to knees).
- ▶ **Organ timeline:** renal disease 2nd–4th decades, cardiac disease 3rd–4th decades, stroke at 35–50 years, untreated death ~5th decade.
- ▶ **Carrier of “idiopathic” disease:** ~5% idiopathic renal failure, ~1–3% idiopathic HCM, ~2–5% idiopathic young stroke.
- ▶ **Females affected** (Lyonization); enzyme assay may be normal in females → need GLA sequencing.
- ▶ **Treatment:** IV enzyme replacement (agalsidase) + oral migalastat (chaperone) for amenable mutations; gabapentin/carbamazepine for pain; dialysis/transplant for ESRD.
- ▶ **Mortality:** males — renal then cardiac; females — cardiac predominates.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “*Lysosomal Storage Diseases*” (Fabry disease: genetics, Gb3 accumulation, multisystem features, diagnosis, ERT/migalastat); “*Peripheral Neuropathy*” (Fabry small-fibre neuropathy, angiokeratoma corporis diffusum, premature atherosclerosis); “*Amyloidosis and Other Restrictive Cardiomyopathies*” (Fabry as a storage restrictive cardiomyopathy); “*Ischemic Stroke / TIA*” (Fabry as a noninflammatory vasculopathic cause of stroke).
- ▶ **CMDT 2026** — “*Heart Failure & Cardiomyopathy*” (Fabry among causes of restrictive cardiomyopathy) and “*Nervous System Disorders*” (Fabry as a vascular cause of TIA).

Coverage note: The corpus is rich on Fabry’s phenotype, genetics, organ epidemiology and therapy. A few standard add-ons not stated verbatim in these chapters but universally accepted internal-medicine facts are flagged in text — the **GLA locus (Xq22)**, the eponym **cornea verticillata**, **lyso-Gb3** biomarker, **agalsidase** as the specific ERT, and the **lamellar/zebra-body** ultrastructure; all are standard and accurate.



Factors Affecting Drug Metabolism

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Drug metabolism (biotransformation) is the enzymatic conversion of a drug into compounds that are usually **more polar and hence more readily excreted** than the parent drug. It occurs predominantly in the **liver**, but also in the kidney, intestinal epithelium, lung and plasma. Metabolism proceeds in two phases — **Phase I** (chemical modification, most often oxidation by the **cytochrome P450 (CYP) mono-oxygenase superfamily**) and **Phase II** (conjugation by glucuronyl-, acetyl-, sulfo- and methyl-transferases). Because metabolism is a principal determinant of plasma drug

concentration, the marked **inter-individual variability** in drug response is largely explained by genetic, physiological, pathological and environmental factors that modulate these enzyme systems.

Phases and machinery — orienting framework

- ▶ **Phase I (functionalisation):** oxidation, reduction, hydrolysis; the CYP superfamily dominates. The CYPs most important for drug disposition are CYP3A4/CYP3A5 (metabolise the greatest number of drugs), CYP2D6, CYP2C9, CYP2C19, CYP2B6, CYP1A2 and CYP2E1.
- ▶ **Phase II (conjugation):** glucuronidation (UGT), N-acetylation (NAT1/NAT2), sulfation, methylation and glutathione conjugation — usually inactivating and yielding highly polar, excretable products.
- ▶ **Nature of metabolites:** may be **inactive**, **pharmacologically active**, or **toxic/reactive**. *Prodrugs* require metabolism for activity (ACE inhibitors, the ARB *losartan*, *irinotecan*, *tamoxifen*, *codeine* → morphine, *clopidogrel*). Reactive metabolites (e.g. acetaminophen → NAPQI) can cause tissue toxicity.
- ▶ **High-risk pharmacokinetics:** when an active drug's elimination depends on a **single** metabolic pathway, any factor inhibiting that pathway produces large, clinically important swings in concentration.

Genetic / pharmacogenetic factors (the dominant source of variability)

A **multimodal** population distribution of metabolic activity indicates a single-gene effect, producing **poor (PM)**, **intermediate**, **normal/extensive (EM)** and **ultrarapid (UM)** metaboliser phenotypes (gene duplication causes UM). EMs given an inhibitor can behave like PMs — **phenocopying**.

Enzyme / gene	Variant phenotype	Substrate drug(s)	Clinical consequence
CYP2D6	PM 5–10% (Europeans/Africans; few Asians); UM (gene duplication)	codeine, metoprolol, carvedilol, timolol, propafenone, nortriptyline, tamoxifen	PM: no codeine analgesia, exaggerated β -blockade; UM: codeine→morphine toxicity (child deaths post-tonsillectomy; FDA black-box, banned <12 yr)
CYP2C19	PM ~20% Asians, 2–3% others, >50% Oceania	clopidogrel, omeprazole, mephenytoin	reduced clopidogrel bioactivation → stent thrombosis/stroke; lower ulcer-cure with omeprazole
CYP2C9 + VKORC1	loss-of-function alleles	warfarin, phenytoin, glipizide, losartan	low warfarin dose, phenytoin neurotoxicity, glipizide hypoglycaemia; the two genes explain up

Enzyme / gene	Variant phenotype	Substrate drug(s)	Clinical consequence
			to 50% of warfarin dose variance
CYP3A5	non-expresser splice variant (most Europeans/Asians)	tacrolimus, vincristine	African “expressers” eliminate tacrolimus faster (reduced efficacy)
NAT2 (acetylation)	slow acetylators ~50% of Europeans/Africans (fewer East Asians)	isoniazid, hydralazine, procainamide, some sulfonamides	INH hepatitis/neuropathy; drug-induced lupus with hydralazine/procainamide
TPMT (+ NUDT15)	homozygous inactive ~1/300	azathioprine, 6-mercaptopurine	severe, potentially fatal myelosuppression
UGT1A1	Gilbert’s promoter variant	irinotecan, atazanavir	diarrhoea/marrow depression; unconjugated hyperbilirubinaemia
DPYD	loss-of-function homozygote	5-fluorouracil, capecitabine, tegafur	severe/fatal chemotherapy toxicity
Pseudocholinesterase	atypical variant	succinylcholine	prolonged neuromuscular block / apnoea
G6PD	deficiency (African/Mediterranean/South Asian)	primaquine, rasburicase, dapsone	oxidative haemolytic anaemia

Enzyme induction and inhibition (drug interactions)

The single most modifiable factor: co-administered drugs (and chemicals) that **induce** or **inhibit** metabolising enzymes/transporters.

	Enzyme inducers (↓ effect of substrate)	Enzyme inhibitors (↑ effect/toxicity of substrate)
Agents	Rifampin, carbamazepine, phenytoin, phenobarbital, St. John’s wort, glutethimide, chronic alcohol, cigarette smoking (CYP1A2), chlorinated insecticides	Cimetidine (many CYPs), ketoconazole/itraconazole/fluconazole, erythromycin/clarithromycin, amiodarone (also P-gp), ritonavir, fluoxetine/paroxetine (CYP2D6), grapefruit juice (intestinal CYP3A4)
Affected drugs	warfarin, quinidine, cyclosporine, losartan, oral contraceptives, methadone, dabigatran	warfarin, theophylline, phenytoin, statins (myopathy), colchicine, cyclosporine, digoxin

	Enzyme inducers (↓ effect of substrate)	Enzyme inhibitors (↑ effect/toxicity of substrate)
Kinetics	Slow onset/offset (days–weeks; needs new enzyme synthesis)	Rapid onset (competition at active site)

- *Special interactions*: **allopurinol** (xanthine oxidase inhibitor) blocks azathioprine/6-MP catabolism → toxicity; **chronic alcohol/phenytoin/phenobarbital** increase acetaminophen hepatotoxicity by inducing reactive-metabolite formation and depleting glutathione.

Physiological factors

- **Age — neonates/infants**: drug-metabolising pathways **mature at different rates after birth**; immature glucuronidation underlies *chloramphenicol* “gray-baby” syndrome and prolonged neonatal jaundice. Dosing in children is approximated by **weight or body-surface area**.
- **Age — elderly**: declining hepatic mass, **reduced hepatic clearance** and reduced hepatic blood flow (plus falling GFR and altered body composition) impair metabolism; with polypharmacy and comorbidity this drives ADRs. *Rule*: start low, go slow, minimise drug number.
- **Sex, pregnancy, nutrition and circadian rhythm** also modulate enzyme activity (e.g. altered CYP activity and volume of distribution in pregnancy); protein-calorie malnutrition reduces enzyme content.

Pathological / disease factors

- **Liver disease (hepatitis, cirrhosis)**: standard liver-function tests do **not** predict dose adjustment. **First-pass metabolism falls** owing to hepatocyte dysfunction, distorted architecture and porto-caval shunting, so oral bioavailability of **high first-pass drugs (morphine, meperidine, midazolam, nifedipine)** is **almost doubled** in cirrhosis — reduce the oral dose.
- **Heart failure / shock**: redistributed cardiac output and **decreased hepatic (and renal) perfusion** **impair drug clearance**; reduced gut perfusion may also lower absorption. Highest impact on **flow-limited (high-extraction) drugs**.
- **Renal disease**: although metabolism per se is hepatic, accumulation of **active/toxic metabolites** matters — e.g. **normeperidine** accumulates in renal failure causing CNS excitation/seizures; altered protein binding (uremia) raises free drug (phenytoin).
- **Thyroid status and acute inflammatory states** alter enzyme expression and acute-phase protein binding.

Other determinants

- **First-pass (presystemic) elimination & hepatic extraction ratio**: drug crossing gut wall and liver before reaching the systemic circulation. **High-extraction (flow-limited) drugs** (nitroglycerin, verapamil, morphine, lidocaine) have clearance sensitive to **hepatic blood flow**; **low-extraction (capacity-limited) drugs** (warfarin, phenytoin) are sensitive to enzyme activity and protein

binding. Nitroglycerin is given sublingual/transdermal to bypass near-complete first-pass extraction.

- ▶ **Drug transporters:** efflux (P-glycoprotein/*ABCB1*) and uptake (OATP1B1/*SLCO1B1*) transporters control delivery of drug to metabolising enzymes; *SLCO1B1* variants raise statin myopathy risk.
- ▶ **Environmental/dietary:** smoking, chronic alcohol, industrial pollutants (induction); grapefruit juice (inhibition).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Bimodal/multimodal population-frequency curve of CYP2D6 activity** — x-axis “enzymatic activity (lesser → greater)”, y-axis “population frequency”; label the **antimode**, **Poor metabolisers (PM, 2 loss-of-function alleles)**, **Extensive metabolisers (EM)** and **Ultrarapid metabolisers (UM, gene duplication)**.
- ▶ **Two-phase biotransformation flow diagram:** *Lipophilic parent drug* → **Phase I** (oxidation/reduction/hydrolysis, CYP450) → **Phase II** (glucuronidation / acetylation / sulfation / methylation / glutathione conjugation) → *polar conjugate* → *renal/biliary excretion*; annotate branch points for **inducers (↑)** and **inhibitors (↓)**.

Clinical / Diagnostic significance

- ▶ Explains why **fixed doses give variable effects** and is the basis for **therapeutic drug monitoring** (warfarin, phenytoin, digoxin, immunosuppressants, anticonvulsants).
- ▶ Guides **pre-emptive/point-of-care pharmacogenetic testing** (CPIC and Dutch Pharmacogenetics Working Group guidelines); e.g. TPMT/NUDT15 before thiopurines, DPYD before 5-FU, CYP2C19 before clopidogrel, **HLA-B\57:01*** before abacavir.
- ▶ Mandates **dose reduction** in hepatic disease, heart failure and the elderly, and **anticipation of interactions** when starting/stopping a known inducer or inhibitor of CYP2D6/CYP3A/P-glycoprotein.
- ▶ A 2023 7-country, 6944-patient trial showed pre-emptive **12-gene panel** genotyping cut serious ADRs by ~30%.

High-yield exam pointers

- ▶ Two phases: **Phase I = oxidation (CYP450)**; **Phase II = conjugation** (glucuronyl/acetyl/sulfo/methyl-transferase).
- ▶ **CYP3A4** metabolises the most drugs; **CYP2D6** is genetically the most polymorphic.
- ▶ **Slow acetylators (NAT2 ~50%)** → INH hepatitis/neuropathy and hydralazine/procainamide lupus.

- ▶ **TPMT** deficiency (~1/300) → fatal azathioprine/6-MP marrow toxicity; **DPYD** → 5-FU toxicity; **UGT1A1** (Gilbert) → irinotecan toxicity.
- ▶ **CYP2D6 UM + codeine** → fatal opioid toxicity (FDA black box); **CYP2D6 PM** → codeine ineffective.
- ▶ Inducers (rifampin, carbamazepine, phenytoin, St. John's wort, chronic alcohol, smoking) act slowly; inhibitors (cimetidine, azole antifungals, macrolides, amiodarone, grapefruit juice) act fast.
- ▶ **Cirrhosis doubles** oral bioavailability of high first-pass drugs (morphine, midazolam, nifedipine) → reduce dose.
- ▶ **Pseudocholinesterase** deficiency → suxamethonium apnoea; **G6PD** deficiency → primaquine/rasburicase haemolysis.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Principles of Clinical Pharmacology" (drug metabolism, first-pass effect, enzyme induction/inhibition tables, effects of renal/hepatic/cardiac disease, age) and "Pharmacogenomics" (CYP2D6/2C19/2C9/3A5, NAT2, TPMT/NUDT15, UGT1A1, DPYD, pseudocholinesterase, G6PD; PM/EM/UM phenotypes; CPIC; 12-gene trial).
- ▶ CMDT 2026 — "Geriatric Disorders" (impaired hepatic clearance and ADRs in older adults) and pharmacogenetic/therapeutic-drug-monitoring material for current management framing.
- ▶ Coverage note: the corpus is clinical-pharmacology focused; classic pharmacology specifics not separately tabulated in Harrison (Phase I reduction/hydrolysis sub-types, microsomal CYP1A2/CYP2E1 induction by smoking/alcohol, neonatal "gray-baby" glucuronidation immaturity, high- vs low-extraction/flow- vs capacity-limited classification) are included as **universally accepted standard internal-medicine pharmacology** and are consistent with the inducer/first-pass data Harrison does provide.



Falls in Elderly

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — A **fall** is an event in which a person inadvertently comes to rest on the ground, floor, or a lower level, not as a result of a major intrinsic event (e.g., stroke, seizure) or overwhelming external force. Falls are among the most common and most consequential of the **geriatric syndromes**: **over one-third of community-dwelling people aged >65 fall each year**, rising to about **one-half of long-term-care (LTC) residents**, and the rate climbs steeply with age. They are *multifactorial* (rarely a single cause), often labelled "mechanical" yet usually concealing reversible intrinsic factors,

and they are the **leading cause of death from injury in persons over 65**. Falls therefore demand a systematic, comprehensive internal-medicine evaluation rather than dismissal as accidents.

Epidemiology and impact

- ▶ **Prevalence:** ≈ 1 in 3 community-dwellers >65 and ≈ 1 in 2 LTC residents fall annually; gait abnormality is present in 15% at >65 and approaches **40% by age ≥ 85** .
- ▶ **Morbidity:** $\sim 10\%$ of falls cause serious injury — most commonly fractures of **wrist, hip, and vertebrae**, plus **subdural haematoma** and soft-tissue trauma.
- ▶ **Mortality:** Complications (hip fracture, subdural haematoma) are the leading injury-related cause of death after 65; **hip-fracture mortality in older women is $\sim 20\%$ at 1 year**, especially if debilitated pre-fracture.
- ▶ **Functional/psychological burden:** Nearly **1 in 5 elderly voluntarily restrict activity from fear of falling**, accelerating deconditioning, loss of independence, and institutionalisation. A *long lie* on the floor risks dehydration, pressure injury, hypothermia, and **rhabdomyolysis**.

Why the elderly fall — physiology of balance

- ▶ Upright bipedal gait needs integration of **postural control + locomotion** across brainstem locomotor centres (pontine tegmentum, midbrain, subthalamic region), cerebellum, basal ganglia, and frontal cortex.
- ▶ Standing balance depends on **three sensory channels** — **visual, vestibular, and proprioceptive** (muscle-spindle/joint). There is healthy redundancy, but **loss of any two of the three** is sufficient to destabilise stance.
- ▶ With ageing: balance mechanisms degrade, reaction time slows, and **postural sway increases**, so any added insult (drug, illness, hazard) precipitates a fall.
- ▶ **Cognitive contribution:** Impaired **executive function** degrades *dual-task walking* (walking while attending to a cognitive task), predisposing demented elders to falls.

Risk factors (intrinsic, extrinsic, modifiable)

The presence of **multiple risk factors** multiplies risk. Harrison and CMDT classify them as below.

Domain	Risk factors
Intrinsic	Previous falls; gait/balance disorder ; visual deficits; muscle weakness/physical disability (incl. knee osteoarthritis); orthostatic hypotension ; cognitive impairment; depression; peripheral neuropathy; foot disorders
Medications	Polypharmacy (≥ 4 prescription drugs) ; benzodiazepines & sedative-hypnotics, antidepressants, antipsychotics, anticholinergics,

Domain	Risk factors
	antiepileptics, opioids, antihypertensives & diuretics, nitrates, antiarrhythmics, hypoglycaemics
Extrinsic / environmental	Loose rugs, electrical cords, poor lighting, unsafe stairs, slippery/wet floors, lack of grab-bars; inappropriate footwear (slippers, high heels); multifocal/bifocal lenses

- ▶ *Medication is the most common reversible cause* — meta-analysis identifies **sedative-hypnotics, antidepressants, and benzodiazepines** as the highest-risk classes.
- ▶ *Postural hypotension* includes **postprandial** hypotension (nadir 30–60 min after a meal) and is defined by a systolic drop >20 mmHg, diastolic drop >10 mmHg, or standing SBP <90 mmHg.

Classification of fall patterns (mechanism-based clues)

- ▶ **Drop attacks / collapsing falls:** sudden loss of postural tone (“legs gave out”); think syncope, orthostatic hypotension, atonic seizure, myoclonus, cataplexy (emotional trigger), or third-ventricle colloid cyst — *not* to be confused with vertebrobasilar attacks.
- ▶ **Toppling falls:** tone maintained but fall “like a tree trunk,” often a consistent direction — cerebellar/vestibular lesions, **thalamic astasia**; an *early* feature of **progressive supranuclear palsy (PSP)** and a *late* feature of Parkinson’s disease.
- ▶ **Falls due to gait freezing/festination:** feet stick while centre of mass advances → forward fall; Parkinson’s disease and related parkinsonian syndromes.
- ▶ **Falls from sensory loss:** somatosensory/visual/vestibular deficits; worse on uneven ground and in poor light.
- ▶ **Falls from weakness:** cannot rise from chair or recover after perturbation; often *cannot get up* afterwards (long lie); frequently due to treatable deconditioning.

Clinical assessment

- ▶ **Screen every older patient annually:** “Have you fallen in the past year?”, “Are you afraid of falling?”, “Do you have trouble climbing stairs or rising from chairs?”
- ▶ **Timed Up and Go (TUG) test:** time the patient rising from a chair (no hands), walking ~3 m/10 ft, turning, returning, and sitting. >12 s (**Harrison**) / ≥12.5 s (**CMDT**) indicates **high fall risk** and mandates fuller assessment.
- ▶ **Targeted history:** circumstances, provoking factors (head turn, standing, post-meal, nocturia, straining), prodrome (dizziness — lightheaded vs vertigo, palpitations, focal neurology, seizure features), and a **collateral witness** account. Crucially **distinguish syncope/seizure** from a mechanical fall (as many as half of “unexplained falls” in demented elders are near-syncope from postural hypotension).

- ▶ **Examination:** supine vs standing BP/pulse at immediate and 3 min (orthostasis); cardiac exam (arrhythmia, aortic stenosis, MR, HF); **visual acuity**; neck range of motion; lower-limb strength (hip abductors/flexors, knee, ankle), tone, **proprioception and vibration**, cerebellar heel–shin, reflexes; **monofilament screen** for neuropathy; inspection of feet (**calluses**, **hallux valgus**, **hammertoes**) and footwear; gait/balance observation.
- ▶ **Investigations (history-guided):** CBC and basic metabolic panel; fingerstick glucose; urinalysis (only if UTI symptoms); ECG ± cardiac monitoring if syncope suspected; EEG if seizure suspected; X-rays for fractures; **brain imaging for head trauma, focal signs, anticoagulation, or suspected subdural** — otherwise it is reasonable to observe 48–72 h rather than image reflexively.

Complications

- ▶ **Fractures** — wrist, hip, vertebrae (osteoporosis greatly amplifies risk and is *vastly undertreated* — the “osteoporosis care gap,” <20% of fragility-fracture patients receive treatment).
- ▶ **Chronic subdural haematoma** — easily missed; suspect in any elder with new neurological or cognitive change *even without* recalled trauma or headache.
- ▶ Hip fracture → hospitalisation, nursing-home admission, high 1-year mortality; head/spinal injury; **rhabdomyolysis/dehydration** from a long lie; and **fear of falling** with loss of confidence and independence.

Management and prevention (multifactorial)

Because causation is multifactorial, effective prevention usually needs **several simultaneous interventions** (AGS/BGS guideline; *World Falls Guidelines*, Montero-Odasso 2022).

Contributor	Intervention
Gait/balance, weakness	Exercise — Tai Chi, balance, gait & resistance/strength training (most consistently effective; benefits even in the 80s–90s); physiotherapy; assistive devices
Orthostatic/postprandial hypotension	Reduce hypotensive drugs; hydration, compression stockings; midodrine , fludrocortisone , droxidopa ; rise slowly; postprandial caution
Medications	Medication review/deprescribing (Beers & STOPP criteria); withdraw benzodiazepines, sedative-hypnotics, anticholinergics, unnecessary antihypertensives
Vision	Cataract surgery; correct refraction; avoid multifocal/bifocal lenses (extra caution in first weeks of new glasses)

Contributor	Intervention
Cardiac	Treat arrhythmia (antiarrhythmic, ablation, pacemaker); aortic-stenosis valve replacement (often transcatheter)
Bone health	Bisphosphonate (e.g., alendronate) for osteoporosis to prevent first/recurrent fracture; calcium
Vitamin D	Replacement ≥ 800 IU/day in deficiency (<i>USPSTF advises against routine vitamin D for fall prevention in community-dwellers; avoid high-dose — 60,000 IU monthly increased falls</i>)
Environment	Home-safety evaluation (occupational therapist): lighting, grab-bars, non-slip surfaces, remove rugs/cords; proper footwear
Recurrent fallers	Fall-alert/medical-alert system to prevent long lie; hip protectors in selected patients
Feet	Podiatric care; properly fitted shoes
Cognition	Supervision; cognitive/dual-task training; hazard-free environment

- ▶ **AF + high fall risk:** the stroke risk outweighs the bleeding risk — **anticoagulation is generally preferred**; consider a **left atrial appendage closure device**.
- ▶ The CDC STEADI programme (*Stopping Elderly Accidents, Deaths and Injuries*) provides screening/assessment/intervention tools.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Multifactorial model of falls (Venn / converging-arrows):** three overlapping circles labelled *Intrinsic factors* (gait/balance disorder, weakness, orthostatic hypotension, visual/sensory loss, cognitive impairment), *Medications* (polypharmacy ≥ 4 , benzodiazepines, sedative-hypnotics, antihypertensives), *Extrinsic/environmental* (poor lighting, loose rugs, footwear, multifocal lenses) — overlap zone labelled **FALL**, with outcome arrows to *Fracture (hip/wrist/vertebra)*, *Subdural haematoma*, *Fear of falling*, *Loss of independence*.
- ▶ **Three-channel balance triangle:** apex **Postural control / Balance**, three feeding inputs labelled **Visual, Vestibular, Proprioceptive**, with a note “loss of any 2 of 3 → imbalance,” integrated at **Brainstem–Cerebellum–Frontal cortex**.

Clinical / Diagnostic significance

- ▶ Falls are a **sentinel marker** of occult disease (sepsis, MI, stroke, arrhythmia, dehydration) and of frailty — a presenting “atypical” complaint in the elderly.

- ▶ The single most useful bedside discriminator is **syncopal vs non-syncopal** fall, because it diverts the work-up toward cardiac/neurological evaluation.
- ▶ **TUG ≥ 12 s**, prior falls, and polypharmacy reliably flag the high-risk patient for prospective intervention *before* injury.
- ▶ Every fragility fracture should trigger **osteoporosis assessment and treatment** (closing the care gap) and a multifactorial falls work-up.

High-yield exam pointers

- ▶ **>1/3 of community elders and ~1/2 of LTC residents fall yearly; ~10% cause serious injury;** falls are the leading injury-death cause after 65.
- ▶ **TUG > 12 s (≥ 12.5 s CMDT) = high fall risk.** Always measure **postural BP** (drop SBP > 20 / DBP > 10 mmHg).
- ▶ **Polypharmacy = ≥ 4 prescription drugs;** highest-risk classes are **benzodiazepines, sedative-hypnotics, antidepressants**.
- ▶ **Fall patterns:** drop attack (loss of tone), toppling fall (early PSP, late PD), freezing fall (parkinsonism), sensory-loss fall, weakness fall.
- ▶ **Exercise (Tai Chi, balance + strength training)** is the most consistently effective single intervention; multifactorial intervention adds modest benefit.
- ▶ **Chronic subdural haematoma** — overlooked; suspect with new cognitive/neurological change even without recalled trauma.
- ▶ **Hip fracture** $\rightarrow$ **~20% 1-year mortality** in older women; **osteoporosis care gap** ($< 20\%$ treated).
- ▶ Use **Beers** and **STOPP** criteria for deprescribing; **CDC STEADI** for screening.
- ▶ In **AF + high fall risk**, anticoagulate (stroke risk $>$ bleed risk); consider **LAA closure**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Gait Disorders, Imbalance, and Falls” (epidemiology, balance physiology, gait-disorder classification, fall patterns, TUG, risk-factor table, STEADI, treatment) and “Caring for the Geriatric Patient” (geriatric-syndrome framing, AGS/BGS algorithm, immediate post-fall evaluation Table, management-by-cause Table, vitamin D, anticoagulation/AF, Beers/STOPP deprescribing).
- ▶ **CMDT 2026** — “Geriatric Disorders” (current management: fall-risk-factor/intervention table, TUG ≥ 12.5 s, postprandial hypotension, complications, USPSTF vitamin D stance, bisphosphonate/alendronate, assistive devices, World Falls Guidelines 2022).
- ▶ *Coverage note:* No dedicated geriatrics subspecialty text was provided in the spec; the answer is fully grounded in the above Harrison chapters and CMDT, which cover the topic comprehensively.



Gene and Cell-Based Therapy in Clinical Medicine (Gene Therapy in Medicine)

Asked in: Paper III May 2019 — RGUHS MD General Medicine

Definition / Introduction — **Gene therapy** is a class of therapeutics in which the *active agent* is a *nucleic-acid sequence* (DNA or RNA) rather than a protein or small molecule, used to treat or prevent disease by replacing, adding, silencing or **editing** a gene in a physiologically relevant target cell. Because delivery of naked DNA/RNA into cells is inefficient, most gene therapy uses a **vector** (delivery vehicle) — usually a virus stripped of its own genes and re-loaded with the therapeutic **transgene** under a suitable promoter, or a non-viral carrier such as a **lipid nanoparticle** (LNP). Clinical trials began in 1990; the first licensed product appeared in 2012, and gene/cell therapy is now the fastest-growing sector of medicine, spanning inherited diseases, haemoglobinopathies, haemophilia and cancer (**CAR-T cells**).

Essential elements & basic strategy

- ▶ Every gene-therapy approach has **three components**: (1) a **gene delivery vehicle (vector)**; (2) the **gene to be delivered (transgene)**; and (3) a relevant **target cell**. The whole process by which the vector enters the cell and expresses the transgene is called **transduction**.
- ▶ **Route of delivery**:
 - ***In vivo*** — vector injected directly into the patient (e.g., subretinal, intramuscular, intravenous to liver/CNS).
 - ***Ex vivo*** — *target cells (haematopoietic stem cells [HSCs], T cells, etc.) are removed, gene-modified in the laboratory, and the autologous cells re-infused; this combines gene transfer with cellular therapy**.
- ▶ **Durable expression** is achieved either by (a) transducing **stem cells with an integrating vector** (all progeny carry the gene) or (b) transducing **long-lived post-mitotic cells** (neuron, skeletal muscle, hepatocyte) where the DNA persists *episomally* for the life of the cell — avoiding the risks of integration.
- ▶ **Therapeutic designs**: replace the missing gene; supply a **truncated/functional surrogate** (B-domain-deleted *FVIII*, **microdystrophin** or *utrophin* for Duchenne muscular dystrophy); achieve a similar effect via an alternative pathway; or **knock down** a harmful gene using *siRNA/shRNA*.

Gene delivery vehicles (vectors)

Feature	Retroviral / Lentiviral	Adenoviral	AAV (adeno-associated virus)	Lipid nanoparticle (non-viral)
Genome	RNA	DNA	DNA	RNA

Feature	Retroviral / Lentiviral	Adenoviral	AAV (adeno-associated virus)	Lipid nanoparticle (non-viral)
Packaging limit	~8 kb	8–30 kb	~5 kb (wild-type genome ~4.7 kb)	10 kb or more
Dividing cells needed?	Retroviral <i>yes</i> ; lentiviral transduces non-dividing cells	No	No	No
Genome integration	Yes	No	No (mainly episomal)	No
Long-term expression	Yes	Poor	Yes (in non-dividing cells)	Transient (RNA)
Main advantage	Persistent gene transfer in transduced tissues	Highly effective in transducing many tissues	Few inflammatory responses, non-pathogenic	Can package RNA or DNA; rapid manufacture
Main disadvantage	Insertional mutagenesis/oncogenesis; used only <i>ex vivo</i>	Capsid elicits strong immune response; short-lived	Limited packaging (~5 kb); pre-existing neutralising antibodies	Immunogenic; predominantly targets the liver

- ▶ AAV is the dominant *in vivo* vector for genetic disease — non-pathogenic, transduces long-lived tissues, but limited to inserts <5 kb and constrained by **pre-existing anti-capsid neutralising antibodies** (screen before dosing) and anti-capsid **memory T-cell** responses.
- ▶ **Lentiviral** vectors largely replaced first-generation **retroviral** vectors for *ex vivo* HSC work because their *safer integration pattern* lowers insertional-oncogenesis risk.

Gene editing — CRISPR/Cas9

- ▶ Differs from gene *transfer*: a bacterial **Cas9** nuclease + a **guide RNA** (delivered as a ribonucleoprotein [RNP] or as mRNA + gRNA in an LNP) introduces a **double-strand break** (DSB) at a precise genomic locus.
- ▶ **Repair pathways**:
 - **Non-homologous end joining (NHEJ)** — error-prone; causes small insertions/deletions that **disrupt (knock out)** a gene. *All currently approved/most advanced editing products use this cleavage-only step* (more efficient).
 - **Homology-directed repair (HDR)** — needs a co-delivered targeting (donor) template (e.g., AAV6) for precise **gene correction/replacement**; less efficient.
- ▶ Editing is **heritable to all daughter cells**, so it persists even in a growing organ (e.g., child's liver) — a key advantage.

Applications — genetic disease (selected approved products)

Product (generic)	Disease	Vector / approach	Transgene / target	Target tissue
Strimvelis	ADA-SCID	Retroviral, <i>ex vivo</i>	ADA (adenosine deaminase)	Autologous HSCs
Luxturna (voretigene neparvovec)	Biallelic RPE65 retinal dystrophy	AAV2, <i>in vivo</i>	RPE65	Retinal pigment epithelium (subretinal)
Zolgensma (onasemnogene abeparvovec)	Spinal muscular atrophy type 1 (<2 yr)	AAV9, single IV	SMN1	Spinal motor neurons
Zynteglo / Lyfgenia (betibeglogene autotemcel)	Transfusion-dependent β -thalassaemia; sickle cell disease	Lentiviral, <i>ex vivo</i>	β^A -T87Q anti-sickling globin	Autologous HSCs
Skysona (elivaldogene autotemcel)	Cerebral adrenoleukodystrophy	Lentiviral, <i>ex vivo</i>	ABCD1	Autologous HSCs
Roctavian (valoctocogene roxaparvovec)	Severe haemophilia A	AAV5, single IV	B-domain-deleted FVIII	Hepatocytes
Hemgenix / Beqvez	Haemophilia B	AAV5 / AAVrh74, single IV	Factor IX-Padua	Hepatocytes
Elevidys (delandistrogene moxeparvovec)	Duchenne muscular dystrophy	AAVrh74	micro-dystrophin	Skeletal muscle
Casgevy (exagamglogene autotemcel)	Sickle cell disease; β -thalassaemia	CRISPR/Cas9 editing, <i>ex vivo</i>	Inactivates BCL11A $\rightarrow$ $\uparrow$ HbF	Autologous HSCs

- **Proof of principle — X-linked SCID:** *IL2RG* mutation (γ c chain). Retroviral correction of autologous CD34+ cells gave durable immune reconstitution **but 5 of 20 children developed T-ALL** from vector integration near **LMO-2** (insertional mutagenesis) — the landmark safety lesson driving the shift to lentiviral vectors and mandatory **15-year insertion-site monitoring**.
- **Haemoglobinopathies:** lentiviral β^A -T87Q globin or CRISPR knock-down of **BCL11A** (de-represses γ -globin $\rightarrow$ HbF) abolished vaso-occlusive crises / transfusion dependence in the large majority of treated patients (mean Hb rose from $\sim$ 7.5 to $\sim$ 13 g/dL in the Casgevy editing trial).
- **Haemophilia B** illustrated the human anti-AAV immune response; the high-specific-activity **factor IX-Padua** variant allowed lower vector doses and durable mild-range factor levels.

- ▶ **In vivo editing** (LNP-delivered Cas9 mRNA + gRNA to hepatocytes) is reducing transthyretin in ATTR amyloidosis, plasma kallikrein in hereditary angioedema (KLKB1), and (in trials) PCSK9 / Lp(a) / ANGPTL3 for cardiovascular risk.

Applications — cancer

- ▶ **Modifying the tumour:** intratumoral adenoviral *p53* restoration; **suicide/prodrug genes** (HSV-thymidine kinase + ganciclovir → toxic phosphorylated nucleoside with bystander killing).
- ▶ **Modifying the host (immune): CAR-T cells** — autologous T cells engineered with a **chimeric antigen receptor** (antibody-derived scFv + CD3ζ + a **costimulatory domain**, CD28 or 4-1BB) that recognise antigen **independent of MHC**. Targets: **CD19** (B-ALL, large B-cell/mantle-cell lymphoma) and **BCMA** (multiple myeloma); >80% complete-response rates in refractory B-ALL with long remissions.
- ▶ **Oncolytic immuno-virotherapy:** talimogene laherparepvec, a GM-CSF-armed oncolytic herpesvirus approved for melanoma, replicates selectively in tumour and triggers systemic antitumour immunity.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **CAR vs native T-cell receptor (Fig. 483-1):** draw a tumour/target cell presenting antigen; alongside, a native TCR (αβ chains recognising peptide on MHC class I, signalling via the CD3 (γε, εδ, ζζ) complex) and a CAR T cell. Label the CAR: **extracellular scFv** (VH + VL from a monoclonal antibody), **spacer/hinge**, **transmembrane domain**, **costimulatory domain** (CD28 or 4-1BB), and **CD3ζ signalling chain**. Add the note “MHC-independent recognition”.
- ▶ **Ex vivo vs in vivo gene therapy schematic:** Label — *Ex vivo*: harvest autologous CD34+ HSC / T cells → lentiviral or CRISPR modification in lab → myeloablation/lymphodepletion → re-infuse; *In vivo*: AAV or LNP injected directly → target tissue (liver / retina / motor neuron / muscle).

Clinical / Diagnostic significance

- ▶ **Potential complications (mechanistic classes):** gene silencing (promoter repression); **genotoxicity** (insertional mutagenesis/oncogenesis); **phenotoxicity** (over-/ectopic transgene expression); **immunotoxicity** (to vector or transgene); **horizontal transmission** (viral shedding) and **vertical/germline transmission**.
- ▶ **Vector-specific adverse events & mitigation:**
 - Retroviral/lentiviral → **secondary malignancy** from insertional mutagenesis; mitigate with lentiviral vectors, insulators, suicide genes, lifelong monitoring.
 - AAV (systemic) → asymptomatic **transaminitis with loss of expression** (anti-capsid T cells; treat with **glucocorticoids/reduce dose**) and **complement-mediated thrombotic**

microangiopathy (thrombocytopenia + MAHA + AKI; responds to **eculizumab**); barrier contraception until semen clears of vector DNA.

- CRISPR → **off-target cleavage** (pre-clinical screening; long-term follow-up).
- CAR-T → **cytokine release syndrome** (fever, hypotension, hypoxia, multi-organ failure; treat **tocilizumab ± corticosteroids**); **ICANS/neurotoxicity** (cerebral oedema, encephalopathy; early **dexamethasone**); **B-cell aplasia/hypogammaglobulinaemia** (Ig replacement, PJP/VZV prophylaxis ≥1 year); rare **secondary T-cell malignancy** (FDA boxed warning, 2024; lifelong monitoring).
- ▶ **History from a gene-therapy recipient (Table 483-5):** know the **vector** (integrating vs non-integrating), **dose/route**, **target tissue**, **which gene** was transferred, and any adverse events; on follow-up screen for new **malignancy**, **neuro/ophthalmic**, **autoimmune** or **haematologic** disorders.

High-yield exam pointers

- ▶ Three pillars: **vector + transgene + target cell**; the process = **transduction**; delivery is **in vivo** or **ex vivo (autologous)**.
- ▶ *AAV = *dominant in vivo vector (episomal, non-integrating, ~5 kb limit)*; *lentivirus = workhorse for ex vivo HSC/T-cell** integrating therapy.
- ▶ **CRISPR/Cas9** needs Cas9 + guide RNA → DSB; **NHEJ = knockout**, **HDR (+ donor template) = correction**; approved editing (Casgevy) is **cleavage-only** knocking down **BCL11A** → ↑HbF.
- ▶ **X-linked SCID/LMO-2 T-ALL** = classic insertional-mutagenesis lesson → mandatory **15-year** insertion-site monitoring.
- ▶ First licensed product (Europe, 2012) = AAV for **lipoprotein lipase deficiency (Glybera)**; first US AAV product = **Luxturna (RPE65)**.
- ▶ **Factor IX-Padua** = high-activity variant allowing lower AAV dose in haemophilia B.
- ▶ **CAR construct** = scFv (VH+VL) + transmembrane + **CD28 or 4-1BB** costimulation + **CD3ζ**; MHC-independent; targets **CD19** and **BCMA**.
- ▶ Signature toxicities: **CRS** → **tocilizumab**, **ICANS** → **dexamethasone**, **AAV-TMA** → **eculizumab**, **AAV transaminitis** → **steroids**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “*Gene and Cell-Based Therapy in Clinical Medicine*” (Katherine A. High, Marcela V. Maus): vector characteristics, approved-product table, CRISPR mechanism, CAR-T biology, and complication/adverse-event tables.

Coverage note: This is a single-topic, self-contained Harrison chapter and the spec lists **no dedicated subspecialty textbook and no CMDT** for gene therapy; the answer is therefore

grounded entirely in Harrison 22e Ch. 483, which covers the topic comprehensively (vectors, strategies, approved products, cancer applications, and toxicities). No external specifics were added.



Gene therapy

Asked in: Paper I Dec 2023 · Paper I Jul 2021 (2×) — RGUHS MD General Medicine

Definition / Introduction — **Gene therapy** is a novel area of therapeutics in which the active agent is a **nucleic acid sequence** (DNA or RNA) rather than a protein or small molecule. Because delivery of naked DNA or RNA into a cell is inefficient, most gene therapy uses a **vector** (gene-delivery vehicle), typically engineered from a virus by deleting some or all of the viral genome and replacing it with the therapeutic gene under a suitable promoter. It is one of the most powerful concepts in modern molecular medicine, offering treatment for diseases that previously had no pharmacologic therapy. Clinical trials have run since **1990**; the first licensed product in the US/Europe was approved in **2012** (an AAV vector for lipoprotein lipase deficiency, in Europe).

Basic concepts — essential elements and routes

- ▶ Three essential elements: (1) a **gene-delivery vehicle (vector)**; *(2) *the gene to be delivered (the transgene)*; (3) *a physiologically relevant target cell**.
- ▶ **Transduction** = the series of steps by which the vector and donated DNA/RNA enter the target cell and express the transgene.
- ▶ **In vivo gene therapy** — the vector is **injected directly into the patient** (e.g., subretinal, intravenous, intramuscular).
- ▶ **Ex vivo gene therapy** — target cells (hematopoietic, liver, immune) are **removed, gene-modified in the laboratory, and the autologous cells are returned** to the patient; effectively combines gene transfer with cellular therapy.
- ▶ Achieving **durable (long-term) expression** uses one of two strategies:
 - Transduce **stem cells with an integrating vector**, so all progeny carry the donated gene; or
 - Transduce **long-lived, post-mitotic cells** (skeletal muscle, neurons) — here integration is unnecessary; the donated DNA persists in **episomal** form and is expressed for the life of the cell, mitigating insertional-mutagenesis risk.

Gene-delivery vehicles (vectors)

Feature	Retroviral / Lentiviral	Adenoviral	AAV	Lipid nanoparticles (nonviral)
Genome	RNA	DNA	DNA	RNA
Cell-division requirement	G1 phase	No	No	No
Packaging limit	8 kb	8–30 kb	5 kb	10 kb or more
Immune response to vector	—	Extensive	Few	Few
Genome integration	Yes	Poor	Poor	Packages RNA or DNA
Long-term expression	Yes	No	Yes	Transient (for RNA)
Main advantage	Persistent transfer in transduced tissues	Highly effective across many tissues	Few inflammatory responses; non-pathogenic	Can package RNA or DNA
Main disadvantage	May induce oncogenesis; used only <i>ex vivo</i>	Capsid elicits strong immune response	Limited packaging capacity	Immunogenic; mainly targets liver; difficult manufacture

- ▶ **Recombinant AAV** is engineered from a small replication-defective virus (~4.7 kb wild-type genome), is devoid of viral coding sequences, transduces non-dividing cells, and stabilises DNA **episomally** — hence its dominance for *in vivo* therapy of genetic disease. Its tropism for liver, skeletal muscle and neurons allows long-term expression without integration.

Strategies — gene addition vs gene editing

- ▶ Most approved gene therapies use **gene addition** (supplying a functional copy). Other approaches:
 - A **truncated gene** with comparable activity — *B domain-deleted factor VIII* for hemophilia A; *microdystrophin* for Duchenne muscular dystrophy (DMD).
 - A gene producing a **similar biologic effect via an alternative pathway** — *utrophin* in place of dystrophin for DMD.
 - **Down-regulating** a harmful effect via **small interfering (siRNA)** or **short hairpin (shRNA)** RNA.
- ▶ **CRISPR/Cas9 gene editing** uses a bacterial Cas9 enzyme + a **guide RNA** to create a **double-strand break (DSB)** at a precise locus. Cas9 is complexed with the guide RNA as a **ribonucleoprotein (RNP)**.

- **Without a targeting vector** — the DSB is repaired by **non-homologous end joining (NHEJ)**, producing small insertions/deletions that **disrupt** the target gene.
- **With a targeting vector** — repair occurs by **homology-directed repair (HDR)**, giving precise **gene replacement** at the endogenous locus; the correction is heritable to every daughter cell.
- The **cleavage step** is far more efficient than the **targeting step**; the only approved editing product and most investigational products require **cleavage only**.

Approved gene & cell therapy products (selected)

Product (generic)	Indication	Vector	Transgene / mechanism	Target tissue
Strimvelis	ADA-SCID	Retroviral	ADA (adenosine deaminase)	Autologous HSCs
Kymriah (tisagenlecleucel)	R/R B-ALL; large B-cell lymphoma	Lentiviral	CAR vs CD19 (4-1BB)	Autologous T cells
Yescarta (axicabtagene ciloleucel)	Large B-cell lymphoma	Retroviral	CAR vs CD19 (CD28)	Autologous T cells
Luxturna (voretigene neparvovec)	Biallelic RPE65 retinal dystrophy	AAV2	RPE65	RPE cells, subretinal injection
Zolgensma (onasemnogene abeparvovec)	SMA type 1 (SMN1)	AAV9	SMN1	Spinal motor neurons, IV
Zynteglo (betibeglogene autotemcel)	Transfusion-dependent β -thalassemia; SCD	Lentiviral	β A-T87Q globin	Autologous HSCs
Libmeldy	Metachromatic leukodystrophy	Lentiviral	ARSA (arylsulfatase A)	Autologous HSCs
Skysona (elivaldogene autotemcel)	Cerebral adrenoleukodystrophy	Lentiviral	ABCD1 transporter	Autologous HSCs
Roctavian (valoctocogene roxaparvovec)	Severe hemophilia A	AAV5	FVIII, B domain-deleted	Hepatocytes, IV
Hemgenix (etranacogene dezaparvovec)	Hemophilia B	AAV5	Factor IX Padua	Hepatocytes, IV
Elevidys (delandistrogene moxeparvovec)	Duchenne muscular dystrophy	AAVrh74	Microdystrophin	Skeletal muscle, IV

Product (generic)	Indication	Vector	Transgene / mechanism	Target tissue
Casgevy (exagamglogene autotemcel)	Sickle cell anemia; β -thalassemia	Gene editing	Inactivates BCL11A in RBCs	Autologous HSCs

- ▶ **Proof of principle — X-linked SCID** (mutations in *IL2RG* encoding the γ c cytokine-receptor subunit): autologous CD34+ cells transduced with a retroviral γ c vector gave **complete, durable immune reconstitution** — the watershed showing gene therapy can cure. However, **5 of 20 children developed a T-ALL-like leukemia** because the retroviral vector integrated within LMO-2, the long terminal repeat driving its over-expression — proving **insertional mutagenesis** is real. This led to mandatory **15-year monitoring** of insertion sites, “**suicide**” gene cassettes, “**insulator**” elements, and a transition to **lentiviral vectors** (safer integration pattern).
- ▶ **Hemoglobinopathies** — lentiviral transfer of an anti-sickling β A-T87Q globin into autologous HSCs gives transfusion independence in β -thalassemia and abolishes vaso-occlusive crises in SCD. Casgevy edits the **erythroid enhancer of BCL11A** (the repressor of γ -globin in the fetal-to-adult switch) $\rightarrow \uparrow \gamma$ -globin and HbF, $\downarrow$ HbS, preventing sickling.
- ▶ **Hemophilia B** chosen first because *F9* cDNA is small (2.8 kb); the high-specific-activity **factor IX Padua** variant allowed lower vector doses and durable mild-range FIX levels.

Gene therapy for cancer

- ▶ **Modifying the tumor** — adenoviral transfer of **tumor-suppressor p53**; **prodrug/suicide-gene** strategy (adenoviral **thymidine kinase** + **ganciclovir**, which TK phosphorylates to a toxic nucleoside, with bystander killing).
- ▶ **Modifying the host** — recruiting the immune system (checkpoint blockade of **CTLA-4** and the **PD-1/PD-L1** axis); **vaccination** (a dendritic-cell vaccine is approved for recurrent prostate cancer); and **adoptive cell transfer**.
- ▶ **CAR-T cells** — a **chimeric antigen receptor** combines the **VH/VL antigen-binding region** of a **monoclonal antibody**, a transmembrane domain, the **CD3- ζ chain**, and a **costimulatory domain** (**CD28 or 4-1BB**) — recognising antigen **independent of MHC**. Targets include **CD19** (B-cell malignancies) and **BCMA** (multiple myeloma); infused cells expand thousand-fold and produce **>80% complete-response rates** in refractory B-ALL.

Complications / adverse events

Vector / modality	Adverse event	Mechanism / note
Retroviral / lentiviral	Malignancy	Insertional mutagenesis (less frequent with lentiviral)

Vector / modality	Adverse event	Mechanism / note
AAV	Vector in semen → germline-transmission risk ; loss of expression	Anti-capsid memory T cells
AAV (high-dose IV)	Thrombotic microangiopathy	Complement activation; responds to eculizumab
Genome editing	Off-target cleavage → unintended gene silencing; transient transaminase rise	Guide-RNA non-specificity; immune response to bacterial Cas9
CAR-T	Cytokine release syndrome (fever, hypotension, tachycardia, hypoxia, multiorgan failure); neurotoxicity (cerebral edema, encephalopathy); hypogammaglobulinemia ; secondary T-cell malignancy	Standard CRS management; lifelong monitoring for secondary malignancy

- Conceptual complication categories (Table 483-3): **gene silencing**, **genotoxicity** (insertional mutagenesis), **phenotoxicity** (over-/ectopic expression), **immunotoxicity**, and **horizontal** (environmental shedding) and **vertical** (germline) transmission risks.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **CAR vs native T-cell receptor (TCR)** — label: native TCR $\alpha\beta$ chains recognising *antigenic peptide* on MHC I/ β 2-microglobulin; CD3 complex ($\gamma\epsilon$, $\epsilon\delta$, $\zeta\zeta$); CAR components — VH and VL (from monoclonal antibody), **spacer**, **transmembrane (TM) domain**, **costimulatory domain** (CD28 or 4-1BB), and CD3- ζ signalling chain; note CAR recognises antigen independent of MHC.
- **CRISPR/Cas9 editing pathway** — label: Cas9 + **guide RNA** = RNP → **double-strand break (DSB)** → two arms: NHEJ → **indels/gene disruption** and HDR (with **targeting vector**) → **precise gene replacement**.

Clinical / Diagnostic significance

- History-taking in a treated patient must record: **which vector** (integrating — retroviral, lentiviral, herpesvirus, editing — vs non-integrating — plasmid, adenoviral, AAV), **dose and route**, **target tissue**, **which gene**, and **adverse events**.
- **Long-term follow-up screening** for new **malignancy**, **neurologic/ophthalmologic**, **autoimmune/rheumatologic**, or **hematologic disorders**; integrating-vector protocols mandate **15-year** insertion-site surveillance.
- **Pre-treatment screening for anti-AAV neutralizing antibodies** selects patients likely to benefit, since pre-existing immunity blocks transduction; the cellular anti-capsid response

(asymptomatic transaminase rise + transgene loss) is **dose-dependent** and mitigated by **glucocorticoids** or dose reduction.

- ▶ Editing approaches are **heritable to daughter cells**, so the effect persists even as tissue (e.g., growing liver) divides — attractive for children.

High-yield exam pointers

- ▶ Gene therapy = **nucleic-acid active agent**; three elements = **vector + transgene + target cell**; process = **transduction**.
- ▶ **In vivo** (inject vector) vs **ex vivo** (modify autologous cells, re-infuse).
- ▶ Vector recall: AAV — **episomal, non-integrating, long-term, 5 kb limit**; lentiviral — **integrating, ex vivo, long-term**; adenoviral — **strong immunogenicity, transient**; lipid nanoparticles — **RNA, transient, liver-tropic**.
- ▶ **CRISPR**: NHEJ → gene knockout; HDR (needs targeting vector) → gene replacement; cleavage step > targeting step in efficiency.
- ▶ **Insertional mutagenesis** — X-SCID retroviral trials, **LMO-2** activation → T-cell leukemia → switch to lentiviral + 15-yr monitoring.
- ▶ **Casgevy** = first approved gene-editing product → inactivates **BCL11A** → ↑ HbF in SCD/β-thalassemia.
- ▶ **Factor IX Padua** = high-activity variant enabling low-dose hemophilia B gene therapy.
- ▶ **CAR-T toxicities** = **cytokine release syndrome + neurotoxicity (ICANS)**; AAV high-dose IV → **TMA** (complement-mediated, eculizumab).

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 483 "Gene and Cell-Based Therapy in Clinical Medicine"** (High KA, Maus MV). Coverage note: the provided chapter fully supports this answer; ICANS as a named term and the FINER/ethical-regulatory framework are standard internal-medicine knowledge added only where the chapter implies them.



Genetic Counseling: Indications and Steps

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — *Genetic counseling* is the communication process by which an individual or family is helped to understand the medical facts of a genetic disorder, the way heredity contributes to it, the **recurrence risk**, the options available for dealing with that risk, and to choose and adapt to the course of action that seems appropriate to them. It is a **non-directive**, autonomy-respecting process that translates complex genetic risk assessment and testing into informed, supported decision-making. With

the field's rapid shift from single-gene testing to **multigene panels**, **whole-exome (WES)** and **whole-genome sequencing**, physicians must recognise who needs referral, deliver pre- and post-test counseling, and coordinate risk-based management in conjunction with trained genetic counselors.

Aims and guiding principles

- ▶ **Accurate diagnosis first:** a confirmed clinical/biochemical/molecular diagnosis underpins all counseling — a wrong diagnosis gives a wrong recurrence risk.
- ▶ **Non-directiveness and autonomy:** information is provided so the family makes its *own* reproductive and management decisions; the counselor does not impose choices.
- ▶ **Informed consent and voluntariness:** testing is elective; the option to *decline* or *defer* must remain open.
- ▶ **Confidentiality and protection from discrimination:** results have implications for relatives; the *Genetic Information Nondiscrimination Act (GINA, 2008)* in the U.S. protects against employment and health-insurance discrimination but **not** life, disability or long-term-care insurance.
- ▶ **Anticipatory psychosocial support:** addressing anxiety, despair over risk to children, and “survivor guilt” in those who test negative.

Indications for genetic counseling / referral

A useful framework is by life stage (after *Harrison* Table 479-4) plus reproductive and oncologic triggers.

Setting	Indications
Preconception / reproductive	Consanguinity; known familial Mendelian disorder; previous child with congenital anomaly, intellectual disability or metabolic disease; carrier of an autosomal-recessive/X-linked condition (e.g., thalassemia, cystic fibrosis); recurrent pregnancy loss; ethnic predisposition (e.g., Ashkenazi-Jewish <i>BRCA1/2</i> founder variants, present in 2.5%)
Prenatal	Advanced maternal age; abnormal fetal ultrasound; increased risk on maternal serum screen / positive NIPT; teratogen exposure; parental balanced chromosomal rearrangement
Neonatal / childhood	Multiple congenital anomalies; intellectual disability; autism-spectrum disorder; developmental delay; failure to thrive; short stature; disorders of sexual development; dysmorphism; positive newborn screen; family history of a chromosomal alteration

Setting	Indications
Adult	Infertility / recurrent miscarriage; familial cancer syndromes (hereditary breast–ovarian cancer, Lynch syndrome, FAP); early-onset or unusual disease (premenopausal/male breast cancer, MI in a young non-smoker, medullary thyroid cancer); presymptomatic testing for Huntington’s disease; cardiomyopathies/channelopathies; unexplained syndromes considered for WES/WGS

- ▶ **Red flags in any pedigree:** two or more first-degree relatives affected; *young age of onset*; bilateral/multifocal disease; multiple related cancers in one person; a condition in an unexpected sex.

Steps in the genetic counseling process

A structured, sequential process — *verify, gather, assess, inform, test, disclose, support*:

- ▶ **Verify the diagnosis** — confirm the proband’s diagnosis (records, pathology, biochemistry, imaging) before assigning risk; clarify *locus heterogeneity* (different genes → similar phenotype).
- ▶ **Take a detailed history and construct a pedigree** — record health data on first- and second-degree relatives (conventionally a **three-generation pedigree**) using standard symbols; expand the pedigree when it suggests inherited disease; the *proband* (index case) is marked with an arrow. Document ethnicity, consanguinity, ages of onset, non-hereditary risk factors, and deaths; confirm reported illnesses where decisions will be irreversible.
- ▶ **Determine the mode of inheritance and estimate recurrence risk** — interpret the pedigree (allowing for *incomplete penetrance, variable expressivity, phenocopies*); ~65% of monogenic disorders are autosomal dominant, ~25% autosomal recessive, ~5% X-linked.
- ▶ **Pre-test counseling and informed consent** — explain the indication, the test chosen (single gene vs panel vs WES/WGS), and its *benefits, risks, limitations and alternatives*; warn about an *uninformative negative*, a **variant of uncertain significance (VUS)**, and unexpected/secondary findings; discuss insurance/GINA limits and the option of **DNA banking**; assess the patient’s ability to understand and cope with results.
- ▶ **Perform/interpret testing strategically** — the most informative and cost-effective approach is to **test an affected family member first**; if a pathogenic variant is identified, targeted (site-specific) testing can then be offered to at-risk relatives. Distinguish *presymptomatic* testing (near-100% penetrance, e.g., Huntington’s disease) from *predisposition* testing (<100% risk, e.g., hereditary colon cancer).
- ▶ **Post-test counseling and result disclosure** — interpret the result in the context of personal and family history; explain that a true-negative reassures, an uninformative negative does not, and a positive result implies risk to the patient *and* relatives. Plan management.

- **Follow-up, management and support** — institute risk-based interventions and refer to support services (below); arrange re-contact as variant classification or guidelines evolve.

Recurrence risk by inheritance pattern

Pattern	Recurrence risk / key counseling point
Autosomal dominant	50% to each offspring of an affected parent; consider de novo mutation (advanced paternal age), reduced penetrance, variable expressivity
Autosomal recessive	25% affected, 50% carrier, 25% unaffected for two carrier parents; <i>consanguinity</i> raises risk; pseudodominance if one parent is affected (risk 50%)
X-linked recessive	No male-to-male transmission; carrier mother → 50% of sons affected, 50% of daughters carriers; all daughters of an affected male are obligate carriers
Mitochondrial (mtDNA)	<i>Matrilineal</i> — an affected mother transmits to all children, an affected father to none; heteroplasmy makes phenotype/prediction unreliable; PND/PGD limited; mitochondrial replacement therapy (MRT) is an emerging option
Multifactorial / polygenic	Empiric recurrence risks (2–5× for first-degree relatives in common adult diseases); polygenic risk scores still of uncertain clinical utility

Prenatal diagnosis and reproductive options

- **Non-invasive prenatal testing (NIPT/NIPS)** using *cell-free fetal DNA* (fetal fraction ~5–20%, optimally tested after **10 weeks**): sensitivity >99% for trisomy 21, slightly lower for trisomies 18 and 13; a *screening* test requiring confirmatory diagnosis.
- **Maternal serum screening** (PAPP-A, β -hCG, AFP, inhibin) combined with **first-trimester nuchal translucency**.
- **Invasive diagnosis**: *chorionic villus sampling (CVS)* and *amniocentesis*, ultrasound-guided, carrying a small miscarriage risk; **chromosomal microarray (CMA)** is now preferred over karyotype as it detects copy-number/microdeletion–duplication syndromes (e.g., 22q11 DiGeorge).
- **Preimplantation genetic testing (PGT)** allows selection of embryos free of a known familial pathogenic variant; **DNA banking**, prenatal diagnosis, and the option not to test are all legitimate choices.
- **Testing children**: generally *not* offered for adult-onset disorders with no childhood intervention (protects the child's future autonomy); *is* offered when early management exists — e.g., prophylactic thyroidectomy in **MEN 2* (RET), *colonoscopy from age 10–15 years in FAP* (APC)*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Three-generation pedigree** with standard symbols — labels: *square = male, circle = female, filled = affected, diamond = unknown sex, arrow = proband, horizontal line = mating, double horizontal line = consanguineous union, diagonal slash = deceased, small triangle/dot = spontaneous abortion, half-filled = carrier, brackets = monozygotic vs dizygotic twins*; Roman numerals (I, II, III) for generations.
- ▶ **Flowchart of the counseling steps** — labels: *Verify diagnosis → Pedigree & history → Risk assessment → Pre-test counseling & informed consent → Test affected member first → Cascade/targeted testing → Post-test counseling → Management & support / return to primary care.*

Clinical / Diagnostic significance

- ▶ Drives **risk-based prevention**: risk-reducing salpingo-oophorectomy and intensified MRI surveillance in *BRCA1/2* carriers; early colonoscopy ± aspirin in Lynch syndrome; phlebotomy in hemochromatosis identified through family counseling.
- ▶ Enables **cascade screening** of relatives once a familial variant is known, and reassurance of true-negative relatives (who revert to population risk).
- ▶ Guides **reproductive decisions** (prenatal diagnosis, PGT, MRT, gamete donation, adoption) and avoids over-testing through phenotype-directed strategy.
- ▶ Counseling around **VUS, incomplete penetrance and uninformative negatives** prevents inappropriate management; management of an uninformative negative is based on personal/family history.

High-yield exam pointers

- ▶ Genetic counseling is a **non-directive communication process**; confirm the diagnosis *before* assigning recurrence risk.
- ▶ **Test the affected family member first** — most informative and cost-effective; then cascade-test relatives for the identified variant.
- ▶ Recurrence risks: AD 50%, AR 25%, XL (no male-to-male; daughters of affected males are obligate carriers), mtDNA matrilineal.
- ▶ ~65% of monogenic disorders are AD, ~25% AR, ~5% XL; chromosomal abnormalities occur in ~1% of live births, ~8% of stillbirths and ~50% of spontaneous abortions.
- ▶ **GINA (2008)** protects employment and health insurance but not life/disability/long-term-care insurance; offer **DNA banking**.
- ▶ *Presymptomatic* (Huntington's, ~100%) vs *predisposition* (hereditary cancer, <100%) testing; avoid testing children for adult-onset conditions unless childhood intervention exists (MEN 2, FAP).

- ▶ NIPT (cfDNA, after 10 weeks) is a *screen* (trisomy 21 sensitivity >99%); confirm positives by amniocentesis/CVS with CMA.
- ▶ Anticipate psychosocial impact: anxiety in carriers, *survivor guilt* in non-carriers, implications for the whole family.

SOURCE & COVERAGE

- ▶ *Harrison's Principles of Internal Medicine, 22e* — “The Integration of Inherited Genetics into Clinical Practice” (family history/pedigree, testing strategies, informed consent, GINA, follow-up care, testing of children); “Principles of Human Genetics” (modes of inheritance and recurrence risk, pedigree symbols, indications for cytogenetic/cytogenomic analysis, penetrance/expressivity); “Mitochondrial DNA and Heritable Traits and Diseases” (matrilineal counseling, heteroplasmy, PND/PGD limits, MRT); “Cell-Free DNA in diagnostics” (NIPT/cfDNA, serum markers, nuchal translucency, amniocentesis, CVS, CMA).
- ▶ **Coverage note:** This corpus is rich on indications, inheritance/recurrence risk, testing strategy, informed consent and prenatal options, but does **not** give a single enumerated “steps of genetic counseling” list. The seven-step sequence above is the universally accepted standard genetic-counseling workflow, assembled faithfully from the source elements (verify diagnosis, pedigree, risk assessment, pre-test consent, test affected member first, post-test disclosure, follow-up); the formal ASHG-style definition and the principle of non-directiveness are standard textbook genetics. No specialty genetics textbook or CMDT chapter was specified for this topic.



Genetic counselling

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — Genetic counselling is the communication process by which individuals or families at risk of an inherited disorder are helped to understand the medical facts (diagnosis, natural history, management), the way heredity contributes to the disorder and the **recurrence risk**, the options available for dealing with that risk, and to choose the course of action appropriate to them in keeping with their values. It is intended to be **non-directive, non-coercive and confidential**, respecting patient autonomy. Because genetic information has implications for *entire families*, the physician's role is increasingly to identify at-risk patients, explain the indications, limitations, risks and benefits of testing, and refer appropriately to **trained genetic counselors** while providing risk-based management.

Aims and indications for referral

- ▶ **Aims:** confirm/establish the diagnosis; define the mode of inheritance and calculate recurrence risk; explain prognosis and management; discuss reproductive and testing options; and provide psychosocial support to help informed decision-making.
- ▶ **When to refer / suspect a genetic basis:** two or more first-degree relatives affected (relative risk for common adult diseases rises **two- to fivefold**); *young age of onset* (e.g., a 30-year-old non-smoking woman with myocardial infarction); *unusual disease* (male breast cancer, medullary thyroid cancer); *multiple related diseases in one person* (colon + endometrial cancer); a **proband** (first individual ascertained) with a recognised syndrome; **consanguinity**; recurrent miscarriage, infertility, stillbirth, or a previous child with multiple congenital anomalies/intellectual disability.
- ▶ **Cytogenetic/cytogenomic indications (Table 479-4):** *Prenatal* — advanced maternal age, abnormal ultrasound, abnormal maternal serum screen; *neonatal/childhood* — multiple congenital anomalies, intellectual disability, autism, developmental delay, short stature, disorders of sexual development; *adult* — infertility, recurrent miscarriage, familial cancer.
- ▶ Note: chromosomal disorders occur in ~1% of the general population, 8% of stillbirths, and ~50% of spontaneous abortions — underscoring their importance in reproductive counselling.

The counselling process (sequential steps)

- ▶ **1. Confirm the diagnosis first** — the critical first step before any testing; based on family history, characteristic physical findings, pathology or biochemistry. Careful clinical assessment defines the **phenotype** and avoids unnecessary tests.
- ▶ **2. Construct a pedigree** — record health data on first- and second-degree relatives using **standard pedigree symbols** (proband indicated by arrow; affected = filled symbol; consanguineous union = double line; carrier, deceased, monozygotic/dizygotic twins, spontaneous abortion symbols). Expand the pedigree when inherited disease is suggested. Recall is often inaccurate — confirm reported illnesses from records, pathology reports and death certificates before irreversible decisions.
- ▶ **3. Risk assessment** — assign mode of inheritance and quantify recurrence risk (below), accounting for family size, number of unaffected relatives, ages of onset, ethnicity (e.g., **2.5% of Ashkenazi Jews** carry a *BRCA1/2* founder variant) and non-hereditary risk factors.
- ▶ **4. Pretest counselling and informed consent** — explain what the test can and cannot determine, possibility of *uninformative/inconclusive* results, **variants of uncertain significance (VUS)**, unexpected/secondary findings, implications for relatives and insurance.
- ▶ **5. Testing** (where indicated) — ideally begin with an **affected family member**.
- ▶ **6. Posttest counselling** — disclose results, discuss treatment/surveillance implications for patient *and* family, address psychosocial impact, and arrange follow-up/support and return to primary care.

Risk assessment — modes of inheritance and modifiers

About 65% of monogenic disorders are autosomal dominant, 25% autosomal recessive, and 5% X-linked; mode of inheritance is determined by **pedigree analysis**.

Pattern	Key pedigree features	Recurrence risk
Autosomal dominant	Successive generations affected; males = females; affected child usually has an affected parent (unless <i>de novo</i>)	50% to each offspring
Autosomal recessive	Often single generation; ↑ with consanguinity ; carriers usually asymptomatic	25% if both parents carriers (50% carriers, 25% unaffected); pseudodominance if one parent homozygous affected
X-linked	No male-to-male transmission ; all daughters of an affected male are obligate carriers ; males hemizygous → more often affected	Carrier mother → 50% of sons affected, 50% of daughters carriers
Mitochondrial (matrilineal)	Transmitted only through the mother ; affected father transmits to none; heteroplasmy → variable expression	All children of affected mother at risk; variable

► **Modifiers that complicate counselling:**

- **Incomplete/reduced penetrance** — not all genotype carriers manifest (e.g., HCM from *MYBPC3*); causes generation skipping; penetrance is *age-dependent* (Huntington's, familial ALS).
- **Variable expressivity** — same mutation, different severity/organs/age of onset (MEN, cystic fibrosis).
- **Anticipation** — in **nucleotide (trinucleotide) repeat expansion** disorders a *premutation* enlarges in successive generations, producing earlier onset and increasing severity (e.g., myotonic dystrophy, Huntington's, Friedreich's ataxia).
- **Genomic imprinting / uniparental disomy** — parent-of-origin effect: **Prader-Willi** (loss of paternal 15q) vs **Angelman** (loss of maternal 15q).
- **Mosaicism** (somatic/germline), **de novo mutations** (more frequent with **advanced paternal age** — e.g., new Marfan mutations in fathers averaging ~37 yr), **locus heterogeneity** and **phenocopies** all confound pedigree interpretation.

Genetic testing within counselling

- **Predictive testing has two categories:** **Presymptomatic testing** — for disorders where a variant confers a **near-100%** likelihood of disease (e.g., Huntington's disease); **predisposition testing** — risk <100% (e.g., hereditary colon cancer, *APOE ε4* and Alzheimer's). For most adult-onset

disorders, testing is only *predictive* — it cannot reveal whether, when or how disease will manifest.

- ▶ **Optimal strategy:** test a **disease-affected relative first**; a true-negative result in a relative reassures them and excludes transmission to their children; an *uninformative negative* (no familial variant known) does not lower risk and management stays based on personal/family history.
- ▶ **Informed consent & privacy:** patients must understand long-term medical, psychological, social and insurance implications; **DNA banking** should be offered; in the USA the **Genetic Information Nondiscrimination Act (GINA, 2008)** protects against health-insurance and employment discrimination but **not** life, disability or long-term-care insurance, and does not protect the *symptomatic* individual.
- ▶ **Testing children:** genetic testing for **adult-onset** disorders (e.g., Huntington's) is generally *not* offered in childhood (no childhood intervention; violates the child's future autonomy). It is offered when childhood management exists — **MEN 2** (prophylactic thyroidectomy) and **FAP/APC** (colonoscopy from age 10–15 yr).
- ▶ **Pitfalls to counsel about:** **VUS** (reclassified over time), incidental/secondary findings, and the variable quality of **direct-to-consumer (DTC)** testing (SNP “hot-spots”, not definitive; ACMG advises professional ordering, CLIA/CAP-accredited labs, and proper consent).

Prenatal/preimplantation diagnosis and reproductive options

- ▶ **Amniocentesis** — ~16 weeks; amniotic-fluid cells for karyotype, FISH, mutational analysis. Indications: advanced maternal age (>35 yr), fetal anomaly on ultrasound, **abnormal quad test** (α -fetoprotein, β -hCG, *inhibin-A*, *unconjugated estriol*), family history of chromosomal abnormality, or a testable Mendelian disorder.
- ▶ **Chorionic villus sampling (CVS)** — weeks 9–12, transcervical or transabdominal; earlier than amniocentesis, relevant when termination is considered.
- ▶ **Percutaneous umbilical blood sampling (PUBS/cordocentesis)** — from ~18 weeks, for fetal blood analysis.
- ▶ **Cell-free DNA (cfDNA) screening** — non-invasive analysis of fetal DNA in a *maternal blood sample* to screen for chromosomal abnormalities and fetal sex.
- ▶ **Preimplantation genetic testing (PGT)** — with IVF, a single cell from the 4–8-cell embryo or the first polar body is analysed, allowing selection of unaffected embryos and avoiding therapeutic abortion (costly, labour-intensive).
- ▶ **Key caution:** excluding a specific disorder by any of these methods is **never equivalent to assurance of a normal child**. Other reproductive options to counsel: proceeding with the pregnancy, prenatal diagnosis $\pm$ termination, donor gametes, adoption, or remaining childless.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Three-generation pedigree with standard symbols** — label: *square = male, circle = female, filled = affected, arrow = proband, double horizontal line = consanguineous union, diagonal line = deceased, dot-in-circle = carrier female, vertical line from a horizontal sib-line, monozygotic vs dizygotic twins, small triangle = spontaneous abortion*. Annotate generations I–II–III with Roman numerals.
- ▶ **Inheritance-pattern squares (Punnett) for recurrence risk** — label *Autosomal dominant* ($Aa \times aa \rightarrow 50\% \text{ affected}$), *Autosomal recessive* ($Aa \times Aa \rightarrow 25\% \text{ affected, } 50\% \text{ carrier}$), *X-linked* (*carrier mother* $\rightarrow 50\% \text{ sons affected}$), and *Mitochondrial* (*matrilineal — all children of affected mother*).

Clinical / Diagnostic significance

- ▶ Accurate risk assignment guides **reproductive decisions, surveillance and risk-reducing interventions** — e.g., *BRCA1/2* carriers: risk-reducing salpingo-oophorectomy, breast MRI screening, risk-reducing mastectomy, PARP inhibitors; **Lynch syndrome/FAP**: early/frequent colonoscopy, prophylactic surgery, aspirin/chemoprevention; **MEN 2**: prophylactic thyroidectomy.
- ▶ Counselling enables **cascade testing** of relatives once a familial pathogenic variant is identified, and population/founder screening (e.g., Ashkenazi *BRCA*).
- ▶ Recognising **incomplete penetrance and variable expressivity** is essential — one cannot always predict disease course even when the mutation is known; this must be conveyed honestly.
- ▶ Counselling has medical, **psychosocial and ethical** dimensions: anxiety, *survivor guilt* in test-negative relatives, parental despair over transmission risk, genetic discrimination, and management of secondary findings.

High-yield exam pointers

- ▶ Genetic counselling = **non-directive, voluntary, confidential** communication of facts, inheritance, recurrence risk and options.
- ▶ Recurrence risks: AD 50%, AR 25% (**both carriers**), XL carrier mother $\rightarrow 50\% \text{ sons affected}$, **mitochondrial = matrilineal**.
- ▶ Monogenic disorders: AD ~65%, AR ~25%, XL ~5%.
- ▶ **Always confirm the diagnosis and test an affected relative first.**
- ▶ Key modifiers: **penetrance, expressivity, anticipation, imprinting** (Prader-Willi/Angelman), **mosaicism, de novo mutations** (advanced paternal age), **consanguinity** ($\uparrow$ AR).
- ▶ Prenatal tests: CVS 9–12 wk, amniocentesis ~16 wk, PUBS ~18 wk, cfDNA (non-invasive); **quad test** = AFP + β -hCG + inhibin-A + unconjugated estriol.

- ▶ PGT + IVF selects unaffected embryos; no test guarantees a “normal” child.
- ▶ **Presymptomatic** (Huntington’s, ~100%) vs **predisposition** (hereditary cancer, <100%) testing; defer adult-onset testing in children (test MEN 2, FAP).
- ▶ **GINA (2008)** protects health-insurance/employment, not life/disability/long-term-care insurance; offer **informed consent + DNA banking**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Principles of Human Genetics” (pedigree symbols and analysis; modes of inheritance and recurrence risks; penetrance, expressivity, anticipation, imprinting, mosaicism, consanguinity; prenatal diagnosis — amniocentesis, CVS, PUBS, cfDNA, PGT; ethical issues and GINA) and “The Integration of Inherited Genetics into Clinical Practice” (family-history/pedigree-based risk assessment; pretest/posttest counselling and informed consent; presymptomatic vs predisposition testing; testing of children; VUS; direct-to-consumer testing; cascade testing and risk-reducing interventions).
- ▶ **Coverage note:** Harrison 22e covers risk assessment, inheritance, testing strategy and prenatal/preimplantation diagnosis in depth, but does **not** lay out a discrete numbered “steps of genetic counselling” protocol or explicitly emphasise the *non-directive* principle; these standard, universally accepted counselling tenets have been stated as established internal-medicine practice and synthesised from the chapters’ content. No dedicated clinical-genetics subspecialty text was listed in the spec for this topic.



HLA (Human Leukocyte Antigen) System: Role in Health and Disease

Asked in: Paper I Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — The **human leukocyte antigen (HLA) system** is the human **major histocompatibility complex (MHC)**, a cluster of highly polymorphic, closely linked genes on the short arm of **chromosome 6 (6p21)** that encode cell-surface glycoproteins responsible for **presenting peptide antigens to T lymphocytes**. By dictating what the adaptive immune system “sees” as self versus non-self, the HLA system governs T-cell selection, defence against microbes and tumours, natural-killer (NK)-cell regulation, transplant compatibility, and susceptibility to a large group of immune-mediated and drug-induced diseases. It is the single most polymorphic locus in the human genome, which underlies both its protective versatility and its strong disease associations.

Genomic Organisation and Classification

- ▶ The MHC on **chromosome 6** is conventionally divided into three regions encoding **class I, class II and class III** molecules; the genes are **co-dominantly expressed** (both parental alleles are transcribed) and inherited en bloc as a **haplotype**.
- ▶ Because of strong **linkage disequilibrium**, certain alleles travel together as conserved **extended/ancestral haplotypes** — e.g. the A1-B8-DR3-DQ2 (AH 8.1) haplotype linked to high TNF- α production and autoimmunity (Harrison, HIV chapter).

Class	Principal loci (HLA)	Chain structure	Cells expressing	Presents peptide to
Class I (Ia)	HLA-A, -B, -C	Polymorphic heavy (α) chain + invariant β 2-microglobulin; closed groove binds short (~9–13 aa) peptides	All nucleated cells + platelets	CD8+ cytotoxic T cells
Class I (Ib)	HLA-E, -F, -G (+ MIC-A)	Limited polymorphism	Restricted (e.g. HLA-G on trophoblast)	NK cells / regulatory
Class II	HLA-DR, -DQ, -DP	Two chains (α + β); open groove binds longer peptides	Professional APCs — dendritic cells, macrophages, B cells (inducible on others)	CD4+ helper T cells
Class III	C4, C2, factor B, TNF, HSP	Secreted/soluble effectors (not antigen-presenting)	—	—

Structure, Antigen Processing and Presentation

- ▶ T cells (unlike B cells) **do not recognise native antigen**; the TCR sees only short **peptide fragments** (~9–13 amino acids) embedded in the groove of a self-MHC molecule — the basis of **MHC restriction**.
- ▶ **Endogenous (class I) pathway** — cytosolic proteins (e.g. viral, tumour) are degraded by the **proteasome**, peptides are pumped into the endoplasmic reticulum by **TAP (transporters associated with antigen processing)**, loaded onto class I molecules, and displayed to **CD8+ T cells** (which bind via CD8 to class Ia HLA-A/B/C).
- ▶ **Exogenous (class II) pathway** — extracellular antigens taken up by endocytosis/phagocytosis are degraded in acidified vesicles, fused with class II-containing vesicles, and presented to **CD4+ T cells** (CD4 binds DR/DQ/DP).

- ▶ **Non-classical/lipid presentation** — CD1 molecules present microbial lipid antigens (e.g. *M. tuberculosis*) to $\gamma\delta$ and some CD8+ T cells, an MHC-independent route.

Physiological Roles of HLA in Health

- ▶ **Initiation of adaptive immunity** — antigen presentation is the obligatory first signal for T-cell activation and downstream antibody and cytotoxic responses.
- ▶ **Thymic T-cell selection** — developing thymocytes that interact appropriately with self-MHC are positively selected, while strongly self-reactive clones are negatively selected, shaping a **self-tolerant repertoire**.
- ▶ **NK-cell regulation (“missing-self” hypothesis)** — NK cells kill host cells expressing **low/absent self class I** (e.g. virus-infected or tumour cells that down-regulate HLA); high self-MHC engages inhibitory **killer-cell immunoglobulin-like receptors (KIRs)** and switches NK killing off. KIR ligands include **HLA-C1/C2 epitopes, the Bw4 motif, and HLA-E**.
- ▶ **Reproductive tolerance** — non-classical **HLA-G** on trophoblast protects the semi-allogeneic fetus from maternal NK/T-cell attack.
- ▶ **Transplantation & transfusion biology** — HLA molecules are the dominant **transplantation antigens**; HLA disparity drives allograft rejection and graft-versus-host disease, and anti-HLA antibodies cause transfusion complications (see below).

HLA and Disease Associations

Disease linkage arises through altered peptide presentation, molecular mimicry, defective tolerance, or linkage disequilibrium with true susceptibility genes.

Disease	HLA association	Notes / mechanism
Axial spondyloarthritis / ankylosing spondylitis	HLA-B27 (class I)	Present in 85–90% of radiographic axSpA vs ~5% of healthy Caucasians; strongest known genetic risk factor
Reactive arthritis, psoriatic, IBD-associated, anterior uveitis	HLA-B27	Part of the B27-linked spondyloarthritis spectrum
Behçet syndrome	*HLA-B*51**	Positive in 50–60% of patients (also ~20% of normals — not diagnostic)
Type 1 diabetes mellitus	HLA-DR3 / DR4, DQ2/DQ8	Class II–driven islet autoimmunity
Celiac disease	HLA-DQ2 / DQ8	Near-obligate; gluten-derived peptides presented by DQ2/DQ8
Graves’ disease	DR3	Iodine as initiating factor

Disease	HLA association	Notes / mechanism
Addison's disease / APS-2	DR3 / DR4; MIC-A 5.1	MIC-A5.1 association independent of DR3/DR4
Myasthenia gravis	DR3, DR7	Thymoma / penicillamine triggers

- ▶ **Arthritogenic peptide / molecular-mimicry theory (AS):** HLA-B27 presents pathogenic microbial peptides to CD8+ cytotoxic T cells that cross-react with self-peptides. Subtype specificity matters — **HLA-B\2704 and B\2705 confer risk, whereas B\2706 and B\2709 do not, differing by single amino-acid residues. ERAP1 (a peptide-trimming enzyme) shows genetic epistasis with B27. Risk of axSpA is ~5% in B27-positive individuals, rising to ~20% in B27-positive first-degree relatives**.
- ▶ **Non-HLA susceptibility genes** that interact with HLA: PTPN22, CTLA4, IL-2Rα (autoimmune endocrinopathies).
- ▶ **HLA in infection / host defence:** in HIV, class I alleles **HLA-B\27* and *HLA-B\57* are associated with slower progression (“elite controllers”), whereas *HLA class I homozygosity* (a narrower epitope repertoire) and the *AH 8.1 haplotype* accelerate progression; *KIR3DL1 + HLA-B\57:01*** interaction modifies protection.

HLA in Pharmacogenomics — Drug Hypersensitivity

HLA risk alleles are **necessary but not sufficient** for severe cutaneous and hepatic drug reactions; pre-prescription typing can prevent them.

Drug	HLA allele	Reaction
Abacavir	<i>*HLA-B\57:01**</i>	Abacavir hypersensitivity / SJS-TEN (~55% of carriers react); RCT shows testing eliminates the reaction
Flucloxacillin	HLA-B*57:01	Drug-induced hepatotoxicity (low penetrance)
Carbamazepine	<i>*HLA-B\15:02**</i>	Stevens-Johnson syndrome / toxic epidermal necrolysis (testing mandated in parts of SE Asia)

- ▶ Severe reactions linked to specific HLA alleles span SJS/TEN, DRESS, and **drug-induced liver injury**; risk-allele frequency varies by ancestry, which guides population-specific screening.

Transplantation and Transfusion Medicine

- ▶ HLA molecules are the **major histocompatibility (transplantation) antigens**; donor–recipient HLA matching reduces rejection in solid-organ and **haematopoietic stem-cell transplantation**, and HLA disparity is the substrate for **graft-versus-host disease (GVHD)**.
- ▶ **Pre-formed anti-HLA antibodies** (from pregnancy, transfusion, prior grafts) cause **hyperacute/antibody-mediated rejection**; **plasma-based removal of anti-HLA antibody** may be performed before kidney transplantation.
- ▶ In transfusion: **leukoreduction** lowers HLA alloimmunisation and febrile non-haemolytic reactions; **irradiation** of cellular products prevents **transfusion-associated GVHD**; donor anti-HLA antibodies are a cause of **TRALI**; HLA alloimmunisation underlies **platelet refractoriness** (requiring HLA-matched platelets).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Structure of MHC class I vs class II.** Class I: single α (heavy) chain with domains $\alpha 1$, $\alpha 2$, $\alpha 3$ + $\beta 2$ -microglobulin, closed **peptide-binding groove** (short peptide), label “**binds CD8 / all nucleated cells**”. Class II: α and β chains ($\alpha 1/\alpha 2$, $\beta 1/\beta 2$ domains), **open-ended groove** (longer peptide), label “**binds CD4 / professional APCs**”.
- ▶ **Diagram 2 — Antigen-processing pathways.** Show **endogenous pathway** (cytosolic protein → **proteasome** → TAP → ER → **class I** → cell surface → **CD8+ T cell**) and **exogenous pathway** (endocytosis → endosome/lysosome → fusion with **class II vesicle** → cell surface → **CD4+ T cell**). Label proteasome, TAP, ER, MHC I, MHC II, CD8, CD4.

Clinical / Diagnostic significance

- ▶ **HLA-B27 testing** supports (does not confirm) a diagnosis of axial spondyloarthritis in a patient with inflammatory back pain and equivocal imaging.
- ▶ **HLA-DQ2/DQ8 negativity** has a very high negative predictive value to exclude **celiac disease**.
- ▶ **Pharmacogenomic HLA screening** before abacavir (B\57:01) and carbamazepine (B\15:02 in at-risk ancestries) prevents life-threatening cutaneous reactions.
- ▶ **HLA typing and crossmatching** are mandatory for solid-organ and stem-cell transplantation; **panel-reactive/anti-HLA antibody** assessment stratifies sensitisation and rejection risk.
- ▶ Disease-association data also illuminate **pathogenesis** (e.g. class I associations implicate CD8 T cells; class II associations implicate CD4-helper-driven autoimmunity).

High-yield exam pointers

- ▶ HLA = human MHC on **chromosome 6 (6p21)**; **co-dominant**, most **polymorphic** genes; inherited as **haplotypes** in **linkage disequilibrium**.
- ▶ **Class I (A, B, C) + $\beta 2$ -microglobulin** → **CD8** (endogenous/proteasome–TAP); **Class II (DR, DQ, DP)** → **CD4** (exogenous/endosomal); **class III** = complement C4/C2/Bf, TNF.

- ▶ **MHC restriction + thymic positive/negative selection** = central tolerance.
- ▶ NK “**missing-self**”: low self class I → NK killing; inhibitory KIRs sense self-MHC; HLA-G mediates fetal tolerance.
- ▶ Strongest single association: **HLA-B27 with ankylosing spondylitis (85–90%)**; *B\2704/2705 risk, B\2706/2709 *protective*; ERAP1* epistasis.
- ▶ Class II autoimmunity: T1DM DR3/DR4, Celiac DQ2/DQ8, Graves/Addison DR3/DR4; *Behçet B\51**.
- ▶ Pharmacogenetics: *B\57:01–abacavir, B\15:02–*carbamazepine*, B\57:01–flucloxacillin (necessary-not-sufficient).
- ▶ Transplant/transfusion: HLA matching, anti-HLA antibodies → **rejection, GVHD, TRALI, platelet refractoriness**.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Introduction to the Immune System” (MHC class I/II structure, antigen processing/TAP/proteasome, CD1, NK/KIR missing-self); “Spondyloarthritis” (HLA-B27, subtypes, ERAP1, arthritogenic-peptide theory, axSpA risk figures); “Behçet Syndrome” (HLA-B\51); “*Autoimmune Polyendocrine Syndromes*” (HLA-disease association table — Graves, MG, celiac, T1DM, Addison, MIC-A 5.1; PTPN22/CTLA4); “Pharmacogenomics” (HLA-B\57:01 abacavir/flucloxacillin, HLA-B\15:02 *carbamazepine*, SJS-TEN/DRESS); “*Human Immunodeficiency Virus Disease: AIDS and Related Disorders*” (*protective* HLA-B\27/B\57, AH 8.1 haplotype, KIR3DL1–B\57:01); “Transfusion Biology and Therapy” (leukoreduction, irradiation/GVHD, anti-HLA antibodies, TRALI).
- ▶ **Coverage note:** This Harrison 22e corpus has **no dedicated standalone HLA/MHC chapter** — content was synthesised across the immunology, rheumatology, pharmacogenomics, HIV and transfusion chapters. The corpus gives allele-level associations but **not a single consolidated relative-risk table** (e.g. the classic AS relative risk of ~90 is not quoted); the **class III region composition** (C4/C2/Bf, TNF) and **β2-microglobulin** as the class I light chain are stated here as universally accepted standard immunology, as the corpus describes them only in passing.



How does pregnancy affect drug pharmacokinetics? What are principles to consider while prescribing to a pregnant patient?

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — *Drug disposition* is the sum of **absorption, distribution, metabolism and excretion (ADME)**, which together determine the concentration of drug delivered to its target. Pregnancy imposes profound, dynamic and progressive physiological changes (in plasma volume, body composition, plasma proteins, hepatic enzyme activity and renal function) that alter every one of these processes, usually lowering plasma concentrations of many drugs and necessitating dose individualisation. Simultaneously, the **placenta is permeable to most drugs**, so the prescriber must balance maternal therapeutic benefit against fetal risk (teratogenicity, fetotoxicity). Rational prescribing therefore requires understanding of *both* altered maternal pharmacokinetics *and* the safety hierarchy of drugs across gestation.

Physiological changes of pregnancy that drive altered pharmacokinetics

System	Change in pregnancy	Pharmacokinetic consequence
Blood / fluid	Plasma volume ↑ ~40–50%; total body water ↑ (~8 L); body fat ↑	↑ volume of distribution (Vd) → lower peak concentration for a given dose
Plasma proteins	Dilutional ↓ albumin (and α1-acid glycoprotein)	↑ free (unbound) fraction of highly protein-bound drugs
Cardiovascular	Cardiac output ↑ ~30–50%; skin, renal & uteroplacental flow ↑	Faster absorption from IM/SC/transdermal/inhaled routes; ↑ hepatic & renal delivery
Gastrointestinal	↓ Gut motility & delayed gastric emptying (progesterone); ↑ gastric pH; nausea/vomiting	Delayed/erratic oral absorption (delayed <i>T_{max}</i>); altered ionisation of weak acids/bases
Hepatic	Induction of CYP3A4, CYP2D6, CYP2C9, UGT (oestrogen/progesterone); ↓ CYP1A2, CYP2C19	↑ Clearance of many substrates; ↓ clearance of a few
Renal	Renal plasma flow ↑ ~50–80%; GFR ↑ ~50%	↑ Renal clearance of renally-eliminated drugs

Effect of pregnancy on each pharmacokinetic phase (ADME)

- ▶ **Absorption** — Delayed gastric emptying and reduced bowel motility delay the *rate* (later, lower peak) but usually not the *extent* of oral absorption; nausea/vomiting and hyperemesis make oral dosing unreliable. Raised gastric pH alters ionisation. Increased cardiac output and cutaneous/pulmonary blood flow enhance absorption from **intramuscular, subcutaneous, transdermal and inhalational** routes.
- ▶ **Distribution** — Expanded plasma volume, total body water and fat **increase Vd**, particularly for hydrophilic drugs, lowering peak plasma levels and sometimes requiring a larger loading dose

(recall: the loading dose is governed by V_d , the maintenance dose by clearance). The fall in albumin **increases the free fraction** of acidic, highly bound drugs (e.g., phenytoin, valproate); since *only unbound drug is pharmacologically active*, total (bound + free) levels under-read true exposure — **free drug monitoring is preferred** (as Harrison notes for phenytoin).

- ▶ **Metabolism** — Sex-steroid-mediated **induction of CYP3A4, CYP2D6, CYP2C9 and UDP-glucuronosyltransferase (UGT)** accelerates clearance and lowers levels of their substrates (the classic example is **lamotrigine**, a UGT substrate whose clearance rises sharply, demanding dose escalation and monthly level monitoring). By contrast **CYP1A2 and CYP2C19 activity fall**, raising concentrations of substrates such as caffeine and theophylline.
- ▶ **Excretion** — The ~50% rise in GFR **increases renal clearance** of drugs eliminated unchanged by the kidney (e.g., **lithium, digoxin, low-molecular-weight heparin, atenolol, penicillins, cephalosporins, aminoglycosides**), so standard doses may be sub-therapeutic. Harrison explicitly notes that **antiepileptic drug doses often must be escalated because of increased clearance in pregnancy**, with monthly level checks.
- ▶ **Net result** — For *most* affected drugs, clearance rises and free/total levels fall as pregnancy advances, with a return towards baseline postpartum — hence **therapeutic drug monitoring (TDM)** and proactive dose adjustment (up in pregnancy, back down after delivery) are central.

Placental drug transfer and the timing of fetal vulnerability

- ▶ **Placental transfer** is mainly by passive diffusion; transfer is favoured by **low molecular weight (<500 Da), high lipid solubility, low ionisation and low protein binding**. Large/polar/highly-bound molecules (e.g., heparin, LMWH, insulin) cross poorly — a property exploited therapeutically.
- ▶ **Gestational timing determines the type of harm:**
 - **Pre-implantation (0–2 weeks post-conception)** — *all-or-none* phenomenon: insult either causes loss or has no residual effect.
 - **Embryonic period / organogenesis (~3–8 weeks)** — **maximum risk of major structural malformation**; this is the *critical period* for classical teratogens.
 - **Fetal period (9 weeks–term)** — growth restriction and *functional/organ-specific* toxicity rather than gross malformation (e.g., ACE-inhibitor fetopathy, third-trimester NSAID-induced ductus closure, tetracycline tooth staining).

Drugs that are teratogenic / fetotoxic (avoid) and safer alternatives

Teratogen / fetotoxic drug	Characteristic fetal effect
ACE inhibitors, ARBs, MRAs	2nd/3rd-trimester fetopathy: oligohydramnios, renal failure, skull/lung hypoplasia

Teratogen / fetotoxic drug	Characteristic fetal effect
Warfarin / coumarins	Fetal warfarin syndrome (nasal hypoplasia, stippled epiphyses), CNS injury
Valproate, phenytoin, carbamazepine	Neural-tube & other major malformations; neurodevelopmental harm
Isotretinoin / retinoids	Retinoid embryopathy (craniofacial, cardiac, CNS)
Thalidomide	Limb-reduction defects (phocomelia)
Methotrexate, cyclophosphamide	Aminopterin-type syndrome / cytotoxic malformation
Lithium	Cardiac (Ebstein anomaly)
Tetracyclines (3rd trimester)	Tooth discolouration, impaired bone growth
Aminoglycosides	Fetal ototoxicity
NSAIDs (3rd trimester)	Premature ductus arteriosus closure, oligohydramnios
Diethylstilbestrol	Vaginal clear-cell adenocarcinoma in offspring
Others	Androgens, oestrogens, danazol, misoprostol, ergotamine, radioiodine, ribavirin, sulfonamides (late), griseofulvin, alcohol, tobacco

- ▶ **Preferred (relatively safer) agents by indication:** Hypertension — **methyldopa, labetalol, nifedipine** (ACEi/ARB/MRA contraindicated). Epilepsy — **lamotrigine, levetiracetam** (with 4 mg/day folic acid). Anticoagulation — **LMWH / unfractionated heparin** (do not cross placenta). Hypothyroidism — **levothyroxine**, with the dose increased ~30% (≈two extra tablets/week) once pregnancy is confirmed. UTI suppression — **nitrofurantoin or cephalexin**. Nausea/vomiting — **pyridoxine ± doxylamine**. Asthma — managed as in the non-pregnant state. Diabetes — **insulin**. Infections — penicillins, cephalosporins, erythromycin/azithromycin generally acceptable.

Principles to consider when prescribing to a pregnant patient

- ▶ **Prescribe only when clearly indicated** — try non-pharmacological measures first; avoid over-the-counter and “social” drugs (alcohol, tobacco, recreational drugs).
- ▶ **Weigh risk versus benefit both ways** — *untreated* maternal disease (epilepsy, asthma, hypertension, diabetes, infection, thyroid disease, venous thrombosis) is itself harmful to mother and fetus; do **not** withhold essential therapy.
- ▶ **Use the lowest effective dose for the shortest duration**, but adjust *upwards* to compensate for increased Vd and clearance, guided by TDM (AEDs, lithium, digoxin, free phenytoin) and clinical response.

- ▶ **Prefer older, well-characterised drugs** with the longest safety record over newer agents with sparse data; choose **monotherapy over combinations**.
- ▶ **Respect gestational timing** — be most restrictive during organogenesis; remember late-pregnancy fetotoxicities (NSAIDs, ACEi, tetracyclines).
- ▶ **Plan before conception** — substitute known teratogens (e.g., warfarin, valproate, ACE inhibitors, isotretinoin) for safer alternatives *before* pregnancy; give **periconceptional folic acid** (high-dose 4 mg/day with AEDs).
- ▶ **Consult authoritative, current resources** — the FDA's old A/B/C/D/X letter categories have been replaced by the **Pregnancy and Lactation Labeling Rule (PLLR, narrative risk summaries)**; teratogen information services and registries should be used.
- ▶ **Consider lactation** — many drugs enter breast milk; check resources such as LactMed before prescribing to a nursing mother.
- ▶ **Anticipate the postpartum reversal** — pregnancy-related PK changes resolve over days to weeks after delivery; doses escalated during pregnancy (e.g., lamotrigine) must be **reduced postpartum** to avoid toxicity.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **“PK changes in pregnancy” schematic (pregnant figure with four ADME boxes):** label —
Absorption: ↓ gastric motility, delayed emptying, ↑ gastric pH, nausea/vomiting;
Distribution: ↑ plasma volume (+40–50%), ↑ total body water & fat, ↓ albumin → ↑ free drug, ↑ V_d; *Metabolism:* ↑ CYP3A4/2D6/2C9/UGT, ↓ CYP1A2/2C19; *Excretion:* ↑ GFR (~+50%), ↑ renal clearance. Net arrow: “↓ plasma levels of many drugs → dose ↑ / monitor.”
- ▶ **Gestational-timing teratogenicity timeline (0 → 40 weeks):** label the three zones — 0–2 wk “all-or-none” | 3–8 wk organogenesis = major malformations (critical period) | 9 wk–term = growth restriction & functional/organ-specific toxicity.

Clinical / Diagnostic significance

- ▶ **Interpret drug levels carefully:** falling *total* phenytoin/valproate levels may reflect lower albumin, not under-treatment — measure **free drug**; conversely rising lamotrigine clearance genuinely lowers exposure and risks breakthrough seizures.
- ▶ **Dose adjustment is bidirectional:** uptitrate during pregnancy and **downtitrate postpartum** for AEDs, lithium and others.
- ▶ **Renally-cleared narrow-therapeutic-index drugs** (lithium, digoxin, LMWH, aminoglycosides) need closer monitoring because of the GFR rise.
- ▶ **Anticoagulation choice:** LMWH/heparin in pregnancy because warfarin is teratogenic and crosses the placenta.

- ▶ **Antihypertensive choice:** methyldopa, labetalol, nifedipine; **never** ACE inhibitors/ARBs/MRAs.
- ▶ **Preconception medication review** is one of the highest-yield interventions to prevent malformation.

High-yield exam pointers

- ▶ ADME framework: pregnancy ↑ **V_d**, ↓ **albumin** (↑ **free fraction**), induces CYP3A4/2D6/2C9/UGT, ↑ GFR ~50% → net ↑ **clearance** / ↓ **plasma levels** of many drugs.
- ▶ **Lamotrigine** is the classic drug whose clearance rises markedly (UGT induction) — escalate dose, monitor monthly, **reduce postpartum**.
- ▶ Harrison: AED doses **must often be increased due to increased clearance in pregnancy** (monthly monitoring).
- ▶ **Organogenesis** = 3–8 weeks is the critical teratogenic window; *all-or-none* before, functional toxicity after.
- ▶ Memorise teratogens: ACEi/ARB, warfarin, valproate/phenytoin/carbamazepine, isotretinoin, thalidomide, lithium (Ebstein), methotrexate, tetracycline, NSAIDs (3rd-trimester ductus), aminoglycosides, DES.
- ▶ Safer choices: HTN → **methyldopa/labetalol/nifedipine**; anticoagulation → **LMWH/heparin**; epilepsy → **lamotrigine/levetiracetam + 4 mg folate**; hypothyroidism → **levothyroxine** ↑ ~30%.
- ▶ **Free drug**, not total, governs effect — monitor free phenytoin.
- ▶ **FDA letter categories replaced by the PLLR** narrative labelling; use registries and **LactMed** for lactation.
- ▶ Treat essential maternal disease — **untreated illness is often more dangerous than the drug**.

SOURCE & COVERAGE

- ▶ Harrison's *Principles of Internal Medicine*, 22e — “Principles of Clinical Pharmacology” (ADME, bioavailability/first-pass, volume of distribution, clearance, half-life and steady state, protein binding and free-drug monitoring, CYP phase I/II metabolism, altered clearance in special populations).
- ▶ Harrison's *Principles of Internal Medicine*, 22e — “Medical Disorders During Pregnancy” (increased AED clearance and dose escalation, antiepileptic choice and folic acid, levothyroxine dose increase, infections and prescribing in pregnancy).
- ▶ **CMDT 2026** — “Obstetrics & Obstetric Disorders” (Table 22–1 teratogenic/fetotoxic drugs; antihypertensives in pregnancy; ACEi/ARB/MRA contraindication; nausea/vomiting therapy; lactation/LactMed; vaccination in pregnancy).

Coverage note: The corpus does **not** provide a single consolidated account of pregnancy pharmacokinetics — Harrison details the general ADME/clinical-pharmacology principles and gives pregnancy-specific clearance data only for antiepileptics, while CMDT supplies the

teratogen list and disease-specific drug choices. The quantitative physiological changes of pregnancy (plasma-volume +40–50%, GFR +50%, specific CYP induction/inhibition, +8 L body water) and the gestational-timing/all-or-none framework are stated here as **universally accepted standard internal-medicine pharmacology**, applied to the general PK principles that Harrison does cover. The FDA A/B/C/D/X categories and their replacement by the PLLR are standard regulatory knowledge not found verbatim in the corpus.



How is cardiac risk assessment done for a patient undergoing surgery? Make an algorithm for the same

Asked in: Paper II May 2025 — RGUHS MD General Medicine

Definition / Introduction — Perioperative cardiac risk assessment is the individualized, stepwise evaluation of a patient scheduled for **noncardiac surgery** to estimate the probability of **major adverse cardiovascular events (MACE)** — myocardial infarction (MI), pulmonary edema, ventricular fibrillation/cardiac arrest, complete heart block and cardiac death — and to guide risk-reduction strategies. Cardiovascular complications remain a leading cause of perioperative morbidity and mortality. The contemporary approach (ACC/AHA 2024 and ESC 2022 guidelines) integrates **surgical urgency, active cardiac conditions, validated risk indices, functional capacity, cardiac biomarkers and selective noninvasive testing**, with the primary aim of detecting clinical cardiovascular instability rather than indiscriminate testing.

Initial Clinical Evaluation and Surgical Urgency

- ▶ **History and physical examination** with a **12-lead resting ECG** form the foundation; standardized preoperative questionnaires (age, anticoagulant use, prior MI/angina/heart failure/arrhythmia, renal disease, diabetes, orthopnea) identify intermediate- and high-risk patients needing detailed evaluation.
- ▶ History should focus on **occult cardiac or pulmonary disease**; examination should look for signs of failure (*raised JVP, S3 gallop, bilateral rales*) and significant murmurs (especially **aortic stenosis**).
- ▶ **Determine surgical urgency first**: a true **emergency** procedure proceeds without further risk stratification (risk is unavoidably higher); medical optimization and surveillance continue postoperatively.
- ▶ Screen for **active/unstable cardiac conditions** that mandate evaluation and treatment *before* elective surgery: **acute coronary syndrome (ACS)**, decompensated heart failure, severe symptomatic valvular disease (especially aortic stenosis), and uncontrolled symptomatic

arrhythmias. Patients with ACS are managed with goal-directed therapy before any preoperative assessment proceeds.

- ▶ Routine preoperative laboratory testing is **not** required in healthy patients undergoing elective low-risk procedures; tests are ordered only for specific clinical indications.

Estimating Risk: Surgery-Specific Risk and Validated Risk Indices

- ▶ Perioperative risk is a **combination of surgical (procedure-specific) and clinical (patient-specific) risk**, dichotomized into **low (<1%)** versus **elevated (≥1%)** risk of MACE.

Surgical risk gradient	Procedures
Higher	Emergent major operations (especially elderly); aortic and other non-carotid major vascular surgery; prolonged surgery with large fluid shifts/blood loss
Intermediate	Major thoracic or abdominal surgery; carotid endarterectomy; head/neck; orthopedic; prostate surgery
Lower	Eye (e.g., cataract), skin and superficial surgery; endoscopic procedures

- ▶ The **Revised Cardiac Risk Index (RCRI)**, *Lee et al., 1999*) is the favored index for its accuracy and simplicity — six predictors, one point each:

RCRI predictor (1 point each)	Defining features
High-risk surgery	Intraperitoneal, intrathoracic, or suprainguinal vascular surgery (except carotid endarterectomy)
Ischemic heart disease	Prior MI, current ischemic angina, sublingual nitrate use, positive exercise test, pathological Q waves, prior PCI/CABG with current angina
Congestive heart failure	History of pulmonary edema or paroxysmal nocturnal dyspnea, S3 gallop, bilateral rales, pulmonary edema on chest x-ray
Cerebrovascular disease	History of TIA or stroke
Diabetes mellitus	Preoperative treatment with insulin
Chronic renal insufficiency	Serum creatinine >2 mg/dL (>176.8 μmol/L)

- ▶ **Estimated rates of major cardiac events:** 0 points ≈ 0.4%, 1 point ≈ 0.9–1.3%, 2 points ≈ 6–7%, ≥3 points ≈ 11% (derivation cohort); pooled external validation gives 0.4%, 1%, 2.4% and 5.4% respectively. Patients with **≥3 predictors are very high risk (≥11%)** and benefit most from further stratification or avoidance of surgery.
- ▶ “Elevated risk” (ACC/AHA) = **≥2 RCRI predictors or** calculated risk of perioperative MI/cardiac arrest **>1%**.

- ▶ Other validated tools:

Tool	Key inputs / remarks
<i>Goldman</i> multifactorial index (1977)	Original 9-variable index (age >70, recent MI, S3/JVD, arrhythmia, aortic stenosis, emergency/major surgery) — historical
NSQIP MICA calculator (<i>Gupta</i> , 2011)	Age, ASA class, functional dependence, creatinine, procedure type — predicts 30-day MI/cardiac arrest
ACS-NSQIP universal surgical risk calculator (<i>Bilimoria</i> , 2013)	21 preoperative variables; best overall discrimination
SORT (Surgical Outcome Risk Tool)	ASA-PS grade, urgency, severity of surgery, malignancy, age >65
AUB-HAS2 index	Heart disease, Angina/dyspnea Symptoms, Age ≥75, Hemoglobin <12, vascular Surgery, emergency Surgery — predicts 30-day death/MI/stroke; outperformed RCRI in validation
ASA-PS classification	P1 (normal healthy) → P6 (brain-dead organ donor); component of several calculators

Functional Capacity Assessment

- ▶ Functional capacity is expressed in **metabolic equivalents (METs)**. **Poor exercise tolerance** = inability to walk **four blocks** or climb **two flights of stairs** at normal pace, or failure to achieve 4 METs (e.g., carrying 15–20 lb, golf, doubles tennis) because of dyspnea, angina or fatigue.
- ▶ Patients with **moderate or better** (≥4 METs) capacity (climbing a flight of stairs, walking up a hill, walking on level ground at 4 mph) generally need **no further cardiac testing** before elective surgery.
- ▶ *Subjective clinician estimates of capacity are unreliable* (METS study); the structured **Duke Activity Status Index (DASI)** is the advocated instrument — a 12-item questionnaire (estimated METs = $[DASI \times 0.43 + 9.6]/3.5$); a **DASI score ≥34** → **proceed to surgery**.
- ▶ **Cardiopulmonary exercise testing (CPET)**: an anaerobic threshold of approximately **10 mL O₂/kg/min** (range 9.9–11) discriminates patients at higher perioperative risk; used for “prehabilitation” planning and shared decision-making.

Cardiac Biomarkers

- ▶ **BNP/NT-proBNP** measurement is recommended (ACC/AHA 2024) in patients with **both elevated calculated risk and poor/unknown functional capacity**.
- ▶ **Normal values** — **BNP <92 ng/L or NT-proBNP <300 ng/L** — **imply acceptable cardiac risk**; no further risk-stratification testing is needed. Levels above these thresholds carry a **fourfold increase in 30-day death/MI** (meta-analysis); in the VISION cohort, preoperative NT-proBNP correlated directly with vascular death and myocardial injury.

- ▶ Preoperative **troponin** elevation predicts 30-day mortality; Canadian/European guidelines also advocate **routine postoperative troponin surveillance in high-risk patients**.

Noninvasive Testing and Coronary Angiography

- ▶ There is **no role for routine preoperative stress testing**; testing is reserved for patients with **poor** (<4 METs) or **unknown functional capacity** in whom results would **change management**.
- ▶ Options: **dobutamine stress echocardiography** or **myocardial perfusion imaging** with vasodilator stress (dipyridamole, adenosine or regadenoson) using thallium-201/technetium-99m; **coronary CT angiography (CCTA)** improves prognostication over RCRI but without proven outcome benefit.
- ▶ The 2024 guideline emphasis: ischemia testing is performed primarily to **exclude high-risk coronary anatomy** (left main or multivessel CAD with reduced EF), not to detect any CAD.
- ▶ **Prophylactic coronary revascularization** (CABG/PCI) purely to “get the patient through surgery” is **not recommended** — the **CARP trial** showed no perioperative or long-term benefit (left main disease excluded). Revascularize only for guideline-concordant indications independent of surgery.

Stepwise Algorithm for Perioperative Cardiac Risk Assessment (ACC/AHA-based)

- ▶ **Step 1 — Urgency**: Emergency surgery → **proceed to surgery** with medical optimization, intra-/postoperative surveillance; no further preoperative testing.
- ▶ **Step 2 — Active cardiac conditions**: Evidence of ACS, decompensated HF, severe symptomatic valvular disease, unstable arrhythmia → **treat per guideline-directed therapy first**; multidisciplinary (cardiology–anesthesia–surgery) discussion. Severe valve disease, severe pulmonary hypertension, CIEDs, congenital heart disease, recent stroke and severe frailty warrant condition-specific evaluation regardless of calculated score.
- ▶ **Step 3 — Estimate combined risk with RCRI or NSQIP MICA**: if <1% MACE risk / <2 RCRI **predictors** (or low-risk surgery such as cataract or endoscopy) → **proceed to surgery**.
- ▶ **Step 4 — Functional capacity**: elevated risk but ≥4 METs (DASI ≥34) → **proceed to surgery**.
- ▶ **Step 5 — Biomarkers**: poor/unknown capacity → measure BNP/NT-proBNP; if BNP <92 ng/L / NT-proBNP <300 ng/L → **proceed**.
- ▶ **Step 6 — Abnormal biomarker** → **multidisciplinary discussion**: pharmacologic stress imaging or CCTA *only if results will alter management*; if **high-risk findings** (left main / multivessel CAD with reduced EF) → optimize guideline-directed therapy, revascularize only for independent indications, consider **alternative invasive/noninvasive or palliative management, deferral**, or proceed with informed knowledge of elevated risk.
- ▶ At every exit point, apply **perioperative medical risk reduction**:

Therapy	Perioperative recommendation
Beta-blockers	Continue if chronic; never start on the day of surgery ; consider initiation ≥ 1 week before surgery only in select high-risk patients (≥ 3 RCRI factors or intermediate/high-risk ischemia) — <i>POISE</i> : fixed high-dose metoprolol reduced MI but increased death and stroke
Statins	Continue if chronic; initiate in vascular surgery patients and those with clinical indications (e.g., atorvastatin 20 mg daily)
ACE inhibitors/ARBs	Continue, or restart as soon as clinically feasible postoperatively
Aspirin	Continue only when cardiac risk outweighs bleeding risk; do not initiate de novo (<i>POISE-2</i>)
DAPT / coronary stents	Delay elective surgery ≥ 30 days after bare-metal stent, 6 months after DES (stable CAD)/elective PCI, 12 months after ACS (3 months acceptable if delay is risky, e.g., cancer surgery). Hold clopidogrel 5 days, prasugrel 7 days, ticagrelor 3–5 days ; continue aspirin and restart P2Y ₁₂ inhibitor early
Alpha-2 agonists	Not recommended — clonidine increased hypotension and nonfatal cardiac arrest (<i>POISE-2</i>)
Calcium channel blockers	No evidence as prophylaxis
SGLT2 inhibitors	Stop 3–4 days before surgery (euglycemic ketoacidosis risk)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Flowchart: stepwise perioperative cardiac risk algorithm.** Boxes top-to-bottom with exact labels: “Patient scheduled for noncardiac surgery” → branch 1 “Emergency surgery? — Yes → Proceed to surgery + postoperative surveillance”; branch “No” → “Acute coronary syndrome / unstable cardiac condition? — Yes → Guideline-directed evaluation and treatment first”; “No” → “Step 1: Estimate MACE risk (RCRI / NSQIP MICA)” → “ $<1\%$ or <2 RCRI predictors → Proceed to surgery”; “Elevated risk” → “Step 2: Functional capacity ≥ 4 METs (DASI ≥ 34)? — Yes → Proceed”; “No/unknown” → “Step 3: BNP <92 ng/L or NT-proBNP <300 ng/L? — Yes → Proceed”; “Abnormal” → “Step 4: Multidisciplinary discussion $\pm$ stress imaging/CCTA (only if it changes management)” → “Step 5: High-risk CAD → optimize GDMT / revascularize for independent indication / alternative or palliative approach / proceed with known risk”. Add a side box: “Perioperative medical therapy: continue beta-blocker and statin, continue/restart ACEi, aspirin individualized, stop SGLT2i 3–4 days”.

Therapy	Perioperative recommendation
	▶ Bar diagram of RCRI risk stratification: x-axis “RCRI 0, 1, 2, ≥ 3”; y-axis “cardiac event rate (%)” with bars labelled “0.4–0.5%, 0.9–1.3%, 6–7%, $\geq 11\%$” and zones “Low / Intermediate / High risk”.

Clinical / Diagnostic significance

- ▶ **Postoperative MI** typically occurs **within 3 days** of surgery and is usually **silent** — suspect it with unexplained hypotension, hypoxemia or delirium; even isolated troponin elevation predicts higher mortality.
- ▶ **Severe aortic stenosis:** symptomatic patients should undergo **valve intervention (SAVR/TAVI)** **first** if surgery can be deferred; asymptomatic severe AS with preserved EF can usually undergo low/intermediate-risk surgery safely; balloon valvotomy is only a bridge.
- ▶ **Heart failure** confers risk equal to or greater than CAD — postpone elective surgery until decompensation (raised JVP, S3, pulmonary edema) is controlled; echocardiography for unexplained dyspnea or clinical deterioration, not routinely.
- ▶ **Hypertension:** only severe BP ($>180/110$ mmHg) justifies considering deferral of elective surgery.
- ▶ **Recent MI:** highest risk within **30 days**; risk declines progressively thereafter — time-stratify surgery accordingly.
- ▶ Mechanism pearl: perioperative stress (tachycardia, hypercoagulability) causes both **type 1 MI (plaque rupture)** and the now-predominant **type 2 MI (supply-demand mismatch)** — explaining why fixed-stenosis testing misses many events.

High-yield exam pointers

- ▶ **RCRI six predictors:** high-risk surgery, ischemic heart disease, CHF, cerebrovascular disease, insulin-treated diabetes, creatinine >2 mg/dL — one point each; event rates $\approx 0.4 / 1 / 6-7 / \geq 11\%$ for 0/1/2/ ≥ 3 points.
- ▶ **Elevated risk** = ≥ 2 RCRI predictors or $>1\%$ calculated MACE; ≥ 3 **RCRI factors** = candidate for noninvasive testing/beta-blocker initiation.
- ▶ **4 METs rule:** able to climb a flight of stairs/walk up a hill $\rightarrow$ proceed without testing; **DASI ≥ 34** is the structured equivalent.
- ▶ **Biomarker gate:** BNP <92 ng/L or NT-proBNP <300 ng/L $\rightarrow$ acceptable risk, proceed.
- ▶ Stress testing only if **poor/unknown capacity AND results would change management**; goal is to exclude left main/multivessel CAD.
- ▶ **No prophylactic revascularization** (CARP trial); stent-to-surgery delays: BMS 30 days, DES 6 months (stable), 12 months after ACS.

- ▶ Never start a beta-blocker on the day of surgery (POISE); continue chronic beta-blockers and statins; stop SGLT2 inhibitors 3–4 days before.
- ▶ Emergency surgery bypasses the algorithm; ACS always trumps the operation.
- ▶ Postoperative MI is usually **painless, within 72 h** — screen high-risk patients with troponin.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — “Medical Evaluation of the Patient Undergoing Noncardiac Surgery” (stepwise algorithm, RCRI, functional status, surgical risk gradation, perioperative therapies) and “Approach to Medical Consultation”; Braunwald's Heart Disease — “Anesthesia and Noncardiac Surgery in Patients With Heart Disease” (2024 ACC/AHA and 2022 ESC algorithms, risk-calculator comparison, DASI, CPET, biomarker data); CMDT 2026 — “Preoperative Evaluation & Perioperative Management” (2024 ACC/AHA five-step approach, biomarker thresholds, perioperative drug management). ASA-PS classification per Harrison 22e table.



Hypersensitivity reaction types and clinical implications

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — *Hypersensitivity* denotes an exaggerated or inappropriate adaptive immune response to an antigen (allergen, autoantigen, drug, or microbial product) that results in host tissue injury rather than protective immunity. Harrison describes four immunopathologic mechanisms of immune injury — immediate (IgE-mediated) hypersensitivity, antibody-mediated cytotoxic reactions, immune-complex formation, and delayed-type hypersensitivity — which correspond to the classic **Gell and Coombs Types I–IV**. Types I–III are antibody-mediated and Type IV is T cell (cell)-mediated. A single disease may involve more than one mechanism, and the same effector pathway that normally clears antigen becomes pathogenic when antigen persists or tolerance fails.

Gell and Coombs classification — overview

Type	Synonym	Key immune reactant	Effector mechanism	Onset	Prototype disorders
I	Immediate / anaphylactic	IgE on mast cells/basophils	Allergen cross-links IgE → mediator release	Seconds–minutes (within ~12 h)	Anaphylaxis, allergic rhinitis, atopic asthma, urticaria
II	Cytotoxic	IgG/IgM vs cell-surface or matrix antigen	Complement (classic pathway) + Fc-	Minutes–hours	Transfusion reaction, Goodpasture's,

Type	Synonym	Key immune reactant	Effector mechanism	Onset	Prototype disorders
			mediated lysis/ADCC		pemphigus vulgaris, AIHA
III	Immune-complex	Soluble Ag–Ab complexes (IgG/IgM)	Complex deposition → complement → neutrophil injury	Hours (3–10 h)	SLE, post-streptococcal glomerulonephritis, vasculitis, serum sickness
IV	Delayed / cell-mediated	TH1/TH17/CD8 T cells, macrophages	Cytokine-driven inflammation, no antibody	48–72 h	Tuberculin reaction, contact dermatitis, granulomatous disease

Type I — Immediate (IgE-mediated) hypersensitivity

- ▶ **Sensitisation:** *TH2*-type helper cells (and the *TFH13* subset) secreting IL-4, IL-5, IL-6, IL-10 (and IL-13) drive B-cell class-switching to IgE on first allergen exposure.
- ▶ **Effector cells:** Mast cells and basophils bear **high-affinity Fc receptors for IgE (FcεRI)**; cell-bound antiallergen IgE effectively “arms” these cells.
- ▶ **Trigger:** Re-exposure → allergen cross-links surface IgE → degranulation and mediator release.
- ▶ **Mediators** released fall into three functional groups (Harrison):
 - *Increase vascular permeability and contract smooth muscle:* **histamine**, **platelet-activating factor (PAF)**, **SRS-A** (slow-reacting substance of anaphylaxis = leukotrienes), bradykinin.
 - *Chemotactic/activating for other inflammatory cells:* **ECF-A** (eosinophil chemotactic factor of anaphylaxis), **NCF** (neutrophil chemotactic factor), **leukotriene B4**.
 - *Modulate release of other mediators:* PAF, BK-A.
- ▶ **Clinical spectrum:** systemic **anaphylaxis** (hypotension, bronchospasm, angioedema), allergic rhinitis/conjunctivitis, atopic (extrinsic) asthma, urticaria–angioedema, food and drug allergy.
- ▶ A *late-phase* reaction (4–12 h) driven by recruited eosinophils and TH2 cells follows the immediate wheal-and-flare in many patients.

Type II — Antibody-mediated cytotoxic hypersensitivity

- ▶ **Mechanism:** Complement-fixing (C1-binding) antibodies — IgM, IgG1, IgG2, IgG3 — directed against antigens on *normal or foreign cells/tissues* bind complement via the **classic pathway**, initiating a cascade (analogous to immune-complex injury) that culminates in **cell lysis or tissue injury** (membrane-attack complex) and Fc-mediated opsonophagocytosis/ADCC.

- ▶ **Three sub-patterns** (standard immunology): (a) *complement/cell lysis*, (b) *opsonisation–phagocytosis*, (c) *antibody alters cell function* without destruction (receptor stimulation or blockade).
- ▶ **Examples cited in Harrison:**
 - **Red-cell lysis in transfusion reactions** (and autoimmune haemolytic anaemia, haemolytic disease of the newborn).
 - **Goodpasture’s syndrome** — anti-glomerular basement membrane antibody against the **type IV collagen $\alpha 3$ chain**.
 - **Pemphigus vulgaris** — anti-epidermal (desmoglein) antibody inducing blistering skin disease.
- ▶ **Receptor-directed (functional) variants** — Graves’ disease (stimulating anti-TSH-receptor Ab) and myasthenia gravis (blocking anti-AChR Ab) — are the classic “Type V/Type II functional” examples.

Type III — Immune-complex-mediated hypersensitivity

- ▶ **Mechanism:** After antigen exposure, soluble **antigen–antibody (immune) complexes** circulate; if **not cleared by the reticuloendothelial system**, they deposit in **blood-vessel walls** and in tissues such as **renal glomeruli**, activate complement, and recruit neutrophils → **vasculitis or glomerulonephritis**.
- ▶ **Determinants of injury:** the quantity and physicochemical properties (size, charge, antigen:antibody ratio) of complexes determine whether they are pathogenic; complexes formed in slight antigen excess deposit most readily.
- ▶ **Complement link:** deficiencies of early classic-pathway components (C1q, C1r/s, C4, C2) cause *inefficient clearance of immune complexes*, predisposing to immune-complex–mediated autoimmune syndromes — **SLE and SLE-like syndromes, glomerulonephritis, and vasculitis** (Harrison Table 360-12).
- ▶ **Clinical examples:** systemic lupus erythematosus, post-streptococcal/membranoproliferative glomerulonephritis, cryoglobulinaemic and other small-vessel vasculitides, serum sickness, and the local *Arthus reaction*.

Type IV — Delayed-type (cell-mediated) hypersensitivity

- ▶ **Definition (Harrison):** inflammatory reactions **initiated by mononuclear leukocytes, not by antibody alone**; “delayed” because the secondary cellular response appears **48–72 h** after antigen exposure, versus the **<12 h** immediate response.
- ▶ **Effector axis:** antigen processed by DCs → presented to CD4⁺ T cells; **IL-12 from APCs induces IFN- γ (TH1 response)**. Classic DTH is centred on **IFN- γ –, IL-2–, and TNF- α –secreting TH1 cells and macrophages**; **NK cells** contribute to contact hypersensitivity.

- ▶ **Granuloma formation:** under sustained IFN- γ , macrophages undergo **epithelioid transformation** and fuse into **multinucleated giant cells** → **granulomatous inflammation**.
- ▶ **Prototype test:** intradermal **tuberculin purified protein derivative (PPD)** in a previously *M. tuberculosis*-exposed host produces an **indurated area** at **48–72 h**.
- ▶ **DTH-driven diseases (Harrison):** fungal (histoplasmosis), mycobacterial (**tuberculosis, leprosy**), chlamydial (lymphogranuloma venereum), helminthic (schistosomiasis), toxin (berylliosis), and **hypersensitivity pneumonitis** (organic dusts); DTH also drives tissue damage in **rheumatoid arthritis, temporal arteritis, and granulomatosis with polyangiitis**, and underlies **allergic contact dermatitis**.

Type IV subtype	Dominant T cell / effector	Example
IVa	TH1 + macrophage (IFN- γ)	Tuberculin reaction, granuloma, contact dermatitis
IVb	TH2 + eosinophil	Chronic asthma, DRESS
IVc	Cytotoxic CD8 ⁺ T cell	Stevens-Johnson syndrome / TEN, contact dermatitis
IVd	T cell + neutrophil	Acute generalised exanthematous pustulosis (AGEP), Behçet

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Four-panel Gell-Coombs schematic** (one box per type). Labels: *Type I* — allergen, IgE, Fc ϵ RI, mast cell, granules (histamine/leukotrienes/PAF); *Type II* — target cell-surface antigen, IgG/IgM, complement (C1→MAC), phagocyte (Fc receptor); *Type III* — soluble antigen + antibody → immune complex, deposition in vessel wall/glomerulus, complement, neutrophil; *Type IV* — antigen-presenting cell, CD4⁺ TH1 cell, IFN- γ /IL-2/TNF- α , macrophage → epithelioid/giant cell granuloma.
- ▶ **Time-course line graph** of skin reaction: x-axis = hours after challenge; label *immediate wheal-and-flare* (minutes, *Type I*), *late-phase* (4–12 h), and *delayed induration* (48–72 h, *Type IV / tuberculin*).

Clinical / Diagnostic significance

- ▶ **Mechanism guides diagnosis:** serum tryptase and skin-prick/specific-IgE testing for *Type I*; direct/indirect Coombs (antiglobulin) test and tissue immunofluorescence for *Type II*; complement (low C3/C4), ANA/anti-dsDNA, cryoglobulins and immune-complex glomerular deposits for *Type III*; **patch testing** and the **tuberculin/IGRA** read at 48–72 h for *Type IV*.
- ▶ **Mechanism guides therapy:** *Type I* — adrenaline (first-line for anaphylaxis), H1-antihistamines, glucocorticoids, allergen avoidance/immunotherapy, anti-IgE (omalizumab); *Types II/III* — glucocorticoids, plasma exchange, rituximab/cytotoxic agents, IVIg for selected immune-

complex disease; Type IV — topical/systemic glucocorticoids, calcineurin inhibitors, and avoidance of the contact/drug allergen.

- ▶ **Tolerance failure is the upstream lesion:** breakdown of **central (AIRE-dependent thymic) and peripheral (Treg/anergy) tolerance** converts physiologic responses into autoimmune Type II/III/IV disease (Harrison Ch 361). Environmental triggers — drugs (**procainamide, phenytoin** → **drug-induced lupus**), infections (EBV), and loss of Treg cells — precipitate disease in genetically susceptible hosts (e.g., **HLA-B27**).
- ▶ **Severe cutaneous adverse reactions** (SJS/TEN, DRESS, AGEP) are T cell-mediated (Type IV) drug hypersensitivities and demand immediate drug withdrawal.

High-yield exam pointers

- ▶ **Types I–III are antibody-mediated; Type IV is T cell-mediated** — the single most testable contrast.
- ▶ **Type I onset within ~12 h vs Type IV induration at 48–72 h** — memorise the tuberculin timing.
- ▶ Type I effector = **mast cell + FcεRI + IgE**; key mediators histamine, SRS-A (**leukotrienes**), PAF, ECF-A.
- ▶ Type II antibodies that fix complement = **IgM, IgG1, IgG2, IgG3**; triad of examples — **transfusion reaction, Goodpasture's (anti-type IV collagen α3), pemphigus vulgaris**.
- ▶ Type III injury site = **vessel walls and renal glomeruli**; **early complement deficiency (C1q, C4, C2) → poor clearance → SLE/immune-complex disease**.
- ▶ Type IV hallmark = **granulomatous inflammation** (epithelioid + multinucleated giant cells, IFN-γ-driven); seen in TB, leprosy, sarcoid-type reactions, contact dermatitis.
- ▶ **Adrenaline is the first-line drug for Type I anaphylaxis** — not antihistamines.
- ▶ **Procainamide and phenytoin** are classic causes of drug-induced lupus (immune-complex/Type III autoimmunity).

SOURCE & COVERAGE

Harrison 22e — Ch 360 “Introduction to the Immune System” (Immediate-Type Hypersensitivity, Cytotoxic Reactions of Antibody, Immune-Complex Formation, Delayed-Type Hypersensitivity Reactions; Table 360-12) + Ch 361 “Mechanisms of Regulation and Dysregulation of the Immune System” (tolerance, Treg, autoimmunity). **Coverage note (spec gap = true):** Harrison describes the four immune-injury mechanisms but does **not** use the eponym “*Gell and Coombs*” nor the explicit numbered labels *Type I–IV*; this universally accepted immunology framework has been mapped onto Harrison's named mechanisms. The **Type IV sub-classification (IVa–d)**, the **Type II sub-patterns / functional “Type V”** (Graves', myasthenia gravis), the **Arthus/serum-sickness** examples, and specific **diagnostic test and drug-dose** details

are standard textbook internal medicine added for completeness and are not verbatim in the provided chapters.



Inherited Mitochondrial Disorders in Adults

Asked in: Paper I Jul 2021 — RGUHS MD General Medicine

Definition / Introduction — Mitochondrial disorders are a clinically and genetically heterogeneous group of multisystem diseases caused by defective **oxidative phosphorylation (OXPHOS)**, arising from mutations in either the **mitochondrial genome (mtDNA)** or the **nuclear genome (nDNA)**. Because mitochondria generate ATP in virtually every nucleated cell, any organ can be affected, but high-energy tissues — brain, eye, skeletal and cardiac muscle, endocrine glands, kidney and liver — dominate the picture. The term *inherited mitochondrial disorders* in adults principally denotes the **maternally transmitted mtDNA diseases** (e.g., LHON, MELAS, MERRF) plus nuclear-encoded disorders that secondarily destabilise mtDNA (e.g., POLG-related PEO, MNGIE). Many present for the first time in adolescence/adulthood, or are childhood diseases surviving into adult life.

Mitochondrial genome and unique genetic principles

- ▶ **mtDNA structure:** a circular, double-stranded molecule of **16,569 nucleotides** containing **37 genes** — **13** encode protein subunits of the ETC, **22** encode tRNAs and **2** encode rRNAs (12S, 16S). The non-coding **control region (D-loop)** governs replication/transcription.
- ▶ **Division of labour:** mtDNA encodes only 13 of the ~89 respiratory-chain subunits — **Complex I** (7: ND1, 2, 3, 4, 4L, 5, 6), **Complex III** (1: cytochrome *b*), **Complex IV/COX** (3: COX1, 2, 3) and **Complex V** (2: ATPase 6, 8). **Complex II (SDH), CoQ10 and cytochrome c are entirely nuclear-encoded** — hence SDH staining serves as an internal control. ~1500 nuclear genes support mitochondrial biogenesis; mtDNA is replicated by nuclear-encoded **polymerase-γ (POLG)**.
- ▶ **Maternal inheritance:** mtDNA is transmitted exclusively through the **ovum**; sperm mitochondria are degraded. Affected **mothers transmit to all offspring of both sexes, but only daughters transmit onward**; an affected father never transmits — paternal transmission virtually excludes an mtDNA disorder.
- ▶ **Heteroplasmy & homoplasmy:** each cell carries hundreds–thousands of mtDNA copies. Coexistence of mutant and wild-type mtDNA = **heteroplasmy**; uniformity = **homoplasmy**. Pathogenic mutations are usually heteroplasmic (LHON and m.1555A>G deafness are homoplasmic exceptions).
- ▶ **Threshold effect:** disease appears only when mutant load exceeds a critical level (typically **70–90%**), and the threshold is lower in oxidative-dependent tissues (brain, eye, heart, muscle).

- ▶ **Mitotic segregation & the bottleneck:** random partition of mtDNA at cell division shifts heteroplasmy across tissues and with age (clonal expansion), explaining variable, age-dependent penetrance and intrafamilial variability. A **germline bottleneck** during oogenesis produces large, unpredictable shifts in mutant load between mother and child.
- ▶ **Nuclear (Mendelian) mtDNA disorders:** mutations in nuclear maintenance genes (POLG, Twinkle/PEO1, ANT1, TYMP) cause **multiple mtDNA deletions or depletion**, inherited autosomal dominant/recessive.

Classic mtDNA syndromes affecting adults

Syndrome	Cardinal features	Commonest mutation (gene)	Genetics
LHON (Leber hereditary optic neuropathy)	Subacute, painless, sequential central visual loss in young men	m.11778G>A (<i>ND4</i> , ~69%), m.14484T>C (<i>ND6</i>), m.3460G>A (<i>ND1</i>) — Complex I	Homoplasmic, maternal; M:F ≈ 8:1
MELAS	Stroke-like episodes <40 y, encephalopathy (seizures/dementia), lactic acidosis, migraine, short stature, deafness, diabetes	m.3243A>G (<i>MT-TL1</i> , tRNA-Leu, ~80%); m.3271T>C (~10%)	Heteroplasmic, maternal
MERRF	Myoclonus , epilepsy, cerebellar ataxia , myopathy with ragged-red fibres , deafness, lipomas	m.8344A>G (<i>MT-TK1</i> , tRNA-Lys, ~80–90%)	Heteroplasmic, maternal
NARP / MILS	Neuropathy, ataxia, retinitis pigmentosa ; >90% load → maternally inherited Leigh syndrome	m.8993T>G (<i>MT-ATP6</i> , Complex V)	Heteroplasmic, maternal
CPEO	Late bilateral ptosis + ophthalmoplegia , proximal myopathy, exercise intolerance	Single large-scale deletion/duplication	Mostly sporadic (somatic)
Kearns-Sayre syndrome	Triad: PEO + onset <20 y + pigmentary retinopathy ; plus cardiac conduction block , ataxia, CSF protein >100 mg/dL, short stature, diabetes	Single large deletion (4977-bp “ common deletion ”)	Sporadic

Syndrome	Cardinal features	Commonest mutation (gene)	Genetics
Pearson syndrome	Infantile sideroblastic anaemia + pancytopenia + exocrine pancreatic insufficiency + lactic acidosis; survivors evolve to KSS	Large single deletion	Sporadic
MIDD	Maternally inherited diabetes + sensorineural deafness	m.3243A>G	Maternal
Aminoglycoside / non-syndromic deafness	Sensorineural hearing loss, precipitated by aminoglycosides (<i>ecogenetic</i>)	m.1555A>G (12S rRNA)	Homoplasmic, maternal (1:500)

- ▶ **MNGIE** (mitochondrial neurogastrointestinal encephalomyopathy): an **autosomal-recessive** (nuclear) disorder of the **thymidine phosphorylase gene** (TYMP/ECGF1) causing secondary multiple mtDNA deletions/depletion — ptosis, PEO, severe **GI dysmotility with pseudo-obstruction**, cachexia, peripheral neuropathy and **leukoencephalopathy**; onset in late teens, death usually before 40. Diagnosed by low leukocyte thymidine phosphorylase and raised **plasma thymidine and deoxyuridine**.
- ▶ **POLG-related disease**: adPEO/arPEO, **SANDO** (sensory ataxic neuropathy, dysarthria, ophthalmoplegia), parkinsonism and Alpers syndrome — **valproate is contraindicated** (risk of fatal hepatic failure).
- ▶ **Other nuclear “dynamics” genes**: *MFN2* → Charcot-Marie-Tooth type 2; *OPA1* → dominant optic atrophy with deafness/neuropathy.

Clinical features by organ system

- ▶ **CNS**: stroke-like episodes, seizures, myoclonus, migraine, cerebellar ataxia, dystonia, parkinsonism, cognitive decline/dementia, sensorineural deafness, optic atrophy.
- ▶ **Peripheral nerve**: length-dependent sensorimotor or autonomic polyneuropathy.
- ▶ **Skeletal muscle (mitochondrial myopathy)**: ptosis, external ophthalmoplegia, exercise intolerance, myalgia, proximal weakness, rhabdomyolysis/myoglobinuria.
- ▶ **Cardiac**: **conduction block** (especially KSS — may need pacemaker), hypertrophic then dilated cardiomyopathy, Wolff-Parkinson-White pre-excitation (with m.3243A>G).
- ▶ **Endocrine**: diabetes mellitus, short stature, hypothyroidism, hypoparathyroidism, hypogonadism, premature ovarian failure.

- ▶ **Ophthalmic:** pigmentary (“salt-and-pepper”) retinopathy, cataract, optic atrophy, ophthalmoplegia.
- ▶ **GI / hepatic / renal:** dysphagia, gastroparesis, pseudo-obstruction, pancreatitis; hepatopathy; renal tubular acidosis / **Fanconi syndrome**.

Investigation of suspected mtDNA disease

- ▶ **Biochemistry:** blood and CSF **lactate** (CSF lactate more specific with CNS disease), **lactate-to-pyruvate ratio** (>20 suggests an OXPHOS defect; <20 suggests pyruvate dehydrogenase defect), CK (often normal/mildly raised), plasma/urine amino acids, urinary organic acids (TCA intermediates), plasma acylcarnitines, and **GDF-15** (sensitive/specific serum marker of mitochondrial myopathy).
- ▶ **Neuroimaging:** MRI — MELAS shows cortical stroke-like lesions in **posterior cerebrum that do not respect vascular territories**, sparing white matter; Leigh syndrome shows symmetrical T2/FLAIR signal in **basal ganglia (putamen), globus pallidus and brainstem**; basal-ganglia calcification on CT; **MR spectroscopy** detects a lactate peak.
- ▶ **Cardiac/other:** ECG and echocardiography (conduction defects, cardiomyopathy); EMG/NCS; audiometry; ophthalmology/ERG.
- ▶ **Muscle biopsy:** **ragged-red fibres** on modified Gomori trichrome (subsarcolemmal mitochondrial accumulation), intensely “**ragged-blue**” fibres on SDH stain, scattered **COX-negative fibres**, and **paracrystalline “parking-lot” inclusions** on electron microscopy. RRFs are absent in NARP/MILS and LHON.
- ▶ **Molecular genetics (now first-line):** targeted PCR/RFLP for common point mutations (3243, 8344, 8993, 11778/14484/3460); whole **mtDNA next-generation sequencing**; **long-range PCR / Southern blot** for deletions; nuclear gene panels and WES/WGS. Because heteroplasmy varies between tissues, a **negative blood test (e.g., m.3243A>G load falls in blood with age)** should **prompt urine sediment or skeletal-muscle testing**; deletions are best detected in muscle.

Management

- ▶ **General:** no curative therapy — multidisciplinary, largely **supportive and surveillance-based**. Aggressively treat seizures (recognise subtle/subclinical seizures in MELAS), cardiac conduction disease (**pacemaker/ICD in KSS**), diabetes, endocrinopathy, dysphagia/PEG feeding, ptosis (props/surgery), cataract, and hearing loss (aids, **cochlear implant**).
- ▶ **Cofactors/vitamins (limited evidence):** **CoQ10** (up to ~200 mg three times daily; clearly beneficial in primary CoQ10 deficiency), riboflavin, **L-carnitine**, creatine, α-lipoic acid, vitamins C/E; **idebenone** (a CoQ analogue) is approved (EMA) for LHON.
- ▶ **Disease-specific:** **L-arginine / L-citrulline** (NO precursors) for MELAS stroke-like episodes (acute and prophylactic); **folinic acid** for CSF folate deficiency; **dichloroacetate (DCA)** lowers

lactate but causes peripheral neuropathy; **allogeneic haematopoietic stem-cell / bone-marrow transplantation** to restore thymidine phosphorylase in MNGIE.

- ▶ **Drugs to avoid:** valproate (especially with *POLG* mutations), **aminoglycosides** in m.1555A>G carriers, propofol/barbiturates, and **metformin/statins** caution (lactic acidosis); strongly advise **LHON carriers to avoid tobacco and alcohol** (penetrance reaches ~93% in male smokers).
- ▶ **Reproductive options:** genetic counselling is difficult because the bottleneck makes transmitted load unpredictable; **prenatal/preimplantation diagnosis is reliable only for NARP m.8993T>G**. Options include **oocyte donation**, PGD, and **mitochondrial replacement therapy (MRT)** — *maternal spindle transfer* or *pronuclear transfer* into a donor egg (licensed in the UK).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Circular mtDNA map (16,569 bp):** draw the circle showing the **D-loop / control region**, the two rRNAs (12S, 16S), and the disease-linked loci — *ND1/ND4/ND6* (LHON), *MT-TL1/tRNA-Leu* position 3243 (MELAS), *MT-TK1/tRNA-Lys* position 8344 (MERRF), *MT-ATP6* position 8993 (NARP/MILS), 12S rRNA 1555 (aminoglycoside deafness) and the “**common deletion**” (4977 bp) region. Label: heavy/light strands, OXPHOS complexes I, III, IV, V encoded.
- ▶ **Diagram 2 — Respiratory chain & heteroplasmy threshold:** Complexes I→II→CoQ10→III→cytochrome c→IV→V across the inner membrane with H⁺ pumping and ATP synthesis; alongside, a bar showing **wild-type vs mutant mtDNA** with a marked “**threshold (70–90%)**” above which disease is expressed.

Clinical / Diagnostic significance

- ▶ Consider mitochondrial disease in any **unexplained progressive multisystem disorder**, particularly combinations that “don’t fit” a single nuclear gene — e.g., diabetes + deafness, stroke + lactic acidosis, ptosis + cardiac block + retinopathy.
- ▶ A **stroke not conforming to a vascular territory** in a young adult with lactic acidosis is MELAS until proven otherwise.
- ▶ **Ragged-red fibres are neither universal nor specific** (also seen in inclusion-body myositis, ageing, zidovudine myopathy) — interpret with COX/SDH histochemistry and genetics.
- ▶ Genetic diagnosis directs **counselling, cascade testing and reproductive planning**, and flags **drug avoidances** (valproate, aminoglycosides).

High-yield exam pointers

- ▶ mtDNA = 16,569 bp, 37 genes (13 protein, 22 tRNA, 2 rRNA); **strict maternal inheritance, no recombination, heteroplasmy, threshold effect**.
- ▶ **LHON** = homoplasmic Complex I point mutations (11778/14484/3460), young men, painless central vision loss; idebenone; avoid tobacco/alcohol.

- ▶ **MELAS** = m.3243A>G (tRNA-Leu); diagnostic triad: stroke-like episode <40 y + encephalopathy + lactic acidosis/RRF; treat with **L-arginine**.
- ▶ **MERRF** = m.8344A>G (tRNA-Lys); myoclonus + epilepsy + ataxia + RRF + lipomas.
- ▶ **NARP/MILS** = m.8993T>G (ATPase 6); >90% load → Leigh syndrome; the **one mutation with reliable prenatal diagnosis**.
- ▶ **KSS** = single large mtDNA deletion (**4977-bp common deletion**); PEO + onset <20 + retinopathy + heart block (**pacemaker**); CSF protein >100.
- ▶ **MNGIE** = autosomal-recessive **TYMP** defect; PEO + GI pseudo-obstruction + neuropathy + leukoencephalopathy; ↑ plasma thymidine; allogeneic SCT.
- ▶ **m.1555A>G 12S-rRNA** = aminoglycoside-induced ototoxic deafness (**ecogenetic** — avoid aminoglycosides).
- ▶ **Lactate:pyruvate >20** = OXPHOS defect; muscle = **ragged-red** (Gomori), **ragged-blue** (SDH), **COX-negative fibres, paracrystalline inclusions**.
- ▶ **Avoid valproate in POLG disease**; therapy is supportive; **MRT (spindle/pronuclear transfer)** prevents transmission.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Mitochondrial DNA and Heritable Traits and Diseases” (Skorecki & Cohen).
- ▶ **Bradley and Daroff's Neurology in Clinical Practice, 8e** — Chapter “Mitochondrial Disorders” (Turner, Pitceathly & Schapira), used for the adult syndrome spectrum (CPEO/KSS, MNGIE, POLG/SANDO), muscle-biopsy histochemistry, the diagnostic algorithm and management.
- ▶ *Coverage note:* CMDT has no dedicated chapter on inherited mitochondrial disease; current-management details (CoQ10/idebenone doses, L-arginine, MRT, allogeneic SCT for MNGIE) are drawn from the two texts above and reflect universally accepted internal-medicine practice.



Limbic system

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — The **limbic system** is a phylogenetically ancient, ring-like (“limbus” = border) network of cortical and subcortical structures encircling the corpus callosum and upper brainstem, formed of **limbic cortex** (hippocampus, amygdala, entorhinal cortex), **paralimbic cortex** (cingulate gyrus, insula, temporopolar and orbitofrontal cortex), the **anterior and medial thalamic nuclei**, the **medial/basal striatum and basal forebrain**, and the **hypothalamus**. It integrates emotion,

motivation, autonomic and endocrine tone, olfaction, and declarative (explicit) memory, and is the substrate of amnesia, temporal-lobe epilepsy and limbic encephalitis.

Components and gross anatomy

- ▶ **Limbic cortex (core)** — *hippocampal formation* (archicortex: hippocampus proper/cornu ammonis, dentate gyrus, subiculum), *amygdala* (housed in the **uncus** of the medial temporal lobe), and *entorhinal cortex* — the gateway for cortical input into the hippocampus.
- ▶ **Paralimbic (mesocortical) belt** — *cingulate gyrus*, *parahippocampal gyrus*, *insula*, *temporopolar* and *orbitofrontal* cortex. The cingulate gyrus sweeps around the splenium of the corpus callosum and **blends into the parahippocampal gyrus**, forming a continuous limbic lobe (pericallosal + mesial-temporal + insular + orbital cortex of Broca).
- ▶ **Olfactory structures** — olfactory bulb/tract, anterior perforated substance and primary olfactory (paleo)cortex; olfaction is the only sensory modality reaching cortex without an obligatory thalamic relay.
- ▶ **Subcortical relays** — *fornix* (efferent hippocampal tract), *mammillary bodies* (hypothalamus), *anterior* and *mediodorsal thalamic nuclei*, *septal nuclei* and *nucleus basalis of Meynert* (basal forebrain, cholinergic), *retrosplenial cortex* and the *cingulum* bundle.
- ▶ **Diencephalic hub** — the *hypothalamus* links the system to homeostasis, the autonomic nervous system and the pituitary (neuroendocrine output).

The Papez circuit (memory loop)

- ▶ Originally proposed by **James Papez (1937)** as the anatomical substrate of *emotion*; in modern usage it is the **posterior limbic circuit for explicit (declarative) memory**.
- ▶ Closed reverberating loop:

Hippocampus → fornix → mammillary body → mammillothalamic tract (of Vicq d'Azyr) → anterior thalamic nucleus → cingulate gyrus (via internal capsule) → cingulum → parahippocampal/entorhinal cortex → back to hippocampus.

- ▶ The *mediodorsal thalamic nucleus*, *retrosplenial cortex* (an alternative hippocampo-thalamic route) and *basal forebrain* are functionally integral; bilateral damage to **any node** of this circuit produces amnesia.

Functional organisation

Functional division	Key structures	Behaviour subserved	Disease correlate
Anterior (emotional-affiliative)	Amygdala, anterior paralimbic/orbitofrontal cortex (overlaps <i>salience network</i>)	Emotion, motivation, fear, autonomic tone, endocrine drive	Temporal-lobe epilepsy; behavioural-variant FTD

Functional division	Key structures	Behaviour subserved	Disease correlate
Posterior (mnemonic) = Papez circuit	Hippocampus, entorhinal cortex, posterior paralimbic cortex, limbic thalamic nuclei	Declarative memory for recent episodes/experiences	Amnesic state; Alzheimer's disease
Olfactory	Olfactory bulb/tract, piriform cortex, amygdala, entorhinal cortex	Smell perception and its emotional/memory linkage	Uncinate fits (olfactory hallucinations)
Homeostatic	Hypothalamus, mammillary bodies, septal nuclei	Autonomic, neuroendocrine, feeding, sexual, rage/defence	Wernicke-Korsakoff; septal rage

- ▶ **Amygdala** — assigns emotional (especially *fearful*) salience to stimuli and tags emotionally charged events for stronger memory; bilateral lesions impair recognition of fear in faces.
- ▶ **Anterior cingulate cortex** — modulates autonomic activity, emotional response selection and the affective component of pain; part of the *rostral limbic system* (with periaqueductal grey, ventral striatum, orbitofrontal and anterior insular cortex). Bilateral lesions cause **akinetetic mutism**; cingulotomy is used for intractable pain/OCD.
- ▶ **Hippocampus** — encodes new declarative memories and spatial maps (*place cells*); damage spares previously consolidated remote memories and **implicit/procedural learning**.

Major connections and neurochemistry

- ▶ **Afferents** — all sensory association cortices funnel into limbic cortex via the entorhinal cortex; the *perirhinal cortex* relays visual/object information and the *parahippocampal cortex* relays spatial (dorsal-stream) information to the hippocampus.
- ▶ **Principal efferent tracts** — the **fornix** (hippocampus → mammillary body/septum), the **mammillothalamic tract** (mammillary body → anterior thalamus), the **stria terminalis** and **ventral amygdalofugal pathway** (amygdala → hypothalamus/septum/brainstem), and the **medial forebrain bundle** (septum/hypothalamus ↔ brainstem).
- ▶ **Cholinergic supply** — the **basal forebrain** (*nucleus basalis of Meynert, medial septal nucleus*) provides the major cholinergic input to hippocampus and neocortex; its degeneration underlies the memory deficit of AD and the rationale for **cholinesterase inhibitors**.
- ▶ **Other modulators** — *mesolimbic dopamine* (ventral tegmental area → nucleus accumbens/amygdala) underlies reward and motivation; serotonergic and noradrenergic projections modulate limbic affective tone; the hippocampus is densely glutamatergic and

selectively vulnerable to hypoxia, hypoglycaemia and seizure-induced excitotoxicity (hippocampal sclerosis).

The amnestic syndrome (clinical hallmark of limbic damage)

- ▶ Defined as a disturbance of **explicit memory** in the absence of deficits of attention, language or visuospatial function; *always implies bilateral limbic injury* (hippocampo-entorhinal complex or thalamus). Unilateral left hippocampal lesions cause only transient amnesia.
- ▶ Components: prominent **anterograde amnesia** (cannot store new information) > **retrograde amnesia** (recent memories more vulnerable than remote — *Ribot's gradient*).
- ▶ **Confabulation** (filling gaps with implausible information) occurs when the lesion also disrupts the frontothalamic network, as in **Wernicke-Korsakoff syndrome** and head trauma.
- ▶ **Implicit/procedural memory is preserved** — patients acquire new motor/perceptual skills without conscious recollection.
- ▶ Bedside test: 4–5 word list registration, then delayed recall at 5–10 min; amnestics fail recall and may forget that a list was given. Recognition better than recall suggests a milder, retrieval-stage defect.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Medial sagittal view of the limbic system** — label: *cingulate gyrus, parahippocampal gyrus, uncus (amygdala), hippocampus, fornix, mammillary body, anterior thalamic nucleus, septal nuclei, olfactory bulb/tract, hypothalamus, corpus callosum*.
- ▶ **Papez circuit loop** — draw the closed loop with labelled arrows: *Hippocampus → Fornix → Mammillary body → Mammillothalamic tract → Anterior thalamic nucleus → Cingulate gyrus → Cingulum → Entorhinal/parahippocampal cortex → Hippocampus*.

Clinical / Diagnostic significance

- ▶ **Alzheimer's disease (AD)** — neurofibrillary degeneration begins in the **entorhinal cortex and hippocampus**, explaining the early selective episodic-memory loss; spreads to limbic then neocortical areas. Prodrome = **amnestic mild cognitive impairment (aMCI)**; MRI shows hippocampal/medial-temporal atrophy; FDG-PET shows posterior-cingulate/precuneus hypometabolism.
- ▶ **Wernicke-Korsakoff syndrome** — thiamine deficiency damages the **mammillary bodies** and medial thalamus; Korsakoff psychosis = persistent recent-memory loss with confabulation.
- ▶ **Herpes simplex encephalitis** — necrotising involvement of medial temporal/limbic cortex causes amnesia and a **Klüver-Bucy-type picture** (hyperorality, hypermetamorphosis, inappropriate sexual displays, emotional blunting, visual agnosia/"psychic blindness") — classically from bilateral anterior-temporal/amygdala damage.

- ▶ **Autoimmune & paraneoplastic limbic encephalitis** — subacute confusion, depression/agitation, severe short-term-memory deficit and temporal-lobe seizures with **bilateral mesial-temporal T2/FLAIR hyperintensity**. Antibodies: **anti-LGI1** (faciobrachial dystonic seizures + hyponatremia), **anti-NMDAR** (young women, psychosis, dyskinesias, ovarian teratoma), **anti-AMPA**, **anti-GABA-B** (seizures, SCLC), **anti-Ma2** (testicular tumour), **anti-Hu** (SCLC).
- ▶ **Temporal-lobe (limbic) epilepsy** — aura of fear, déjà vu, **uncinate fits** (olfactory/gustatory hallucinations); interictal *Geschwind syndrome* (hyposexuality, hypergraphia, hyperreligiosity).
- ▶ **Transient global amnesia** — acute, self-limited (24–48 h) isolated anterograde amnesia with repetitive questioning; ~20% recur.
- ▶ **Other amnestic causes** — PCA/ACA territory infarcts, fornix/septal lesions (colloid cyst, anterior communicating artery aneurysm rupture), thalamic and medial-temporal tumours, head trauma, anoxia, Pick's disease/FTLD, LATE (limbic-predominant age-related TDP-43 encephalopathy).

High-yield exam pointers

- ▶ Limbic system = **emotion + memory + olfaction + autonomic/endocrine homeostasis**; “limbus” = border ring around the corpus callosum.
- ▶ **Papez circuit mnemonic**: *Hippocampus–Fornix–Mammillary body–Mammillothalamic tract–Anterior thalamus–Cingulate–back to Hippocampus*.
- ▶ **Bilateral** limbic lesions are required to produce a *persistent* amnestic state.
- ▶ **Anterograde amnesia > retrograde**; **confabulation** = added frontothalamic involvement (Wernicke-Korsakoff).
- ▶ **Implicit/procedural memory is spared** in pure amnesia.
- ▶ **Mammillary bodies** = Wernicke-Korsakoff; **hippocampus/entorhinal cortex** = early Alzheimer's disease.
- ▶ **Klüver-Bucy syndrome** = bilateral anterior temporal/amygdala damage → placidity, hyperorality, hypersexuality, hypermetamorphosis, visual agnosia.
- ▶ **Limbic encephalitis** = subacute amnesia + seizures + psychiatric change + bilateral mesial-temporal FLAIR signal → screen for **LGI1, NMDAR, AMPAR, GABA-B, Ma2, Hu** antibodies and occult malignancy.
- ▶ **Anterior cingulate** lesion → akinetic mutism; **septal** lesion → rage/irritability.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Aphasia, Memory Loss, and Other Cognitive Disorders” (limbic network for explicit memory, Papez circuit, amnestic state, causes); “Dementia / Alzheimer's Disease” (entorhinal-hippocampal onset, amnestic MCI, LATE); “Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis” (limbic

encephalitis, antibody panel); “Nutrition / Wernicke-Korsakoff” (mammillary bodies, thiamine, Korsakoff psychosis).

- ▶ **Brazis – Localization in Clinical Neurology** — “The Localization of Lesions Affecting the Cerebral Hemispheres” (limbic lobe anatomy, full Papez-circuit node list, amygdala in fear/emotional memory, cingulate emotion processing, temporal-lobe behavioural syndromes, basal forebrain/retrosplenial cortex).
- ▶ Coverage note: The corpus covers limbic *function, circuitry and clinical correlates* in depth; the **Klüver-Bucy** eponym and its component features are universally accepted standard neurology (the feature-set is described in Brazis under herpes-encephalitis/temporal-lobe damage) and are included as such.



Monoclonal Antibodies: Clinical Pharmacology

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — **Monoclonal antibodies (mAbs)** are laboratory-engineered immunoglobulins of a single specificity, directed against one defined epitope (antigen) and produced in large, high-affinity quantities. In therapeutics, animal-derived antigen-combining sequences are grafted into human immunoglobulin genes (**chimerized** or **humanized** products) or generated *de novo* from mice carrying human immunoglobulin gene loci (**fully human** antibodies). They form the backbone of modern targeted and immunologic cancer therapy and of immunomodulation in inflammatory disease, acting with precision but carrying a distinctive class toxicity profile (infusion reactions, immune-related adverse events, cytokine release). The generic suffix **-mab** denotes a monoclonal antibody.

Structure, Nomenclature and Production

- ▶ **Basic unit** is an IgG immunoglobulin: two **Fab** arms carry the antigen-binding *variable regions* (the complementarity-determining regions, CDRs, confer specificity); the **Fc** stem recruits effector functions (complement, Fc-receptor-bearing immune cells).
- ▶ **Production**: very large quantities of high-affinity mAbs against specific tumor/cell antigens are produced, then the rodent antigen-combining sequences are grafted into human Ig genes, or the antibody is derived from mice bearing human Ig gene loci — progressively reducing immunogenicity.
- ▶ **Nomenclature by source** (WHO stem system — standard, see Coverage note):

Type	Suffix	Sequence origin	Examples
Murine	-omab	100% mouse (highly immunogenic)	(largely obsolete)

Type	Suffix	Sequence origin	Examples
Chimeric	-ximab	mouse variable + human constant	Rituximab, Cetuximab, Infliximab
Humanized	-zumab	only CDRs murine	Trastuzumab, Pertuzumab, Bevacizumab, Alemtuzumab, Obinutuzumab
Fully human	-umab	entirely human	Panitumumab, Ofatumumab, Ipilimumab, Nivolumab, Durvalumab

- ▶ Less immunogenic constructs allow repeated dosing with lower risk of anti-drug antibodies and hypersensitivity.

Mechanisms of Action

- ▶ **Direct signal blockade / antiproliferative effect** — binding a growth-driving surface receptor interrupts intracellular signalling (e.g., *trastuzumab* interrupts HER2/neu signals; *pertuzumab* blocks HER2 dimerization; anti-CD20 agents interrupt signals driving lymphomagenesis).
- ▶ **Antibody-dependent cell-mediated cytotoxicity (ADCC)** — Fc engages NK/effector cells; *obinutuzumab* has altered glycosylation that enhances killer-cell activation.
- ▶ **Complement-dependent cytotoxicity (CDC)** — *alemtuzumab* (anti-CD52) activates complement against the target cell.
- ▶ **Immune-response activation** — anti-tumor mAbs both kill tumor cells and stimulate host anti-tumor immune mechanisms.
- ▶ **Checkpoint release** — immunoregulatory mAbs bind antigens on *host* immune cells (not tumor) to reactivate suppressed cytotoxic T cells (anti-PD-1/PD-L1, anti-CTLA4, anti-LAG3).
- ▶ **Bridging (bispecific)** — *BiTe* antibodies physically tether a T cell to a tumor cell, forcing immune killing.
- ▶ **Targeted delivery** — *antibody-drug conjugates (ADCs)* and radio-/toxin-conjugates ferry a cytotoxic “warhead” selectively to the antigen-bearing tumor cell.

Pharmacokinetics and Administration

- ▶ **Large proteins** — not orally bioavailable (digested in the gut); given **intravenously** or **subcutaneously**.
- ▶ **Slow elimination** — therapeutic antibodies are eliminated *very slowly*, probably by **lysosomal uptake and degradation**, giving a long half-life that permits **infrequent dosing** (e.g., **monthly injections**).

- ▶ **Not metabolized by cytochrome P450** and not renally excreted as intact protein — hence few classical pharmacokinetic drug interactions, though pharmacodynamic immune interactions occur.
- ▶ Distribution is largely confined to plasma and interstitial fluid; placental transfer (IgG) is relevant in pregnancy, and all conjugated cytotoxic mAbs carry embryofetal toxicity warranting contraception.

Therapeutic Strategies and Target Classification

Four general antibody strategies are recognised, plus a stroma-directed group:

Strategy	Mechanism	Representative targets and agents
Anti-tumor cell antibodies	Bind tumor surface antigen → block signalling, recruit immune/complement attack	CD20 — Rituximab, Ofatumumab, Obinutuzumab; CD52 — Alemtuzumab; EGFR — Cetuximab, Panitumumab; HER2/neu — Trastuzumab, Pertuzumab; CD38 — Daratumumab, Isatuximab
Bispecific T-cell engagers (BiTe)	One arm binds tumor antigen, other binds CD3 → drags T cell onto tumor	CD19×CD3 — Blinatumomab
Immunoregulatory (checkpoint) antibodies	Target host immune-cell receptors to release the brakes on T cells	CTLA4 — Ipilimumab; PD-1 — Nivolumab, Pembrolizumab, Cemiplimab; PD-L1 — Atezolizumab, Avelumab, Durvalumab; LAG3 — Relatlimab
Antibody conjugates (ADC / radio / toxin)	Antibody delivers a cytotoxic “warhead” to the tumor	See ADC table below
Stroma-directed antibodies	Target tumor-supporting vasculature	VEGF — Bevacizumab; VEGFR2 — Ramucirumab

Major Classes and Antibody-Drug Conjugates

- ▶ **Anti-CD20 (rituximab, ofatumumab):** B-cell lymphomas — used alone and with chemotherapy/radiation; *obinutuzumab* (enhanced ADCC) is valuable in **chronic lymphocytic leukemia**.
- ▶ **Anti-CD52 (alemtuzumab):** complement-activating; chronic lymphoid leukemia and T-cell malignancies; **tumor lysis syndrome prophylaxis** may be needed.
- ▶ **Anti-EGFR (cetuximab, panitumumab):** chemorefractory colorectal cancer and head-and-neck cancer with radiation; cause an **acneiform rash** (topical antibiotic + steroid cream) and photosensitivity.

- ▶ **Anti-HER2 (trastuzumab, pertuzumab):** HER2-overexpressing breast and certain GI cancers; pertuzumab blocks HER2 dimerization and augments trastuzumab; both are **cardiotoxic**, especially after anthracyclines — check and monitor LV function.
- ▶ **BiTe (blinatumomab):** anti-CD19 × anti-CD3; active in B-cell acute lymphocytic leukemia; toxicities are **cytokine release syndrome** (fever, hypotension, tachycardia) and neurologic deterioration (early sign: deteriorating handwriting → cortical dysfunction) needing dose-pausing ± glucocorticoids.
- ▶ **Checkpoint inhibitors:** *ipilimumab* (anti-CTLA4) was the first proof that purely immunoregulatory antibodies are safe and effective; *nivolumab/pembrolizumab* (anti-PD-1) and *atezolizumab* (anti-PD-L1) benefit many cancers; *pembrolizumab* first-line in PD-L1-expressing metastatic NSCLC (a milestone replacing chemotherapy); *relatlimab* (anti-LAG3) augments nivolumab in melanoma. **Tissue-agnostic** approval applies to MSI-high / mismatch-repair-deficient tumors and high **tumor mutational burden** (≥ 10 mutations/megabase).

Antibody-drug conjugates (humanized mAb + linker + cytotoxic payload; linker controls intracellular vs extracellular “bystander” release):

Payload class	ADC	Target	Indication / key toxicity
DNA disruptor (calicheamicin)	Gemtuzumab ozogamicin	CD33	AML; hepatic veno-occlusive disease
	Inotuzumab ozogamicin	CD22	ALL; VOD, myelosuppression
	Loncastuximab tesirine	CD19	Refractory DLBCL; vascular leak
Microtubule (maytansine/auristatin)	Ado-trastuzumab emtansine	HER2	Breast (trastuzumab-resistant); cardiac/pulmonary
	Brentuximab vedotin	CD30	Hodgkin lymphoma; neuropathy
	Enfortumab vedotin	Nectin-4	Urothelial cancer
	Belantamab mafodotin	BCMA	Myeloma; ocular keratopathy
Topoisomerase I	Fam-trastuzumab deruxtecan	HER2	Breast/gastric/NSCLC; interstitial lung disease
	Sacituzumab govitecan	Trop2	Triple-negative breast; diarrhea (UGT1A1*28)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

Payload class	ADC	Target	Indication / key toxicity
▶ IgG monoclonal antibody structure: label <i>Fab region</i>, <i>Fc region</i>, <i>antigen-binding site</i> (<i>variable region V_H / V_L</i>), <i>complementarity-determining regions (CDRs)</i>, <i>heavy chain</i>, <i>light chain</i>, <i>hinge region</i>, <i>disulfide bonds</i>; shade murine vs human portions to contrast <i>chimeric vs humanized vs fully human</i>. ▶ Four therapeutic strategies schematic (after Fig. 78-4): central <i>tumor cell</i> bearing surface <i>tumor antigen (T-Ag)</i>; label (1) <i>anti-tumor-cell antibody</i> → ADCC/CDC/signal block; (2) <i>BiTe</i> bridging a <i>T cell (CD3)</i> to <i>tumor (CD19)</i>; (3) <i>checkpoint axis</i> — <i>PD-1 / PD-L1</i> and <i>CTLA4</i> with <i>immunoregulatory antibody</i>; (4) <i>antibody-drug conjugate</i> (<i>antibody-linker-warhead</i>); and <i>anti-VEGF antibody</i> on a <i>tumor blood vessel</i>.			

Clinical / Diagnostic significance

- ▶ **Biomarker-guided use:** HER2 overexpression, EGFR/RAS status, CD-antigen expression, MSI/mismatch-repair status and tumor mutational burden select responders — molecular/liquid biopsy is integral to prescribing.
- ▶ **Pre-treatment screening:** assess **hepatitis B and C status** before anti-B-cell antibodies (risk of reactivation and opportunistic infection); baseline **echocardiography/LVEF** before anti-HER2 agents; ophthalmologic exam before ocular-toxic ADCs.
- ▶ **Beyond oncology:** the same biology underlies *infliximab* (anti-TNF, chimeric), *rituximab* and *abatacept* used to treat severe immune-mediated disease — including, per Harrison, severe immunologically-mediated **adverse drug reactions** refractory to steroids.
- ▶ **Immune-related adverse events (irAEs)** from checkpoint inhibitors are unpredictable, can appear late even during sustained tumor control, and demand a low threshold for high-dose glucocorticoids; **myocarditis**, though rare, can be rapidly fatal.

High-yield exam pointers

- ▶ Suffix **-mab** = monoclonal antibody; **-ximab** chimeric, **-zumab** humanized, **-umab** fully human (decreasing immunogenicity).
- ▶ Effector mechanisms: **signal blockade**, **ADCC**, **CDC**, **immune activation**; conjugates add targeted cytotoxic delivery.
- ▶ PK: **not oral**, IV/SC, **no CYP metabolism**, slow lysosomal degradation → long half-life → **monthly dosing**.
- ▶ **Trastuzumab/pertuzumab** → **cardiotoxicity** (worse post-anthracycline); **cetuximab** → **acneiform rash**; **bevacizumab** → **hypertension**, **proteinuria**, **thrombosis**, **bleeding**, **GI perforation**.
- ▶ **Blinatumomab (BiTe)** → **cytokine release syndrome + neurotoxicity**; checkpoint inhibitors → **immune-related AEs** (colitis, thyroiditis, hepatitis, myocarditis).

- ▶ Gemtuzumab/inotuzumab ozogamicin → veno-occlusive disease; belantamab → keratopathy; trastuzumab deruxtecan → interstitial lung disease.
- ▶ Checkpoint biomarkers: MSI-high / mismatch-repair deficient / TMB ≥ 10 mut/megabase = tissue-agnostic indication.
- ▶ First-line: **infusion-reaction prophylaxis** (glucocorticoid $\pm$ antihistamine, slow infusion); severe irAEs → **high-dose steroids**, then rituximab/infliximab/abatacept/mycophenolate/plasmapheresis.

SOURCE & COVERAGE

Harrison 22e — Ch 78 “Principles of Cancer Treatment” (antibody-mediated therapeutic approaches, BiTe, immunoregulatory/checkpoint antibodies, stroma-directed antibodies, antibody-drug conjugates; Fig. 78-4; Tables 78-4 and 78-6) and Ch 71 “Principles of Clinical Pharmacology” (antibody pharmacokinetics — slow lysosomal elimination/monthly dosing; immune-checkpoint-related ADRs and their management with steroids/rituximab/infliximab/abatacept/mycophenolate/plasmapheresis).

Coverage note: Harrison does not provide a dedicated mAb-pharmacology chapter (spec gap = true). Antibody **structure detail** (Fab/Fc/CDR domains) and the **WHO -omab/-ximab/-zumab/-umab stem nomenclature** are universally accepted standard immunology/pharmacology added for completeness — they are not stated verbatim in the provided chapters (Harrison uses the broader terms “chimerized,” “humanized,” and “fully human,” and loosely labels some agents “humanized”). The statements that mAbs are non-oral, lack CYP metabolism, and undergo placental transfer are standard pharmacology; only “slow lysosomal elimination with monthly dosing” is given explicitly in Ch 71. Non-oncology examples (infliximab, abatacept use) and individual ADC/checkpoint indications are grounded in the cited tables/figure.



Neurotransmitters

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — **Neurotransmitters** are endogenous chemical messengers synthesised by neurons, stored in synaptic vesicles, released into the synaptic cleft in a calcium-dependent manner on depolarisation, and acting on specific pre- or post-synaptic receptors to alter the excitability of the target cell. They are the molecular currency of **chemical synaptic transmission** and the principal targets of nearly every centrally acting drug — antidepressants, antipsychotics, anxiolytics, anti-parkinsonian agents, analgesics and drugs of abuse all act by modulating neurotransmitter synthesis, release, receptor signalling, reuptake or degradation. Harrison frames their clinical relevance through the **monoamine**

hypothesis of mood disorders, the dopaminergic reward circuit of addiction, and the GABA/glutamate excitatory-inhibitory balance.

Defining criteria and classification

A substance qualifies as a neurotransmitter if it is synthesised in the neuron, stored and released on stimulation, mimics the effect of nerve stimulation when applied exogenously, binds specific receptors, and has a defined mechanism of inactivation (reuptake or enzymatic degradation).

Class	Members	Key biosynthetic point
Amino acids	Glutamate (principal excitatory); GABA (principal inhibitory); glycine (inhibitory)	GABA synthesised from glutamate by glutamic acid decarboxylase (GAD1)
Biogenic amines (monoamines) — catecholamines	Dopamine, norepinephrine, epinephrine	Derived from tyrosine; tyrosine hydroxylase = rate-limiting enzyme of catecholamine biosynthesis
Biogenic amines — indoleamine / imidazole	Serotonin (5-HT, from tryptophan); histamine	Monoamine reuptake/oxidation governs synaptic levels
Acetylcholine	ACh	Synthesised from choline + acetyl-CoA; terminated by acetylcholinesterase
Neuropeptides	Endorphins, enkephalins; orexin (hypocretin); β -endorphin, melanocortin; CRF	Co-released with classical transmitters
Endocannabinoids	Anandamide, 2-arachidonoylglycerol	Retrograde messengers acting on CB1
Gaseous / unconventional	Nitric oxide, carbon monoxide; purines (ATP, adenosine)	Not vesicular; freely diffusible (NO/CO)

Major neurotransmitter systems and their CNS pathways

Harrison's circuit diagram of mood and reward (Fig. 462-3) maps each monoamine to a discrete brainstem/midbrain source nucleus projecting diffusely to the limbic system.

Transmitter	Source / projection	Main receptors	Principal action	Disease correlation
Dopamine	Ventral tegmental area (VTA), substantia nigra → nucleus accumbens, cortex	D1–D5 (metabotropic)	Reward “rheostat”, motor control, cognition	Parkinson disease, schizophrenia, addiction
Norepinephrine	Locus coeruleus (LC) → widespread	α - and β -adrenergic	Arousal, vigilance, mood, stress	Depression, anxiety

Transmitter	Source / projection	Main receptors	Principal action	Disease correlation
Serotonin (5-HT)	Dorsal raphe / raphe nuclei → widespread	5-HT ₁₋₇ (5-HT ₃ is ionotropic)	Mood, sleep, appetite, impulse control	Depression, OCD, anxiety
Glutamate	Cortical/limbic glutamatergic neurons	NMDA, AMPA, kainate, mGluR	Principal excitatory; long-term potentiation/synaptic plasticity	Excitotoxicity, schizophrenia
GABA	Interneurons (GAD1)	GABA-A (ionotropic Cl ⁻), GABA-B (metabotropic)	Principal inhibitory transmitter	Epilepsy, anxiety, spasticity
Acetylcholine	Basal forebrain, brainstem	Nicotinic (ionotropic), muscarinic	Arousal, memory, autonomic control	Alzheimer disease, myasthenia
Endogenous opioids	Arcuate/hypothalamic peptidergic neurons	μ, δ, κ opioid (Gi/o)	Analgesia, reward, mood	Addiction, pain
Endocannabinoids	Post-synaptic, retrograde	CB1	Retrograde dampening of release	Addiction

Life cycle of chemical synaptic transmission

- **Synthesis** — precursor amino acids/choline converted by rate-limiting enzymes (e.g., tyrosine hydroxylase for catecholamines, GAD for GABA).
- **Storage** — packaging into synaptic vesicles by vesicular transporters.
- **Release** — action potential opens voltage-gated **Ca²⁺ channels** at the terminal; Ca²⁺ influx triggers exocytotic, quantal release into the cleft.
- **Receptor activation** — binding to **ionotropic** (ligand-gated ion channel, fast) or **metabotropic** (G-protein-coupled, slow/modulatory) receptors on the post-synaptic membrane.
- **Termination** — (1) **reuptake** by membrane transporters (e.g., the **dopamine transporter, DAT**; serotonin and norepinephrine transporters); (2) **enzymatic degradation** (monoamine oxidase, catechol-O-methyltransferase, acetylcholinesterase).
- **Plasticity** — repeated activity alters **synaptic strength** (long-term potentiation/depression) and **gene expression** via second messengers and transcription factors (**cAMP-CREB, ΔFosB**), the molecular basis of learning and of addiction.

Receptor types and signal transduction

- **Ionotropic receptors** — ligand-gated channels giving rapid responses: **NMDA / AMPA / kainate** (glutamate), **GABA-A (Cl⁻)**, **nicotinic ACh**, **5-HT₃**.

- ▶ **Metabotropic receptors** — G-protein-coupled, modulatory: dopaminergic, adrenergic, most serotonergic, GABA-B, muscarinic, opioid and cannabinoid receptors.
- ▶ **Example (opioid signalling, Fig. 462-2)** — μ -opioid agonists couple to **Gi/o**, **inhibit adenylyl cyclase** $\rightarrow$ $\downarrow$ cAMP $\rightarrow$ $\downarrow$ PKA, activate K^+ channels and inhibit Ca^{2+} channels, hyperpolarising the neuron; chronic exposure **upregulates the cAMP-CREB pathway**, underlying tolerance, dependence and withdrawal.
- ▶ **Second-messenger relevance** — lithium (mood stabiliser) competes with magnesium to inhibit **GSK3 β** and phosphoinositide-signalling enzymes, illustrating how transmitter-downstream cascades are themselves drug targets.

Neurotransmitters and drugs of abuse / reward circuitry

All addictive drugs converge on promoting **dopamine neurotransmission in the nucleus accumbens** (VTA target), though their initial molecular targets differ (Harrison Table 462-1):

Drug	Transmitter affected	Target (action)
Opioids	Endorphins, enkephalins	μ - and δ -opioid receptors (agonist)
Psychostimulants (cocaine, amphetamine, methamphetamine)	Dopamine	DAT (cocaine = antagonist; amphetamine/methamphetamine = reverse transport)
Nicotine	Acetylcholine	Nicotinic cholinergic receptors (agonist)
Ethanol	GABA / glutamate / 5-HT / ACh	GABA-A (positive allosteric modulator); NMDA glutamate (antagonist); 5-HT ₃ (positive allosteric modulator)
Marijuana	Endocannabinoids (anandamide, 2-AG)	CB1 receptor (agonist)
Phencyclidine, ketamine	Glutamate	NMDA receptor (antagonist)

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Chemical synapse / transmitter life cycle** — label: pre-synaptic terminal, mitochondrion, synaptic vesicles, voltage-gated Ca^{2+} channel, synaptic cleft, **transmitter molecules**, post-synaptic **ionotropic and metabotropic receptors**, **reuptake transporter** (e.g., DAT), degrading enzyme (MAO/acetylcholinesterase), post-synaptic density.
- ▶ **Monoamine source-nuclei map** (after Fig. 462-3) — label: **VTA (dopaminergic)**, **locus coeruleus (noradrenergic)**, **dorsal raphe (serotonergic)**, **nucleus accumbens**, amygdala, hippocampus, prefrontal cortex, hypothalamus; arrows for glutamatergic, GABAergic, dopaminergic and peptidergic projections.

Clinical / Diagnostic significance

- ▶ **Mood disorders** — tricyclics (imipramine) block serotonin/norepinephrine reuptake and MAO inhibitors (tranylcypromine) raise monoamines, giving rise to the **monoamine deficiency hypothesis** of depression; the delayed (weeks) clinical response shows efficacy depends on downstream **neuroplastic/BDNF-mediated adaptation**, not the acute rise in transmitter.
- ▶ **Rapid-acting antidepressants** — **ketamine**, a non-competitive NMDA **glutamate-receptor antagonist**, produces antidepressant effects within hours in treatment-resistant depression, redirecting focus to **glutamatergic transmission and synaptic plasticity**.
- ▶ **Psychedelics / MDMA** — 5-HT_{2A} partial agonism (psychedelics) and serotonin-releasing action (MDMA) are under study for depression and PTSD.
- ▶ **Parkinson disease** — degeneration of **midbrain dopaminergic neurons**; basis for dopamine-replacement therapy and experimental fetal/stem-cell-derived dopamine-neuron grafts.
- ▶ **Addiction** — convergence on the **VTA–nucleus accumbens dopamine reward pathway**; cAMP–CREB and ΔFosB adaptations drive tolerance, dependence and relapse.
- ▶ **Gut–brain axis** — gut bacteria synthesise **GABA and serotonin** and signal to the CNS via the vagus nerve, modulating anxiety- and depression-like behaviour (Ch. 435).

High-yield exam pointers

- ▶ **Glutamate** = principal excitatory; **GABA** = principal inhibitory transmitter of the CNS.
- ▶ **Tyrosine hydroxylase** = rate-limiting enzyme of catecholamine synthesis; **GAD (GAD1)** synthesises GABA from glutamate.
- ▶ Source nuclei: **dopamine** — **VTA/substantia nigra**; **norepinephrine** — **locus coeruleus**; **serotonin** — **raphe nuclei**.
- ▶ **Ionotropic** (NMDA, AMPA, GABA-A, nicotinic, 5-HT₃) = fast; **metabotropic** (GPCR: dopaminergic, adrenergic, GABA-B, opioid, muscarinic) = slow/modulatory.
- ▶ Transmitter action terminated by **reuptake (DAT, SERT, NET)** or **enzymatic degradation (MAO, COMT, acetylcholinesterase)**.
- ▶ **Ketamine** = **NMDA antagonist**, a rapid-acting antidepressant; **lithium** acts on GSK3β / phosphoinositide signalling.
- ▶ Drugs of abuse converge on **dopamine release in the nucleus accumbens** (Table 462-1).
- ▶ Opioids → Gi/o → ↓cAMP/PKA, with chronic cAMP–CREB upregulation underlying dependence.

SOURCE & COVERAGE

Harrison 22e — Ch 462 “Biology of Psychiatric Disorders” (monoamine hypothesis, signal transduction, Fig. 462-2 opioid/LC signalling, Fig. 462-3 mood–reward circuitry, Table 462-1)

drugs of abuse) and Ch 435 “Pathobiology of Neurologic Diseases” (GABA/serotonin and the gut–brain axis; dopaminergic-neuron degeneration).

Coverage note (spec gap = true): Harrison covers neurotransmitters *through disease biology*, not as a basic-physiology topic — the defining criteria, the systematic chemical classification (amino-acid / monoamine / cholinergic / peptide / endocannabinoid / gaseous-purinergic), the stepwise synaptic-transmission cycle, the ionotropic-vs-metabotropic receptor framework, and individual receptor subtype lists (D1–D5, α/β -adrenergic, 5-HT1–7, κ -opioid, glycine, histamine, muscarinic) are supplied here as **universally-accepted standard internal-medicine/neuroscience** scaffolding, not verbatim from the two provided chapters. All transmitter-source nuclei, enzymes, receptor mechanisms, drug-of-abuse targets and clinical correlations stated are grounded in Ch 462/435.



Newer Anticoagulant Drugs

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — *Newer anticoagulants* are agents developed to overcome the limitations of the classical drugs (unfractionated heparin and vitamin K antagonists such as warfarin) — namely the need for parenteral administration or routine laboratory monitoring, the slow onset/offset, the narrow therapeutic window, and numerous food/drug interactions. The term encompasses the synthetic pentasaccharide **fondaparinux**, the parenteral **direct thrombin inhibitors** (argatroban, bivalirudin, desirudin), and, most importantly for current practice, the oral **direct-acting oral anticoagulants** (DOACs) — the direct thrombin inhibitor *dabigatran* and the direct factor Xa inhibitors *rivaroxaban*, *apixaban* and *edoxaban*. DOACs target a single activated clotting factor, have rapid onset, predictable pharmacokinetics, and are given in fixed doses without routine coagulation monitoring.

Classification of newer anticoagulants

Class	Target	Drugs	Route
Synthetic pentasaccharide	Factor Xa (via antithrombin)	Fondaparinux	SC
Parenteral direct thrombin (IIa) inhibitors	Thrombin active site $\pm$ exosite 1	Argatroban, Bivalirudin, Desirudin (lepirudin withdrawn)	IV/SC
Oral direct thrombin inhibitor	Thrombin (IIa)	Dabigatran etexilate	Oral
Oral direct factor Xa inhibitors (“-xabans”)	Factor Xa	Rivaroxaban, Apixaban, Edoxaban	Oral

- ▶ The DOACs are **small molecules that bind reversibly to the active site** of their target enzyme, inhibiting *free and clot-bound* factor (unlike heparin, which acts only on circulating factors and cannot inhibit fibrin-bound thrombin).
- ▶ Mnemonic for Xa inhibitors: the “-**xa-bans**” (riv-a-ROXA-ban) all *ban factor Xa*; *dabigatran* is the lone direct thrombin inhibitor.

Direct oral anticoagulants — comparative pharmacology

Characteristic	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin (IIa)
Prodrug	No	No	No	Yes (etexilate)
Bioavailability	80%	60%	50%	6%
Usual dosing	once daily (bid)	twice daily	once daily	twice daily
Half-life	7–11 h	12 h	9–11 h	12–17 h
Renal excretion	33%	25%	35%	80%
Key interactions	CYP3A4 + P-gp	CYP3A4 + P-gp	P-gp	P-gp

- ▶ **Dabigatran** is the only prodrug (absorbed as dabigatran etexilate, converted by esterases); its very low bioavailability explains *dyspepsia* (the capsule contains tartaric acid) and the need for an intact capsule.
- ▶ **Renal clearance is the critical safety pivot**: dabigatran (80% renal) is the most dialysable and the most affected by chronic kidney disease; factor Xa inhibitors are less renally dependent. All require dose reduction or avoidance in significant renal impairment.
- ▶ Potent **dual P-gp + CYP3A4 inhibitors** (e.g., azole antifungals, ritonavir) raise drug levels; strong inducers (rifampicin, carbamazepine, phenytoin, St John’s wort) lower them — these are the main interactions to avoid.

Indications and dosing

Licensed indications (all four DOACs unless stated):

- ▶ **Non-valvular atrial fibrillation** — stroke prevention (NOT in mechanical heart valves or moderate–severe rheumatic mitral stenosis).
- ▶ **Treatment of venous thromboembolism (VTE)** — DVT and PE, and secondary prevention.
- ▶ **Thromboprophylaxis after elective hip or knee arthroplasty** — dabigatran, rivaroxaban, apixaban (edoxaban only in Japan).
- ▶ **Secondary prevention in coronary/peripheral artery disease** — low-dose rivaroxaban with aspirin (*COMPASS* regimen).

Indication	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
AF stroke prevention	20 mg OD (15 mg if CrCl 15–49)	5 mg BD (2.5 mg BD if ≥ 2 ABC)	150 mg BD (75 mg BD if CrCl 15–30)	60 mg OD (30 mg if CrCl 15–50, wt ≤ 60 kg, or potent P-gp inhibitor)
Acute VTE	15 mg BD $\times 21$ d $\rightarrow$ 20 mg OD	10 mg BD $\times 7$ d $\rightarrow$ 5 mg BD	150 mg BD <i>after</i> ≥ 5 d parenteral	60 mg OD <i>after</i> ≥ 5 d parenteral
VTE — extended (after 6 mo)	10 mg OD	2.5 mg BD	—	—
Hip/knee prophylaxis	10 mg OD	2.5 mg BD	220 mg OD	—
CAD/PAD (with aspirin)	2.5 mg BD	—	—	—

- ▶ **ABC dose-reduction criteria for apixaban in AF** = Age > 80 y, Body weight < 60 kg, serum Creatinine ≥ 1.5 mg/dL — reduce to 2.5 mg BD if *any two* are present.
- ▶ **Single-drug (“all-oral”) regimens:** only *rivaroxaban* and *apixaban* can be started without a heparin lead-in for VTE; *dabigatran* and *edoxaban* require ≥ 5 days of parenteral anticoagulant (LMWH) first.
- ▶ Rivaroxaban 15/20 mg **must be taken with food** to ensure absorption; apixaban and edoxaban are food-independent.
- ▶ Landmark non-inferiority trials vs warfarin in AF: *RE-LY* (dabigatran), *ROCKET AF* (rivaroxaban), *ARISTOTLE* (apixaban), *ENGAGE AF-TIMI 48* (edoxaban).

Parenteral newer agents

- ▶ **Fondaparinux** — synthetic analogue of the antithrombin-binding pentasaccharide (MW 1728). It binds only to antithrombin and is *too short to bridge thrombin*, so it catalyses **factor Xa inhibition only**. Given SC once daily; 100% bioavailable; plasma half-life **17 h**; cleared **unchanged renally** (contraindicated if CrCl < 30 mL/min). Dose: **2.5 mg OD** (prophylaxis/ACS), 5–10 mg OD by weight for VTE treatment. It **does not cause HIT** (no PF4 binding, no cross-reactivity) and so is useful in HIT, but **has no antidote** (protamine ineffective).
- ▶ **Parenteral direct thrombin inhibitors** — used chiefly in *heparin-induced thrombocytopenia (HIT)* and PCI:
 - *Argatroban* — univalent active-site inhibitor, **hepatically metabolised**, half-life ~ 45 min, monitored by aPTT; drug of choice in **HIT with renal failure**.
 - *Bivalirudin* — bivalent (active site + exosite 1) 20-amino-acid hirudin analogue, shortest half-life (~ 25 min), partly renally cleared; an alternative to heparin in PCI and HIT.
 - *Desirudin* — recombinant hirudin; renally cleared.

Monitoring, reversal and management of bleeding

- ▶ **Routine monitoring is not required.** When assessment is needed (adherence, overdose, pre-urgent surgery, suspected accumulation): a *normal PT* largely excludes clinically relevant levels of factor Xa inhibitors and a *normal aPTT/thrombin time* excludes dabigatran. Quantitative assays = **chromogenic anti-Xa assay** (calibrated) for the xabans; **dilute thrombin time / ecarin clot time** for dabigatran. Apixaban has minimal effect on PT, so anti-Xa assay is needed.
- ▶ **Bleeding — general measures:** hold the drug, local haemostasis, fluids/blood products; **activated charcoal** if ingested within ~2–4 h; *vitamin K is of no value*. Calculate residual effect from last dose and renal function.
- ▶ **Specific reversal agents:**
 - **Idarucizumab** — humanised monoclonal antibody *fragment* that binds dabigatran with very high affinity; **5 g IV** (two 2.5 g vials); rapidly normalises aPTT/dilute thrombin time. If unavailable, **activated PCC 50 units/kg**.
 - **Andexanet alfa** — recombinant, catalytically inactive **decoy factor Xa** that sequesters the xabans (and also heparin/LMWH). *Low dose* = 400 mg bolus + 4 mg/min infusion (≤120 min); *high dose* = 800 mg bolus + 8 mg/min. High dose if last dose was large (rivaroxaban >10 mg / apixaban >5 mg) and taken <8 h ago. If unavailable, **four-factor PCC 25–50 units/kg** (≈2000 units).
 - Fondaparinux and argatroban/bivalirudin have **no licensed antidote**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Coagulation cascade with drug targets:** draw the common pathway — *Factor X* → *Xa* → (*prothrombinase*) → *Prothrombin (II)* → *Thrombin (IIa)* → *Fibrinogen* → *Fibrin*. Label arrows blocking **Factor Xa**: Rivaroxaban, Apixaban, Edoxaban, Fondaparinux (via antithrombin) and blocking **Thrombin (IIa)**: Dabigatran, Argatroban, Bivalirudin. Show Warfarin acting upstream on synthesis of factors *II, VII, IX, X* (and *proteins C, S*). Mark Idarucizumab → dabigatran and Andexanet alfa → Xa inhibitors as reversal arrows.
- ▶ **Antithrombin-mediated inhibition schematic:** antithrombin bridging unit — heparin neutralises both *Xa* and *IIa*; LMWH mainly *Xa*; **fondaparinux only Xa** (pentasaccharide too short to bridge thrombin).

Clinical / Diagnostic significance

- ▶ **Advantages over warfarin:** fixed oral dosing, rapid onset/offset, predictable response, no routine INR monitoring, few food and fewer drug interactions, and **significantly less intracranial haemorrhage**.

- ▶ **Disadvantages/cautions:** higher-dose dabigatran, rivaroxaban and edoxaban cause **more GI bleeding**; renal clearance limits use in advanced CKD; cost; short half-life means missed doses rapidly lose protection.
- ▶ **Contraindications / avoid:** mechanical prosthetic valves and moderate–severe rheumatic mitral stenosis (warfarin superior — *RE-ALIGN* showed harm with dabigatran); **pregnancy and lactation** (cross placenta/breast milk — use LMWH); triple-positive **antiphospholipid syndrome** (DOACs inferior to warfarin); severe renal/hepatic impairment.
- ▶ **Peri-procedural:** stop DOAC 1–2 days before moderate/high-risk procedures (longer if renal impairment); unlike warfarin, **no heparin “bridging” is needed** because of rapid offset.
- ▶ **Special populations:** in cancer-associated VTE, apixaban/edoxaban/rivaroxaban are acceptable alternatives to LMWH but are **avoided in GI/genitourinary tumours** (bleeding) and where chemotherapy interactions exist.

High-yield exam pointers

- ▶ DOACs = **dabigatran (anti-IIa) + rivaroxaban / apixaban / edoxaban (anti-Xa)**; only dabigatran is a *prodrug*.
- ▶ **Dabigatran is 80% renally excreted** → most affected by CKD and the only DOAC removed by dialysis.
- ▶ **Apixaban** has the least GI bleeding and is often preferred in CKD; remember the **ABC** reduction rule (Age>80, Body wt<60, Creatinine≥1.5).
- ▶ **Dabigatran & edoxaban need a ≥5-day parenteral lead-in** for VTE; rivaroxaban & apixaban are all-oral.
- ▶ **Idarucizumab** → **dabigatran**; **Andexanet alfa** → **factor Xa inhibitors**; 4-factor PCC is the fallback for both.
- ▶ **Fondaparinux** = pure anti-Xa pentasaccharide, $t_{1/2}$ 17 h, no HIT, no antidote.
- ▶ DOACs are **contraindicated in mechanical valves, rheumatic MS, pregnancy and antiphospholipid syndrome** — these patients need warfarin.
- ▶ DOACs cause **less intracranial bleeding than warfarin** but sometimes **more GI bleeding**.
- ▶ Qualitative tests: **PT** for xabans, **aPTT/TT** for dabigatran; quantitative = **anti-Xa assay** and **dilute thrombin/ecarin clot time** respectively.

SOURCE & COVERAGE

- ▶ Harrison’s Principles of Internal Medicine, 22e — “Antiplatelet, Anticoagulant, and Fibrinolytic Drugs” (parenteral anticoagulants, fondaparinux, parenteral direct thrombin inhibitors, warfarin, and the Direct Oral Anticoagulants section incl. Table 123-9 pharmacology comparison, dosing, monitoring and reversal).

- ▶ CMDT 2026 — “Disorders of Hemostasis, Thrombosis, & Antithrombotic Therapy” (Tables 16-9/16-10: DOAC dosing, transitions; DOAC-associated major-bleeding reversal guidance with idarucizumab and low/high-dose andexanet alfa; cancer-associated VTE and APS cautions).
- ▶ Trial names (RE-LY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48, COMPASS, RE-ALIGN) are universally accepted landmark internal-medicine references; COMPASS appears in Harrison’s further reading.



Pharmacogenomics

Asked in: Paper I Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — **Pharmacogenetics** is the study of how *single* inherited genetic variants determine unusual (beneficial or adverse) responses to a drug in an individual or family; **pharmacogenomics** extends this to *multiple* variants across whole genomes and populations to explain variability in drug efficacy and toxicity. The genes involved — those governing drug metabolism, transport, targets, and immune recognition — are collectively termed **pharmacogenes**. The discipline aims to choose effective drugs and doses, avoid adverse drug reactions (ADRs) in high-risk individuals, guide drug development, and serves as a cornerstone of **precision (personalised) medicine**.

Core concepts and metabolizer phenotypes

- ▶ The commonest variant is a **single nucleotide polymorphism (SNP)**; *non-synonymous* (amino-acid-changing) SNPs are a frequent cause of altered pharmacogene function. Other variants: small insertions/deletions, splice and promoter variants, **copy-number variation** (gene deletion or duplication). SNP assays may miss large duplications, and the highly polymorphic **HLA locus** on chromosome 6 is best characterised by sequencing.
- ▶ The frequency of pharmacogene variants **varies strikingly by ancestry**, so specific ethnic groups can be at unusually high risk of aberrant drug response.
- ▶ A **multimodal (non-unimodal)** distribution of plasma drug concentration signals that one gene predominates in that drug’s metabolism, classically yielding four phenotypes (illustrated by CYP2D6):

Phenotype	Genotype	Enzyme activity	Consequence for a substrate
Poor metabolizer (PM)	2 loss-of-function alleles	Absent/very low	↑ steady-state level, longer time to steady state; toxicity (or no effect if prodrug)

Phenotype	Genotype	Enzyme activity	Consequence for a substrate
Intermediate metabolizer (IM)	1 functional / 2 reduced-function alleles	Reduced	Modestly altered handling
Normal / extensive metabolizer (EM)	1–2 functional alleles	Normal	Expected response
Ultrarapid metabolizer (UM)	Gene duplication (2–12 copies)	Very high	↓ parent-drug level (drug failure), or toxicity if active metabolite formed

- ▶ The combination of alleles on the two chromosomes (the **diplotype**) determines the phenotype. **Phenocopying** occurs when a co-prescribed inhibitor converts a genetic EM into a functional PM.

Genetic variants affecting pharmacokinetics (PK)

- ▶ Discovery uses **candidate-gene** approaches (knowing the metabolic pathway) and unbiased **genome-wide association (GWA)** studies; results require replication.

Gene / product	Drug(s)	Clinical effect of variant
CYP3A4 / CYP3A5	Tacrolimus, vincristine	CYP3A5 splice variant in Europeans/Asians → low activity; African “expressers” eliminate tacrolimus faster (↓ efficacy), lower vincristine-neuropathy risk
CYP2D6	Codeine, metoprolol/carvedilol, propafenone, nortriptyline, tamoxifen	PM 5–10% of Europeans/Africans (few Asians); codeine→morphine fails in PMs and is dangerous in UMs
CYP2C19	Clopidogrel, omeprazole	PM ~20% Asians, 2–3% others, >50% Oceania; LOF → clopidogrel failure (stent thrombosis/stroke); **2C1917** UM → ↑ bleeding
CYP2C9 (+ VKORC1)	Warfarin, phenytoin, glipizide, losartan	↑ phenytoin neurotoxicity, glipizide hypoglycaemia; ↓ warfarin dose; losartan (prodrug) fails
DPYD (dihydropyrimidine dehydrogenase)	5-fluorouracil, capecitabine, tegafur	LOF (2A, 13, rs67376798) → severe/fatal toxicity; dose-reduce IMs
TPMT	Azathioprine, 6-mercaptopurine	Inactive homozygote (~1/300) → fatal pancytopenia (2, 3A, 3B, 3C)

Gene / product	Drug(s)	Clinical effect of variant
NUDT15	Thiopurines	LOF → excess myelosuppression (esp. East Asians)
NAT2	Isoniazid, procainamide, hydralazine	“Slow acetylators” (~50% Europeans/Africans) → INH hepatitis, drug-induced lupus
UGT1A1	Irinotecan, atazanavir	Gilbert’s promoter variant → irinotecan diarrhoea/marrow suppression, unconjugated hyperbilirubinaemia
SLCO1B1 (OATP1B1)	Simvastatin	Noncoding SNP → ↑ myopathy (accounts for ~60% of risk)
MDR1 (P-glycoprotein) / MATE1, MATE2	Digoxin / metformin	Altered efflux (digoxin toxicity) / uptake (metformin glucose-lowering)

- ▶ For **warfarin**, polymorphisms in **CYP2C9** (PK) plus the **VKORC1** promoter (PD target) account for up to ~50% of dose variability, with a smaller contribution from **CYP4F2** (vitamin K metabolism).

Genetic variants affecting pharmacodynamics (PD) and disease-pathway interactions

- ▶ **VKORC1 promoter** (–1639G>A) variant (common in Asians) lowers transcription and warfarin dose requirement (~30% of variability alone).
- ▶ **β₂- and β₁-adrenergic receptor** polymorphisms modulate response to β-agonists in asthma and β-blocker heart-rate/BP lowering in heart failure/hypertension.
- ▶ **Drug–disease gene interactions**: CYP inducers precipitate attacks in the **porphyrias**; **G6PD** deficiency (African, Mediterranean, South-Asian descent) → haemolysis with **primaquine** and **rasburicase**; **RYR1** (ryanodine receptor) variants → **malignant hyperthermia** with volatile anaesthetics/succinylcholine; subclinical **congenital long-QT** unmasked by QT-prolonging drugs (torsades); **ACKR1** variant → benign ethnic neutropenia.

Immunogenetics — HLA and severe cutaneous/hepatic ADRs

HLA risk alleles are **necessary but not sufficient** (a third, unidentified factor is needed); frequencies vary by ancestry, underpinning population-specific screening.

HLA allele	Drug	Reaction
* <i>HLA-B57:01</i> **	Abacavir	Hypersensitivity (55% of carriers react); also flucloxacillin hepatotoxicity

HLA allele	Drug	Reaction
*HLA-B15:02**	Carbamazepine	SJS/TEN (Han Chinese, SE Asians)
*HLA-A31:01**	Carbamazepine	SJS/TEN, DRESS (Europeans)
*HLA-B58:01**	Allopurinol	SJS/TEN (Korean, Han Chinese, Japanese, Thai)

- ▶ These manifest as Stevens-Johnson syndrome / toxic epidermal necrolysis (SJS/TEN), DRESS, and drug-induced liver injury.

Pharmacogenomics of tumour and pathogen genomes (somatic / targeted therapy)

- ▶ Tumour genotyping selects targeted agents and spares non-responders: **Trastuzumab** for **HER2 (Herceptin-receptor)**-positive breast cancer (and potentiates anthracycline cardiotoxicity); **Imatinib** targets **BCR-ABL1** (Philadelphia chromosome, CML) and **c-KIT** (GIST); **Vemurafenib** inhibits **BRAF V600E** ($\approx 40\%$ of melanomas, not wild-type BRAF); **Crizotinib** for **ALK-rearranged NSCLC**. Rapid emergence of resistance often necessitates combinations (e.g., BRAF + MEK inhibitors).

Pharmacogenomics in drug development

- ▶ Human genetics validates and de-risks targets: rare **gain-of-function PCSK9** variants cause familial hypercholesterolaemia, while **loss-of-function PCSK9** SNPs (2.5% of African-Americans) lower LDL and coronary risk without harm — directly spawning **PCSK9 monoclonal antibodies**. Other genetics-driven targets: **HSD17B13** (chronic liver disease), **ANGPTL3** (hyperlipidaemia). Large biobanks (**UK Biobank**, **All of Us**) and **polygenic risk scores** extend this approach to drug “repurposing”.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Population distribution of CYP2D6 activity (Fig 72-1A)**: x-axis “Enzymatic activity (lesser $\rightarrow$ greater)”, y-axis “Population frequency”; three labelled humps — **Poor metabolizers (PM, 2 mutant alleles)**, **Extensive metabolizers (EM, 1–2 wild-type alleles)**, **Ultrarapid metabolizers (UM, gene duplication >2 copies)**; mark the antimode separating PMs from EMs.
- ▶ **Gene-dose effect on drug concentration (Fig 72-1B)**: plot Concentration vs Time for a single dose then chronic therapy; curves labelled **PM (highest AUC, longest $t_{1/2}$)**, **EM**, **UM (lowest AUC, fastest clearance)** — show higher and later steady state in PMs.

Clinical / Diagnostic significance

- ▶ **Implementation models:** *Point-of-care* (variant assay ordered at prescription, result in 1–2 h) vs *preemptive* genotyping (panel tested in advance, stored in the EHR with real-time clinical decision support [CDS]).
- ▶ **Guidelines:** the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group publish drug–gene dosing recommendations; the FDA embeds pharmacogenetic data in package inserts (e.g., codeine black-box warning forbidding use in children <12 y).
- ▶ **Evidence base:** an RCT showed **HLA-B57:01* testing eliminates abacavir SJS/TEN — the strongest case for mandatory testing. HLA-B15:02 screening was mandated before carbamazepine in parts of SE Asia (though some prescribers simply switched to phenytoin, also an SJS/TEN risk). Warfarin pharmacogenetic dosing trials showed no/modest benefit. A 2023 European trial (Sven et al., 6944 patients, 7 countries) of a 12-gene/50-variant preemptive panel reduced clinically relevant ADRs (across 42 drugs) by 30%***, supporting preemptive screening.
- ▶ **Decision to test** depends on the magnitude/clinical importance of the genetic effect, strength of evidence (anecdote → post-hoc → RCT), availability of alternative therapy or therapeutic drug monitoring, and cost-benefit.

High-yield exam pointers

- ▶ Define and distinguish pharmacogenetics (single variant/individual) from pharmacogenomics (genome-wide/population).
- ▶ Memorise the PM/IM/EM/UM scheme with CYP2D6 and the codeine story (PM = no analgesia; UM = fatal respiratory depression, FDA ban <12 y after tonsillectomy).
- ▶ TPMT/NUDT15 → thiopurine myelosuppression; DPYD → 5-FU/capecitabine toxicity; UGT1A1 → irinotecan; CYP2C19 → clopidogrel failure; SLCO1B1 → simvastatin myopathy.
- ▶ Warfarin = CYP2C9 + VKORC1 (up to 50% of dose variability).
- ▶ **HLA-B57:01–abacavir, HLA-B15:02–carbamazepine, HLA-B58:01–allopurinol*** (necessary-but-not-sufficient).
- ▶ G6PD–primaquine/rasburicase haemolysis; RYR1–malignant hyperthermia; NAT2 slow acetylators–INH hepatitis/drug-induced lupus.
- ▶ Oncology targets: HER2–trastuzumab, BCR–ABL1/c-KIT–imatinib, BRAF V600E–vemurafenib, ALK–crizotinib.
- ▶ Implementation: CPIC guidelines, FDA labels, preemptive EHR + CDS; Sven 2023 panel cut ADRs by 30%.
- ▶ PCSK9 loss-of-function → PCSK9 inhibitors: genetics validating drug targets.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Pharmacogenomics” (Dan Roden) and “Principles of Clinical Pharmacology” (PK/PD variability framework: metabolizer phenotypes, steady state, loading doses).
- ▶ **CMDT 2026** — Appendix “Therapeutic Drug Monitoring, Pharmacogenetic Tests...” (TPMT 2/3A/3B/3C, DPYD 2A/13/rs67376798, CYP2C1917, *VKORC1* -1639G>A, *HLA-B57:01* abacavir, *HLA-B15:02* carbamazepine, *HLA-B58:01* allopurinol screening).
- ▶ *HLA-B58:01-allopurinol* and *HLA-A31:01*-carbamazepine associations cross-checked in CMDT 2026 and *Bologna, Dermatology* (severe cutaneous adverse reactions).
- ▶ Coverage note: The corpus covers this topic richly via a dedicated Harrison chapter; the online Harrison tables (e72-1/e72-2) listing exhaustive allele frequencies are referenced but not reproduced in the text — allele-level detail above is drawn from the CMDT pharmacogenetic appendix.



Plasma enzymes in clinical medicine

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Plasma (serum) enzymes are protein catalysts measurable in circulating blood. A small group are *functional* enzymes that act within plasma (e.g., coagulation factors), but most have no physiological role in serum and, in Harrison's words, “have no known function in the serum and behave like other serum proteins.” Because individual enzymes are concentrated in specific tissues, the **pattern, magnitude and isoenzyme composition** of an enzyme elevation localise the organ injured, gauge its severity, and track response to treatment — the basis of “enzyme diagnosis.” No single enzyme measures total organ function, so enzymes are interpreted together as a *battery*.

Classification of plasma enzymes

Category	Behaviour in disease	Representative enzymes
Functional (plasma-specific)	Synthesised mainly by hepatocytes, act <i>in</i> plasma; levels fall when synthesis fails	Coagulation factors (II, VII, IX, X), pseudocholinesterase, lipoprotein lipase, ceruloplasmin, renin
Non-functional — secretory	Normally secreted by exocrine glands; spill into blood when gland/duct injured	Amylase, lipase (pancreas), prostatic acid phosphatase
Non-functional — cellular (cytosolic / organelle)	Leak from damaged cells; levels rise with tissue injury	AST, ALT, LDH, CK, GGT, 5'-nucleotidase, aldolase

- ▶ Harrison frames hepatic enzymes pragmatically into those whose serum rise reflects (1) **damage to hepatocytes** and (2) **cholestasis** — a clinically useful subdivision of the “cellular” group.

Mechanisms of altered plasma enzyme activity

- ▶ **Increased entry from damaged cells** — the dominant mechanism. Enzymes are “released into the blood in greater amounts when there is damage to the liver cell membrane, resulting in increased permeability.” *Cell necrosis is not required* — increased membrane permeability suffices, and there is a **poor correlation** between enzyme level and degree of damage. Hence the absolute aminotransferase value has **no prognostic significance** in acute hepatocellular injury.
- ▶ **Increased synthesis / enzyme induction** — alkaline phosphatase synthesis is induced in cholestasis and rapid bone turnover; GGT is induced by alcohol and enzyme-inducing drugs.
- ▶ **Decreased clearance** — serum enzymes are probably cleared by the reticuloendothelial system; each has a characteristic **half-life (measured in days)** that determines how long it stays elevated.
- ▶ **Reduced production** — *functional* enzymes (clotting factors) fall when hepatic synthetic capacity fails.

Hepatic plasma enzymes (grounded in Harrison Ch 348)

Hepatocellular (“leakage”) enzymes — the aminotransferases

- ▶ **AST** is present (decreasing order of concentration) in liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes and erythrocytes — so it is **non-specific**. **ALT** is found primarily in liver and is therefore the **more liver-specific** indicator.
- ▶ Normal range $\approx 10\text{--}40$ IU/L. Levels up to **300 IU/L** are non-specific and seen in any liver disorder (commonest cause of minimal elevation = fatty liver disease).
- ▶ **Striking elevation >1000 IU/L** occurs almost exclusively with extensive hepatocellular injury: (1) **viral hepatitis**, (2) **ischemic liver injury** (prolonged hypotension / acute heart failure), (3) **toxin- or drug-induced injury**. A gallstone passing into the common bile duct can transiently push them to **1000–2000 IU/L**, after which they fall quickly into a cholestatic pattern.
- ▶ **AST:ALT ratio** — $\text{ALT} \geq \text{AST}$ in most acute hepatocellular disease; ratio <1 in chronic viral hepatitis and NAFLD, rising >1 as cirrhosis develops. A ratio **$>2:1$ is suggestive** and **$>3:1$ highly suggestive** of alcohol-related liver disease (AST rarely >300 IU/L, ALT often normal because of alcohol-induced **pyridoxal-phosphate [vitamin B6] deficiency**).

Cholestatic enzymes — alkaline phosphatase, 5'-nucleotidase, GGT

- ▶ ALP and 5'-nucleotidase lie *in or near the bile canalicular membrane*; GGT is in the endoplasmic reticulum and bile-duct epithelium — its more diffuse location makes it **less specific** for cholestasis.
- ▶ **ALP isoenzymes** arise from liver, bone, placenta and (less often) small intestine. Physiological rises: age >60 ($1\text{--}1.5\times$), blood groups **O and B** after a fatty meal (intestinal ALP), childhood/adolescent bone growth, and late pregnancy (placental ALP).
- ▶ A **$<3\text{-fold}$** rise is non-specific (almost any liver disease); **$>4\text{-fold}$** points to cholestasis, infiltrative disease (cancer, amyloidosis) or high-turnover bone disease (**Paget's**).

- To confirm a raised ALP is hepatic: **fractionate by electrophoresis**, or measure **GGT / 5'-nucleotidase** (both rise with hepatic ALP but are normal in bone disease). GGT is also a marker of occult alcohol use.

Feature	Hepatocellular pattern	Cholestatic pattern
Dominant enzymes	AST, ALT	ALP, GGT, 5'-NT
Typical magnitude	AST/ALT often very high (may be >1000)	ALP >4× normal
Classic causes	Viral / ischemic / toxic hepatitis	Biliary obstruction, PBC, infiltration, drugs
Confirmatory step	AST:ALT ratio; viral & autoimmune serology	GGT/5'-NT to confirm hepatic ALP; ultrasound for ducts

Extra-hepatic organ-specific enzymes (standard internal medicine)

Organ / system	Enzyme(s)	Principal clinical use
Heart	CK-MB, AST, LDH (LDH-1)	Myocardial infarction — but troponin (a regulatory protein, <i>not</i> an enzyme) is now the preferred marker
Skeletal muscle	Total CK (CK-MM), aldolase	Rhabdomyolysis, inflammatory myopathy, very high CK in Duchenne dystrophy
Pancreas	Amylase, lipase	Acute pancreatitis ($\geq 3\times$ ULN); lipase more specific and longer-lasting
Bone	ALP (bone isoenzyme)	Paget's disease, osteomalacia, rickets, bone metastases
Prostate	Acid phosphatase	Carcinoma prostate (historical; replaced by PSA)
Blood / marrow	LDH	Intravascular hemolysis, megaloblastic anaemia, tumour lysis, lymphoma
Lung / granuloma	Angiotensin-converting enzyme (ACE)	Sarcoidosis disease activity
Serous cavities	Adenosine deaminase (ADA)	Tuberculous pleural / pericardial / peritoneal effusion, TB meningitis
Toxicology	Pseudocholinesterase, RBC acetylcholinesterase	Fall in organophosphate poisoning; deficiency $\rightarrow$ scoline (suxamethonium) apnoea

Organ / system	Enzyme(s)	Principal clinical use
RBC	Glucose-6-phosphate dehydrogenase	Deficiency → drug/infection-triggered hemolysis

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hepatocyte enzyme-leak schematic** — draw a hepatocyte abutting a sinusoid and a bile canaliculus. Label: *cytosol* → AST / ALT (leakage enzymes); *bile canaliculus membrane* → ALP and 5'-nucleotidase; *endoplasmic reticulum & bile-duct epithelium* → GGT; add an arrow “cell-membrane damage → ↑ permeability → enzyme leak into sinusoid → ↑ serum level.”
- ▶ **Serum cardiac-enzyme time-activity curve after acute MI** — x-axis “Days after onset of chest pain,” y-axis “Serum activity (× upper normal),” plotting CK-MB (peak ~24 h), AST (peak ~48 h) and LDH (peak 3–6 days), with **Troponin** overlaid and labelled “not an enzyme.” (*standard medicine*)

Clinical / Diagnostic significance

- ▶ **Use as a battery** — aminotransferases + ALP + bilirubin + albumin + prothrombin time. Multiple or persistently abnormal tests make liver disease likely; all-normal results make occult disease unlikely.
- ▶ **Pattern recognition** directs the work-up: hepatocellular (AST/ALT dominant) vs cholestatic (ALP/GGT dominant) steers imaging and the chronically-abnormal-liver-tests algorithm (Fig. 348-1).
- ▶ **Isoenzymes / second enzymes localise the source** — GGT or 5'-NT confirm that a raised ALP is hepatic; CK-MB confirms myocardial origin of a raised total CK.
- ▶ **Synthetic-function tests gauge severity** — albumin (synthesised exclusively by hepatocytes, half-life 18–20 days, ~4%/day turnover) reflects *chronic* disease, whereas the PT/INR reflects clotting factors with short half-lives (6 h for factor VII to 5 days for fibrinogen) and is the single best *acute* index of hepatic synthesis. PT prolonged >5 s above control and uncorrected by parenteral vitamin K is a poor prognostic sign; INR + bilirubin feed the MELD score.
- ▶ **Caveats** — enzymes lack sensitivity and specificity: they can be normal in serious liver disease and abnormal in disease that does not affect the liver, and their magnitude does not equal prognosis in acute hepatocellular injury.

High-yield exam pointers

- ▶ **Functional enzymes** (clotting factors, pseudocholinesterase) **fall** in disease; **cellular leakage enzymes** (AST, ALT, CK, LDH) **rise**.
- ▶ **ALT is more liver-specific than AST**; aminotransferases >1000 IU/L = viral, ischemic or toxic hepatitis.

- ▶ **AST:ALT >2:1** → alcoholic; <1 → viral/NAFLD; flips to >1 as cirrhosis develops.
- ▶ **ALP >4× normal** = cholestasis / infiltration / Paget's; confirm hepatic origin with **GGT** or **5'-nucleotidase**.
- ▶ **Factor VIII** is the only clotting factor *not* made solely by hepatocytes (vascular endothelium) — so it stays normal in liver failure.
- ▶ **Vitamin-K-dependent factors** = II, VII, IX, X; the PT measures factors II, V, VII, X.
- ▶ **Lipase > amylase** for specificity in acute pancreatitis; **troponin > CK-MB** for MI (troponin is *not* an enzyme).
- ▶ **Pseudocholinesterase** ↓ in organophosphate poisoning and underlies scoline apnoea; **ADA** ↑ in tuberculous effusions; **ACE** ↑ in sarcoidosis; **LDH** ↑ in hemolysis and tumour lysis.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 348 "Evaluation of Liver Function" (hepatocellular leakage vs cholestatic enzymes; AST/ALT tissue distribution, normal ranges, >1000 IU/L causes and AST:ALT ratio; ALP isoenzymes, GGT and 5'-nucleotidase; albumin and coagulation-factor synthetic function). **Coverage note:** Harrison 22e has no dedicated "plasma enzymes" chapter. Ch 348 fully grounds the hepatic and synthetic-function enzymes and *all numerical values, ratios and tissue distributions* stated above. The general functional-vs-non-functional classification and the extra-hepatic enzymes (CK/CK-MB, LDH isoenzymes, amylase/lipase, aldolase, acid phosphatase/PSA, ACE, pseudocholinesterase, ADA, G6PD) and the cardiac-enzyme time-activity curve are *universally accepted standard internal-medicine/biochemistry* that Harrison covers within the respective disease chapters (acute MI, acute pancreatitis, the myopathies) — not the supplied chapter — and are flagged as such.



Polymerase chain reaction technique and application

Asked in: Paper I May 2022 — RGUHS MD General Medicine

Definition / Introduction — The **polymerase chain reaction (PCR)** is a type of **nucleic acid amplification test (NAAT)** that uses specific **oligonucleotide primers** and a **DNA polymerase** to amplify a defined target region of DNA *in vitro*, generating millions of copies from a minute starting template. Because each cycle theoretically doubles the target, amplification is **exponential**, conferring extraordinary analytical sensitivity. PCR underpins modern molecular diagnostics in internal medicine — from genetic mutation analysis to pathogen detection and antimicrobial-resistance genotyping — and permits testing on vanishingly small amounts of DNA (leukocytes, buccal cells, single cells, or even a hair root).

Reaction components (“ingredients”)

Component	Role
Template DNA	The double-stranded DNA containing the target sequence to be amplified
Primer pair (forward + reverse)	Short specific oligonucleotides flanking the target; define the region amplified and provide the free 3'-OH for polymerase extension
Thermostable DNA polymerase (<i>Taq</i> , from <i>Thermus aquaticus</i>)	Heat-stable enzyme that synthesizes the new strand and survives repeated denaturation temperatures
dNTPs (dATP, dGTP, dCTP, dTTP)	Building blocks incorporated into the nascent strand
Mg ²⁺ + buffer	Cofactor essential for polymerase activity; buffer maintains optimal pH/ionic conditions
Thermal cycler	Programmable instrument that rapidly raises and lowers temperature through each cycle

- ▶ **Primer specificity is critical:** highly sensitive amplification methods require a high degree of sequence identity between primer pairs and their short target; even a **single base-pair mismatch** — particularly near the 3' end of the primer — may interfere with detection (Harrison Ch 126). This is the basis of “diagnostic escape” when a pathogen acquires a deletion/mutation at the primer site.

Steps of one PCR cycle (thermal cycling)

- ▶ **1. Denaturation (~94–95 °C):** heat separates the double-stranded template into two single strands by breaking hydrogen bonds.
- ▶ **2. Annealing (~50–65 °C):** temperature is lowered so the forward and reverse primers hybridize to their complementary single-stranded targets.
- ▶ **3. Extension / elongation (~72 °C):** *Taq* polymerase adds dNTPs to the 3' end of each primer, synthesizing a new complementary strand in the 5'→3' direction.
- ▶ These three steps constitute **one cycle**; the cycle is repeated typically **25–40 times**, and because product of one cycle is template for the next, copy number rises **exponentially** ($\approx 2^n$), yielding millions–billions of copies.
- ▶ The amplified product (“**amplicon**”) is then detected — classically by **agarose gel electrophoresis**, or read in real time (see below). **DNA sequencing can be performed directly on PCR products** (Harrison Ch 479).

Major variants / modifications of PCR

Variant	Key principle	Representative use
Reverse-transcriptase PCR (RT-PCR)	RNA first converted to cDNA by reverse transcriptase, then amplified	Detection of RNA viruses — SARS-CoV-2 (core acute-phase assay), HIV, HCV, influenza, RSV (Harrison Ch 126)
Real-time / quantitative PCR (qPCR)	Amplicon accumulation measured cycle-by-cycle via fluorescence, allowing quantification of starting copies	Viral load quantification (HIV PCR can detect as few as 20 copies/mL of blood) and treatment monitoring
Multiplex PCR	Several primer sets in one reaction detect multiple targets simultaneously	Syndromic panels — e.g., respiratory viral panel (influenza, parainfluenza, RSV, adenovirus, rhinovirus, enterovirus, metapneumovirus, coronaviruses)
Nested PCR	Two sequential amplifications with inner primers boost specificity/sensitivity	Detection of low-copy targets (<i>standard molecular biology</i> — see <i>Coverage note</i>)
Isothermal amplification	Amplifies at a single constant temperature, avoiding thermal-cycling hardware	Point-of-care / field testing in resource-limited settings; pairs with CRISPR Cas12a/Cas13a nucleic-acid sensors (Harrison Ch 126)
Digital / droplet PCR	Partitioning enables absolute quantification	Low-abundance targets, minimal residual disease (<i>standard</i> — see <i>Coverage note</i>)

- ▶ A related NAAT chemistry, the **ligase chain reaction**, is also used to amplify/detect nucleic acids (Harrison Ch 126).

Applications in internal medicine

- ▶ Infectious disease — pathogen detection (Harrison Ch 126):
 - **Viral diagnosis and monitoring:** HIV, HBV, HCV, SARS-CoV-2, influenza, RSV — for initial diagnosis, response to therapy, and (in some cases) genotypic prediction of drug resistance. RT-PCR for SARS-CoV-2 was the largest molecular-diagnostic deployment to date.
 - **Tuberculosis:** amplification of the **rpoB** gene for species-specific identification of *M. tuberculosis*.
 - **Fastidious/unculturable bacteria:** *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, *Clostridioides difficile*.
 - **16S ribosomal RNA gene PCR:** broad-range amplification/sequencing of the conserved 16S rRNA gene to identify bacteria in culture-negative infections.

- **Toxin-gene detection:** *C. difficile* toxins A and B, Shiga toxin — distinguishes pathogens from colonizers.
- **Antimicrobial-resistance genotyping (Harrison Ch 126):**

Target gene(s)	Resistance detected
<i>mecA</i>	Methicillin resistance in <i>S. aureus</i> (MRSA)
<i>vanA</i> / <i>vanB</i>	Vancomycin resistance in enterococci (VRE)
<i>rpoB</i> polymorphisms	Rifampin resistance in <i>M. tuberculosis</i> ($\approx 95\%$ of rifampin resistance); probes for <i>inhA</i> and <i>katG</i> detect up to 85% of isoniazid resistance
KPC, NDM, OXA-48, IMP, VIM	Carbapenemase production in Enterobacteriaceae

- **Human genetics (Harrison Ch 479):**
 - **Mutational analysis** of discrete sequence alterations from small DNA amounts (leukocytes, single cells, buccal cells, hair roots).
 - **Direct sequencing of PCR products** to characterize specific mutations and predict disease spectrum.
 - **Genotyping of short tandem repeats (STRs / polymorphic microsatellite markers)** — di-, tri-, tetranucleotide repeats characterized readily by PCR — for **linkage and association studies**.
 - **Preimplantation/prenatal genetic diagnosis:** with IVF, PCR-based diagnosis on a **single cell** from the four- to eight-cell embryo or the first polar body.
- **Oncology (Harrison Ch 479):** somatic (tumor-biopsy) versus germline (peripheral-cell) mutational analysis to guide therapy integrating genetic/genomic information.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — “One PCR cycle”:** a double-stranded template, with three labelled arrows/boxes: (1) Denaturation 94–95 °C → single strands; (2) Annealing 50–65 °C → forward & reverse primers bind; (3) Extension 72 °C → Taq polymerase + dNTPs synthesize new strands. Add a side note “repeat $\times 25\text{--}40$ cycles → exponential 2^n amplification.” Label: *template DNA, forward primer, reverse primer, Taq polymerase, dNTPs, new strand, amplicon*.
- **Diagram 2 — “Exponential amplification curve”:** copy number (y-axis, log scale) versus cycle number (x-axis), showing geometric doubling. Labels: $1 \rightarrow 2 \rightarrow 4 \rightarrow 8 \dots$ copies, *exponential phase, plateau*.

Clinical / Diagnostic significance

- ▶ **Sensitivity:** detects minute pathogen loads (e.g., HIV down to ~20 copies/mL), enabling earlier diagnosis and treatment than antigen detection or serology — the progression from antigen detection to PCR transformed understanding of HIV natural history.
- ▶ **Speed and real-time management:** NAATs supply etiologic diagnosis far faster than culture/serology, informing triage, antibiotic stewardship, and infection control (pivotal in the COVID-19 response).
- ▶ **Resistance prediction:** genotypic detection (e.g., *rpoB* for MDR-TB, carbapenemase genes) guides directed therapy when phenotypic susceptibility is slow or impossible.
- ▶ **Limitations / pitfalls:** technical complexity and reagent/instrument needs; risk of **false negatives** from primer-site mutation/deletion (“diagnostic escape”); risk of **false positives** from contamination — necessitating careful sample processing and standardized pipelines; targets only **known, prespecified** sequences (unlike unbiased metagenomic sequencing).
- ▶ **Emerging deployability:** isothermal amplification, lyophilized reagents (no cold chain), and CRISPR-Cas12a/Cas13a readouts are extending NAATs to point-of-care and field settings.

High-yield exam pointers

- ▶ PCR = a NAAT: amplifies a specific DNA region using **specific oligonucleotide primers + DNA polymerase** (Harrison’s exact definition).
- ▶ **Three steps per cycle:** denaturation → annealing → extension; **25–40 cycles** → **exponential 2ⁿ amplification**.
- ▶ **Taq polymerase** (thermostable, from *Thermus aquaticus*) is the workhorse enzyme; **thermal cycler** drives the temperature changes.
- ▶ RT-PCR converts RNA→cDNA — used for **SARS-CoV-2, HIV, HCV**; **qPCR/real-time PCR** quantifies viral load.
- ▶ **Multiplex PCR = syndromic panels** (respiratory, GI, meningoencephalitis).
- ▶ Resistance genes to remember: **mecA** (MRSA), **vanA/vanB** (VRE), **rpoB** (rifampin/MDR-TB, ~95%), **inhA/katG** (isoniazid, up to 85%), carbapenemases **KPC/NDM/OXA-48/IMP/VIM**.
- ▶ **16S rRNA gene PCR** identifies culture-negative bacteria; **STR/microsatellite PCR** is used in genetic linkage studies.
- ▶ A **single base-pair primer mismatch near the 3’ end** can abolish detection — basis of “diagnostic escape.”
- ▶ PCR enables testing from a **single cell** (preimplantation diagnosis) and **direct sequencing of PCR products**.

SOURCE & COVERAGE

Harrison 22e — Ch 126 “Microbial Genomics and Infectious Disease” (PCR/NAAT definition, RT-PCR, multiplex syndromic panels, 16S rRNA, resistance-gene targets and numbers, primer-

mismatch specificity, isothermal/CRISPR methods); Ch 479 “Principles of Human Genetics” (PCR for mutational analysis from small DNA amounts, direct sequencing of PCR products, STR genotyping, single-cell preimplantation diagnosis). **Coverage note (spec gap = true):** Harrison covers PCR only thinly within these chapters — it gives the formal definition and applications but does **not** spell out the stepwise thermal-cycling temperatures, the *Taq/Thermus aquaticus* enzyme detail, the dNTP/Mg²⁺ reaction mix, the 2ⁿ kinetics, or Kary Mullis’s invention (1983; Nobel Prize 1993). These, together with **nested PCR** and **digital/droplet PCR**, are included here as universally-accepted standard molecular biology to satisfy the “technique” portion of the ask and are flagged as outside the verbatim Harrison text. All organism names, gene targets, percentage figures (95% rpoB, 85% inhA/katG), the 20-copies/mL HIV figure, and the primer 3'-mismatch point are taken directly from Harrison Ch 126.



Pregnancy-Induced Hypertension (Hypertensive Disorders of Pregnancy)

Asked in: Paper II Sep 2025 — RGUHS MD General Medicine

Definition / Introduction — Pregnancy-induced hypertension (PIH) is the development of a blood pressure (BP) ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic, recorded on two occasions ≥ 4 h apart, *after 20 weeks’ gestation* in a previously normotensive woman. It is the clinical anchor of the broader **hypertensive disorders of pregnancy (HDP)** — a spectrum spanning **gestational hypertension, preeclampsia, eclampsia and the HELLP syndrome** — and is a leading cause of maternal and perinatal morbidity and mortality worldwide. The CDC estimated that 16% of US deliveries in 2019 were complicated by an HDP, and the prevalence is rising. The only definitive cure is **delivery of the fetus and placenta**.

Classification of hypertensive disorders of pregnancy

- ▶ **Gestational hypertension** — new-onset BP $\geq 140/90$ after 20 weeks, *without* proteinuria or other end-organ features; BP normalises postpartum. With severe features it is reclassified as preeclampsia.
- ▶ **Preeclampsia** — new-onset hypertension ($\geq 140/90$) *plus* proteinuria, or end-organ dysfunction, after 20 weeks (may occur up to 6 weeks postpartum).
- ▶ **Eclampsia** — new-onset generalised tonic-clonic seizures in a woman with preeclampsia.
- ▶ **Chronic hypertension** — hypertension predating pregnancy or evident before 20 weeks.
- ▶ **Chronic hypertension with superimposed preeclampsia** — new proteinuria/end-organ features arising on a background of chronic hypertension.

Disorder	Onset	Proteinuria / end-organ features
Chronic hypertension	Pre-pregnancy or <20 weeks	Variable
Gestational hypertension	>20 weeks	Absent
Preeclampsia	>20 weeks (up to 6 wks postpartum)	Present (proteinuria <i>or</i> end-organ damage)
Eclampsia	Preeclampsia + seizures	Present

Diagnostic criteria (preeclampsia)

- ▶ **Hypertension:** BP $\geq 140/90$ mmHg on two occasions ≥ 4 h apart after 20 weeks.
- ▶ **Proteinuria:** ≥ 300 mg/24 h, or urine protein/creatinine ratio ≥ 0.3 . *Edema is no longer a diagnostic criterion.*
- ▶ **Preeclampsia without proteinuria** may still be diagnosed when hypertension is accompanied by end-organ involvement (thrombocytopenia, renal/hepatic impairment, pulmonary edema, or cerebral/visual symptoms).
- ▶ **Severe features** (any one qualifies as “preeclampsia with severe features”):
 - Severe hypertension: BP $\geq 160/110$ mmHg.
 - CNS: new headache unresponsive to medication, visual disturbance (scotomas, blurring), clonus, hyperreflexia.
 - Unrelenting severe **epigastric / right-upper-quadrant pain** (hepatic capsule stretch).
 - **Pulmonary edema.**
 - **Thrombocytopenia** platelets $<100 \times 10^9/L$.
 - **Renal insufficiency** creatinine >1.1 mg/dL.
 - **Hepatic impairment** transaminases $\geq 2\times$ normal.
- ▶ **HELLP syndrome** — *Hemolysis, Elevated Liver enzymes, Low Platelets* — a severe subtype of preeclampsia and a major cause of maternal morbidity/mortality; additional complications include coagulopathy/DIC, cerebrovascular accident, hepatic capsular rupture and placental abruption.

Pathophysiology

- ▶ Precise cause unknown; central mechanism is **abnormal placentation** with failed remodelling of spiral arteries $\rightarrow$ **chronic uteroplacental ischaemia**.
- ▶ **Angiogenic imbalance:** excess of the anti-angiogenic factor **soluble fms-like tyrosine kinase-1 (sFlt-1)** and reduced **placental growth factor (PlGF)**. A circulating sFlt-1/PlGF ratio ≥ 40 predicts development of preeclampsia with severe features within the next 2 weeks.

- ▶ **Exaggerated maternal systemic inflammatory response** and generalised endothelial dysfunction → vasoconstriction, raised peripheral resistance, capillary leak and a procoagulant state.
- ▶ **Impaired cerebral autoregulation** explains neurological features and the risk of stroke / seizures even at modestly elevated BP; headache may reflect **posterior reversible encephalopathy syndrome (PRES)** within the reversible cerebral vasoconstriction syndrome spectrum.
- ▶ New-onset hypertension of pregnancy arises from reduced placental perfusion and elevated peripheral resistance, which typically resolves after delivery.

Risk factors

- ▶ Nulliparity (primigravida), previous preeclampsia, multifetal gestation.
- ▶ Chronic hypertension, chronic kidney disease, pregestational and gestational diabetes.
- ▶ SLE, antiphospholipid antibody syndrome, thrombophilia.
- ▶ Maternal age ≥ 35 years, pre-pregnancy BMI >30 (obesity), obstructive sleep apnoea.
- ▶ Assisted reproductive technology / in-vitro fertilisation; low socioeconomic status; family history.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Angiogenic-imbalance pathway of preeclampsia (flow diagram)**. Labels: *Abnormal placentation* → *failed spiral-artery remodelling* → *uteroplacental ischaemia* → $\uparrow$ sFlt-1 and $\downarrow$ PlGF (sFlt-1/PlGF ratio ≥ 40) → *maternal endothelial dysfunction* → *vasoconstriction + capillary leak + procoagulant state* → *Hypertension, Proteinuria, end-organ injury (CNS/PRES, Liver/HELLP, Kidney, Haematological)*.
- ▶ **Target-organ involvement of preeclampsia-eclampsia (labelled body map)**. Labels: *Brain (seizures/eclampsia, PRES, stroke)*, *Eye (retinal haemorrhage, scotomas)*, *Lungs (pulmonary edema)*, *Liver (epigastric pain, HELLP, capsular rupture)*, *Kidney (proteinuria, oliguria, $\uparrow$ creatinine)*, *Blood (thrombocytopenia, haemolysis, DIC)*, *Placenta (abruption, fetal growth restriction, oligohydramnios)*.

Clinical / Diagnostic significance

- ▶ **Investigations:** serial BP; urine dipstick + protein/creatinine ratio or 24-h urinary protein; CBC with platelets; peripheral smear/LDH/haptoglobin/bilirubin (haemolysis); AST/ALT; serum creatinine and uric acid; coagulation profile if HELLP/DIC suspected; fetal surveillance (ultrasound for growth restriction, oligohydramnios, umbilical Doppler, non-stress test). sFlt-1/PlGF ratio aids risk prediction where available.
- ▶ **Differential diagnosis:** chronic hypertension, CKD, primary seizure disorder, immune thrombocytopenia, TTP, haemolytic-uraemic syndrome, acute fatty liver of pregnancy, gallbladder/pancreatic disease.

- ▶ **Prevention: low-dose aspirin (81 mg/day orally)** for women at increased risk, started between **12–28 weeks (optimally before 16 weeks)** and continued until delivery (Harrison: initiated 12–14 weeks in high-risk women). Calcium, antioxidants (vitamins C/E), salt restriction and diuretics are *not* proven effective.

Management

- ▶ **Definitive treatment = delivery** of fetus and placenta; timing balances maternal risk against fetal prematurity.
 - Preeclampsia *without* severe features: expectant management with close maternal–fetal monitoring; **deliver at 37 weeks**.
 - Preeclampsia *with* severe features: **deliver**, unless <34 weeks and eligible for expectant management in a tertiary unit; deliver before 34 weeks for unremitting symptoms, worsening labs, refractory severe hypertension, or fetal compromise.
- ▶ **Acute severe hypertension (BP $\geq$ 160/110):** treat promptly (within 60 min) to reduce stroke risk; target BP **140–150/90–100 mmHg** (avoid over-correction → placental hypoperfusion). First-line IV agents:
 - **Labetalol** 10–20 mg IV every 20 min as needed.
 - **Hydralazine** 5–10 mg IV every 20 min.
 - **Immediate-release nifedipine** 10–20 mg orally, repeat at 20 min, then 10–20 mg every 4–6 h (max 180 mg/day) — useful when no IV access.
- ▶ **Seizure prophylaxis & treatment — magnesium sulfate (drug of choice):**
 - Loading **4–6 g IV** (over 15–20 min for prophylaxis; over ~4 min to abort an eclamptic seizure), then maintenance **2–3 g/hour**; continue **24 h postpartum**.
 - Therapeutic level **4–7 mEq/L**; reduce dose/withhold if serum creatinine >1.0 mg/dL or oliguria.
 - **Monitor for toxicity** — loss of deep tendon reflexes, respiratory depression, oliguria; **antidote = calcium gluconate 1 g IV over 2 min**. Phenytoin/benzodiazepines only if magnesium unavailable.
- ▶ **Fetal lung maturity:** if <34 weeks, give antenatal corticosteroids — **betamethasone 12 mg IM every 24 h $\times$ 2 doses**, or **dexamethasone 6 mg IM every 12 h $\times$ 4 doses** (do not delay delivery in unstable severe disease).
- ▶ **Eclampsia:** turn patient to the side (prevent aspiration), secure airway/oxygenation, control seizures with magnesium sulfate, control BP, stabilise the mother, then deliver (vaginal delivery preferred; caesarean for obstetric indications).
- ▶ **Chronic hypertension in pregnancy:** preferred agents **labetalol** and **extended-release nifedipine**; **methyldopa** has a good safety record. Target BP **<140/90 mmHg** (CHAP trial — treating mild chronic hypertension to <140/90 reduces preeclampsia and preterm birth). **ACE inhibitors**,

ARBs and mineralocorticoid-receptor antagonists are contraindicated (stillbirth, fetal renal/congenital anomalies).

- ▶ **Postpartum:** continue magnesium 24 h; remain vigilant for late-onset (postpartum) preeclampsia/eclampsia — treat as antepartum with hydralazine and magnesium.

Long-term significance

- ▶ Women with gestational hypertension or preeclampsia carry an increased lifelong risk of **chronic hypertension, cardiovascular disease, chronic kidney disease and diabetes mellitus**; preeclampsia is a recognised female-specific cardiovascular risk marker warranting risk-factor modification at postnatal visits.

High-yield exam pointers

- ▶ PIH/HDP = BP $\geq 140/90$ after **20 weeks**; classified into gestational HTN, preeclampsia, eclampsia, chronic HTN, and superimposed preeclampsia.
- ▶ **Preeclampsia = hypertension + proteinuria (or end-organ damage) after 20 weeks**; edema is no longer required.
- ▶ **Severe features:** BP $\geq 160/110$, platelets $<100 \times 10^9/L$, creatinine >1.1 mg/dL, transaminases $\geq 2\times$ normal, pulmonary edema, cerebral/visual symptoms, epigastric pain.
- ▶ **HELLP** = Hemolysis, Elevated Liver enzymes, Low Platelets — severe-subtype preeclampsia.
- ▶ Pathophysiology: $\uparrow$ sFlt-1, $\downarrow$ PlGF; **sFlt-1/PlGF ratio ≥ 40** predicts severe disease.
- ▶ **Magnesium sulfate** is the drug of choice for seizure prophylaxis/treatment; **calcium gluconate** is the antidote.
- ▶ Acute severe BP: **IV labetalol or hydralazine** (target 140–150/90–100); **ACEI/ARB contraindicated** throughout pregnancy.
- ▶ **Low-dose aspirin 81 mg** from 12–16 weeks for prevention in high-risk women.
- ▶ **Delivery is the only cure** — at 37 weeks (no severe features) or earlier for severe disease; corticosteroids if <34 weeks.

SOURCE & COVERAGE

- ▶ Harrison's *Principles of Internal Medicine*, 22e — “Medical Disorders During Pregnancy” (preeclampsia, gestational hypertension, eclampsia/HELLP, pathophysiology, treatment) and “Hypertension” (hypertensive disorders of pregnancy, antihypertensive choice).
- ▶ CMDT 2026 — “Obstetrics & Obstetric Disorders” (diagnostic criteria, severity table, magnesium sulfate protocol, antihypertensive doses, corticosteroids, aspirin prophylaxis, eclampsia management) and “Systemic Hypertension” (chronic hypertension agents, methyldopa safety; CHAP trial).

Coverage note: No dedicated subspecialty obstetrics text was provided in the spec (specialty_books empty); grounding therefore rests on Harrison 22e plus CMDT 2026, which together cover the topic at exam depth.



Pyrogenic cytokines and their role in pathogenesis of fever

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — A **pyrogen** (Greek *pyro*, “fire”) is any substance that causes fever. **Fever** is an elevation of body temperature that exceeds the normal daily variation and occurs *in conjunction with a raised hypothalamic set point* (e.g., from 37°C to 39°C) — fundamentally distinct from hyperthermia, in which the set point is unchanged and no pyrogenic molecules are involved. **Pyrogenic cytokines** are small host-derived proteins (formerly called *endogenous pyrogens*) — chiefly **IL-1, IL-6 and TNF** — that act as the central molecular link translating an infectious or inflammatory stimulus into a rise in the hypothalamic thermostat. They are the obligatory intermediaries between exogenous pyrogens and the prostaglandin E2 (PGE2)-driven elevation of the set point that produces fever.

Classification of pyrogens

- ▶ **Exogenous pyrogens** — derived from *outside* the host; mostly microbial products, microbial toxins, or whole microorganisms (including viruses).
 - Classic example: **lipopolysaccharide (endotoxin)** of all gram-negative bacteria — a highly pyrogenic molecule. An IV dose of just **2–3 ng/kg** in human volunteers produces fever, leukocytosis, acute-phase proteins, and malaise.
 - Cell-wall components of **gram-positive** organisms are less pyrogenic, but these organisms elaborate **superantigen toxins** that induce fever — *Staphylococcus aureus* toxic shock syndrome toxin-1 (TSST-1), staphylococcal enterotoxins, and streptococcal pyrogenic exotoxins — pyrogenic in animals at **1–10 µg/kg**.
- ▶ **Endogenous pyrogens = pyrogenic cytokines** — host proteins produced in response to exogenous pyrogens *or* to sterile inflammation. Fever can therefore arise **without microbial infection** (e.g., pericarditis, trauma, stroke, routine immunizations all induce IL-1, TNF and/or IL-6).

Feature	Exogenous pyrogens	Pyrogenic (endogenous) cytokines
Origin	Outside host (microbes/toxins)	Host myeloid & endothelial cells
Prototype	Endotoxin (LPS)	IL-1, IL-6, TNF

Feature	Exogenous pyrogens	Pyrogenic (endogenous) cytokines
Pyrogenic IV dose	LPS 2–3 ng/kg; superantigens 1–10 µg/kg	IL-1, TNF 10–100 ng/kg; IL-6 1–10 µg/kg
Acts via	Inducing cytokine synthesis (and TLRs)	Inducing PGE ₂ → raises set point
Needs microbe?	Yes	No (also sterile inflammation)

The pyrogenic cytokines

- ▶ Cytokines are small proteins (**molecular mass 10,000–20,000 Da**) that regulate immune, inflammatory and hematopoietic processes; IL-1 and IL-6 also drive the **neutrophilic leukocytosis** of infection.
- ▶ Each pyrogenic cytokine is encoded by a separate gene, and each independently causes fever in laboratory animals and in humans.
- ▶ A wide spectrum of bacterial and fungal products induces their synthesis and release.

Cytokine	Key features in fever
IL-1	Prototype pyrogen; fever at low IV dose 10–100 ng/kg ; shares signalling pathway with Toll-like receptors
TNF	Pyrogenic at 10–100 ng/kg ; central to sterile and septic fever
IL-6	Induced by IL-1/TNF; less potent — fever needs 1–10 µg/kg ; induces hepatic C-reactive protein (CRP)
IFN (esp. interferon-α)	Fever is a <i>prominent side effect of interferon-α therapy</i>
Ciliary neurotrophic factor (CNTF)	A member of the IL-6 family; also pyrogenic

Pathogenesis: how pyrogenic cytokines raise the hypothalamic set point

- ▶ **Source cells:** *Myeloid cells (monocytes/macrophages) and endothelial cells* are the primary producers. On encountering an exogenous pyrogen they release **IL-1, IL-6 and TNF** into the systemic circulation.
- ▶ **Site of action — the circumventricular organs:** During fever, PGE₂ is elevated in hypothalamic tissue and the third cerebral ventricle, with the highest concentrations near the **organum vasculosum of the lamina terminalis (OVLT)** — networks of enlarged (“leaky”) capillaries surrounding the hypothalamic regulatory centres. Destruction of these organs abolishes the febrile response to pyrogens.

- ▶ **Cytokines do NOT enter the brain parenchyma:** Most animal studies show pyrogenic cytokines do *not* cross from the circulation into the brain itself. Instead, circulating exogenous pyrogens and pyrogenic cytokines **interact with the endothelium of these capillaries** — this interaction is the *first step* in raising the set point.
- ▶ **PGE2 is the final common mediator:** Cytokine–endothelium interaction induces PGE2 synthesis. The enzyme **cyclooxygenase** acts on **arachidonic acid** (released from membrane phospholipid — the *rate-limiting step*) to form PGE2. Of the **four PGE2 receptors**, the **EP-3 receptor is essential for fever**: deleting the EP-3 gene in mice abolishes fever after IL-1 or endotoxin, whereas deleting the other receptor genes leaves fever intact.
- ▶ **PGE2 → cAMP → set point:** PGE2 is *not itself a neurotransmitter*. PGE2 released from the brain side of the hypothalamic endothelium triggers **PGE2 receptors on glial cells**, causing rapid release of **cyclic AMP (cAMP)** — the actual neurotransmitter. cAMP activates neuronal endings of the thermoregulatory centre, and this elevation of cAMP **raises the hypothalamic set point** (directly or by inducing other neurotransmitters).
- ▶ **Toll-like receptors (TLRs):** Distinct receptors for microbial products on the hypothalamic endothelium — **Toll-like receptors** — closely resemble **IL-1 receptors** and *share the same signal-transducing mechanism*; direct activation of either TLRs or IL-1 receptors yields **PGE2 production and fever**.
- ▶ **Peripheral PGE2 and constitutional symptoms:** Circulating cytokines also induce PGE2 in peripheral tissues, accounting for the **myalgias and arthralgias** of fever. Some systemic PGE2 escapes pulmonary destruction and reaches the hypothalamus via the **internal carotid**, but it is the rise in *brain* PGE2 that initiates the set-point change.
- ▶ **Effector limb:** Once the set point is raised, the vasomotor centre triggers **vasoconstriction** (heat conservation — cold hands/feet, the patient “feels cold”), **shivering** and **non-shivering thermogenesis** (heat production), plus behavioural adjustments, until blood temperature matches the new febrile setting.

Production of cytokines within the CNS

- ▶ Cytokines made *inside the brain* account for the **hyperpyrexia of CNS haemorrhage, trauma or infection**.
- ▶ Viral CNS infections induce **microglial (and possibly neuronal) production of IL-1, TNF and IL-6**.
- ▶ The cytokine concentration needed to cause fever is **several orders of magnitude lower** with direct intracerebral/intraventricular injection than with systemic injection; thus CNS-generated cytokines raise the set point while **bypassing the circumventricular organs**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Fig. 20-1 — “Chronology of events required for the induction of fever”** (vertical flow chart). Labels, top to bottom:
- Infection, microbial toxins, mediators of inflammation, immune reactions
 - → Monocytes/macrophages, endothelial cells, others
 - → Pyrogenic cytokines: IL-1, IL-6, TNF, IFN (entering Circulation)
 - → Hypothalamic endothelium
 - → PGE2 → Cyclic AMP (cAMP)
 - → Elevated thermoregulatory set point → Heat conservation, heat production → FEVER
 - Include a side arrow labelled “Microbial toxins” acting directly on the hypothalamic endothelium (via Toll-like receptors).
- **Optional inset — hypothalamic set-point thermostat:** label OVLT (*organum vasculosum lamina terminalis*), EP-3 receptor on glial cell, thermoregulatory neuron, normothermic set point 37°C → febrile set point 39°C.

Clinical / Diagnostic significance

- **Measuring circulating cytokines is NOT useful** — IL-1 and TNF are often below assay detection limits or do not coincide with fever. For occult/low-grade fever the most valuable markers are CRP and ESR; IL-6 (which induces CRP) can be informative, but IL-6 levels fluctuate during a febrile illness whereas CRP stays elevated.
- **Anticytokine therapy blunts fever and raises infection risk:** Agents blocking IL-1, IL-6, IL-12/23, IL-17 or TNF (used in Crohn disease, rheumatoid arthritis, psoriasis) lower host defences — e.g., **latent M. tuberculosis can disseminate on anti-TNF therapy**, and anti-IL-17 raises systemic candidiasis risk. Low-grade fever in such patients warrants early, rigorous evaluation.
- **Therapeutic blockade reduces fever in autoinflammatory disease:** Fevers of familial Mediterranean fever, hyper-IgD syndrome, adult/juvenile Still disease (IL-1 β -mediated, often via NLRP3/pyrin inflammasomes) are dramatically reduced by **anakinra** or **canakinumab**.
- **Antipyretics target the PGE2 limb:** Cyclooxygenase inhibitors are potent antipyretics; antipyretic potency correlates with **inhibition of brain cyclooxygenase**. **Aspirin and acetaminophen are equally effective**; acetaminophen is a poor peripheral COX inhibitor but is oxidised by brain P450 (and inhibits COX-3, found only in the CNS). **Glucocorticoids act at two levels** — inhibiting phospholipase A2 ($\downarrow$ arachidonic acid $\rightarrow$ $\downarrow$ PGE2) and blocking transcription of pyrogenic-cytokine mRNA.
- **Blunted febrile response** is expected in newborns, the elderly, chronic hepatic/renal failure, and patients on glucocorticoids/NSAIDs/anticytokines — active disease may exist without fever; septic shock may even cause hypothermia.

High-yield exam pointers

- ▶ Pyrogenic cytokines = the *renamed* endogenous pyrogens: IL-1, IL-6, TNF, IFN, and CNTF (IL-6 family).
- ▶ PGE2 is the final mediator; EP-3 receptor is *essential* for fever (knockout abolishes it).
- ▶ cAMP — not PGE2 — is the neurotransmitter that resets the hypothalamic thermostat.
- ▶ Pyrogenic doses: LPS 2–3 ng/kg; IL-1/TNF 10–100 ng/kg; IL-6 1–10 µg/kg; superantigens 1–10 µg/kg.
- ▶ Cytokines act at the OVLT/circumventricular organs and do *not* cross into brain parenchyma.
- ▶ TLRs and IL-1 receptors share the same signalling pathway → PGE2 → fever.
- ▶ Fever (raised set point, cytokine/PGE2-mediated, *responds* to antipyretics) vs **hyperthermia** (set point unchanged, no pyrogens, *does not* respond to antipyretics).
- ▶ IL-6 induces CRP; CRP is a more stable marker than IL-6 for monitoring occult fever.
- ▶ CNS-generated IL-1/TNF/IL-6 explain **hyperpyrexia of CNS haemorrhage, trauma, infection**.

SOURCE & COVERAGE

Harrison 22e — Ch 20 “Fever” (Dinarello & Surana). Full coverage of pyrogens, pyrogenic cytokines and the PGE2/EP-3/cAMP pathogenesis of fever; spec.gap = false and no fabrication required. All doses, the four-receptor/EP-3 point, OVLT, TLR–IL-1R sharing, and CNS cytokine production are taken verbatim from this chapter. (Inflammasome detail, e.g., NLRP3/pyrin, is referenced by Ch 20 but elaborated in Chaps 360/381, cited only in passing here.)



Recombinant DNA Technology: Principles and Applications

Asked in: Paper I Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — *Recombinant DNA (rDNA) technology* is the set of laboratory techniques by which DNA segments from two or more different sources are joined *in vitro* to create a novel **recombinant (chimeric) DNA molecule**, which is then introduced into a living host cell where it can be propagated (cloned) and/or expressed. It is the foundational enabling technology of modern molecular medicine: as Harrison emphasises, peptide hormones, growth factors, cytokines and vaccines can now be manufactured in large quantities using recombinant DNA and RNA technology, and the same toolkit underpins molecular diagnostics, gene therapy and gene editing. The three essential operations are: **cut** (a specific gene), **paste** (into a vector), and **clone/express** (in a host cell).

Molecular toolkit (key enzymes and reagents)

Tool	Function	Note
Restriction endonucleases	Cleave double-stranded DNA at specific palindromic recognition sequences; the “ <i>molecular scissors</i> ”	Generate cohesive (<i>sticky</i>) or blunt ends; <i>e.g.</i> EcoRI, BamHI, HindIII
DNA ligase	Forms phosphodiester bonds joining vector and insert; the “ <i>molecular glue</i> ”	Seals the recombinant molecule
Reverse transcriptase	Synthesises complementary DNA (cDNA) from an mRNA template	Source of intron-free coding sequence for expression
DNA polymerase (<i>thermostable</i> , Taq)	Template-directed synthesis of new DNA strands	Engine of PCR
Modifying enzymes	Alkaline phosphatase, polynucleotide kinase, terminal transferase	Prevent self-ligation, add/label ends
Vector	Self-replicating DNA vehicle that carries the foreign gene into the host	Plasmid, phage, viral, artificial chromosome
Host cell	Site of replication/expression	<i>E. coli</i> , yeast, mammalian or insect cells

Principle — steps of gene cloning

- ▶ **1. Isolation of the gene/DNA of interest.** The target sequence is obtained by (a) restriction digestion of genomic DNA, (b) reverse transcription of mRNA into **cDNA** (yields the coding sequence without introns — preferred for protein expression in bacteria), or (c) direct amplification by **PCR**.
- ▶ **2. Insertion into a vector (“recombination”).** Vector and insert are cut with the *same* restriction enzyme so that complementary sticky ends anneal; **DNA ligase** then covalently joins them to form the **recombinant (chimeric) DNA molecule**.
- ▶ **3. Introduction into a host cell.** The recombinant vector is taken up by competent bacteria (**transformation**), or by mammalian cells (**transfection**), or delivered by a **viral vector** (**transduction**).
- ▶ **4. Selection and screening of recombinant clones.** Host cells carrying the construct are identified using **selectable markers** (e.g., antibiotic-resistance genes), **blue–white (lacZ / β -galactosidase)** screening with X-gal, and **colony/nucleic-acid hybridisation** with labelled probes.
- ▶ **5. Amplification and expression.** The positive clone is propagated to generate millions of identical copies (a *clone/gene library*); an **expression vector** with a suitable promoter drives synthesis of the encoded protein, which is then harvested and purified.

Vectors — cloning vehicles

Vector	Approx. insert capacity	Host / use
Plasmid	up to ~10 kb	<i>E. coli</i> ; routine cloning, expression
Bacteriophage λ	~15–20 kb	Genomic libraries
Cosmid	~35–45 kb	Larger inserts
BAC (bacterial artificial chromosome)	up to ~300 kb	Large fragments, genome projects
YAC (yeast artificial chromosome)	up to ~1–2 Mb	Very large fragments
Viral vectors — retro-/lentiviral, adenoviral, adeno-associated virus (AAV)	retro/lenti ~8 kb; adeno 8–30 kb; AAV ~5 kb	<i>In vivo/ex vivo</i> gene therapy (see below)

Core analytical & amplification techniques

- ▶ **Polymerase Chain Reaction (PCR):** cyclical *in vitro* amplification — **denaturation** (~94–95 °C) → **primer annealing** (~50–65 °C) → **extension** (~72 °C, *Taq* polymerase); each cycle doubles the target, giving exponential (2^n) amplification. Enables testing from minute amounts of DNA (leukocytes, single cells, buccal cells, hair roots). **RT-PCR** converts RNA → cDNA before amplification (e.g., SARS-CoV-2, HIV viral-load); **quantitative/real-time PCR** measures copy number.
- ▶ **Hybridisation/blotting:** **Southern blot** (DNA), **Northern blot** (RNA), **Western blot** (protein); **FISH** (fluorescence *in situ* hybridisation) and array/bead-based methods detect deletions/duplications and chromosomal rearrangements.
- ▶ **DNA sequencing:** Sanger (dideoxy) sequencing of PCR products, now largely superseded by **next-generation sequencing (NGS)** — whole-exome (WES), whole-genome (WGS) and targeted gene panels — allowing unbiased, cost-effective mutational analysis.
- ▶ **Genome editing:** **CRISPR/Cas9** uses a bacterial Cas9 nuclease complexed with a **guide RNA** (ribonucleoprotein) to introduce a site-specific double-strand break; repair by non-homologous end-joining disrupts a gene, or homology-directed repair with a donor template corrects it.

Applications in clinical medicine

- ▶ **1. Recombinant therapeutic proteins** — produced in microbial/mammalian cells: **human insulin** (the first licensed recombinant drug, 1982) and modified **insulin analogues** with favourable kinetics; **GLP-1 receptor agonists**; growth hormone, erythropoietin, granulocyte colony-stimulating factor, interferons, clotting **factor VIII/IX**, and tissue plasminogen activator. Targeted modification of the recombinant peptide yields improved therapeutics (Harrison's

explicit examples: insulin analogues, GLP-1 agonists for type 2 diabetes and weight management).

- ▶ **2. Vaccines** — recombinant subunit vaccines (e.g., hepatitis B surface antigen, HPV) and, most recently, **mRNA vaccines against SARS-CoV-2**.
- ▶ **3. RNA-based therapeutics** — **small interfering RNA (siRNA)** to treat hypercholesterolaemia; antisense oligonucleotides; guide RNAs/mRNAs delivered by **lipid nanoparticles**.
- ▶ **4. Gene transfer & gene editing therapy** — a nucleic acid is the active agent, delivered by an engineered **vector**; strategies are *gene addition* (supply a missing gene) or *gene editing* (correct the endogenous locus). Approved products include:

Product	Indication	Vector / approach
Strimvelis	ADA-SCID	Retroviral, autologous HSCs (<i>ex vivo</i>)
Luxturna (voretigene neparvovec)	Biallelic <i>RPE65</i> retinal dystrophy (Leber congenital amaurosis)	AAV2, subretinal injection
Zolgensma (onasemnogene abeparvovec)	Spinal muscular atrophy type 1 (<i>SMN1</i>)	AAV9, single IV infusion
Zynteglo (betibeglogene autotemcel)	Transfusion-dependent β -thalassaemia	Lentiviral β^A -T87Q globin gene, autologous HSCs
Kymriah / Yescarta (CAR-T)	R/R B-cell leukaemia/lymphoma	Lenti-/retroviral anti-CD19 CAR, autologous T cells
CRISPR gene-editing therapy	Sickle cell disease, β -thalassaemia	CRISPR/Cas9 (FDA-approved 2023)

- ▶ **5. Molecular diagnosis** — PCR-based detection and identification of pathogens difficult to culture (mycobacteria, viruses, parasites) and tracking of outbreaks; carrier detection and mutational analysis of monogenic disease (e.g., CFTR $\Delta F508$ in cystic fibrosis); **prenatal diagnosis** (amniocentesis, chorionic villus sampling) and **non-invasive prenatal testing/liquid biopsy** using cell-free DNA (cfDNA); tumour genotyping to select **actionable, targeted therapies**.
- ▶ **6. Pharmacogenomics** — genotype-guided drug selection and dosing to optimise efficacy and minimise adverse effects.
- ▶ **7. Research tools** — gene mapping/linkage studies, transgenic and knockout animal models, and functional genomics.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Gene-cloning flowchart (label clearly):** *Gene of interest* (source DNA) and *Plasmid vector* (showing origin of replication, selectable marker / ampR, lacZ) → both cut by the Restriction endonuclease (EcoRI) producing **sticky ends** → joined by DNA ligase →

Recombinant (chimeric) plasmid → **Transformation into E. coli host* → *Selection (antibiotic resistance + blue-white screening)* → *Recombinant colony* → *Cloning / Protein expression**.

- ▶ **PCR cycle:** three boxes — **Denaturation (94–95 °C)** → **Annealing of forward & reverse primers (50–65 °C)** → **Extension (72 °C, Taq polymerase, dNTPs), with an arrow showing exponential amplification (2^n); label template DNA, primers, dNTPs, thermal cycler**.

Clinical / Diagnostic significance

- ▶ Enables manufacture of pure, abundant, non-immunogenic human proteins (insulin, clotting factors), eliminating the infection risk and supply limits of animal/cadaveric/pooled-plasma sources.
- ▶ Permits diagnosis from minute samples and at the molecular level — carrier testing, prenatal/preimplantation diagnosis, infectious-disease detection and viral-load monitoring.
- ▶ Drives **precision/personalized medicine**: tumour mutational profiling guides targeted therapy; pharmacogenomic genotyping individualises prescribing.
- ▶ Provides definitive (potentially curative) therapy for previously untreatable genetic diseases via gene transfer and CRISPR gene editing.

High-yield exam pointers

- ▶ rDNA = joining DNA from two sources *in vitro*; three steps — **cut (restriction enzyme)** → **paste (ligase)** → **clone/express (vector + host)**.
- ▶ **Restriction endonucleases = molecular scissors; DNA ligase = molecular glue.**
- ▶ **Sticky (cohesive) ends** allow vector–insert annealing; same enzyme must cut both.
- ▶ Recombinant selection: **antibiotic-resistance markers + blue-white (lacZ) screening + colony hybridisation.**
- ▶ **PCR:** denature 94–95 °C → anneal 50–65 °C → extend 72 °C (*Taq*); RT-PCR for RNA targets.
- ▶ Blotting mnemonic: Southern–DNA, Northern–RNA, Western–protein.
- ▶ **Human insulin (1982)** = first licensed recombinant therapeutic protein; mRNA SARS-CoV-2 vaccines and siRNA for hypercholesterolaemia are modern rDNA/RNA products.
- ▶ Gene-therapy vectors: **retro/lentiviral (integrating, ex vivo), adenoviral, AAV (non-integrating), lipid nanoparticles**; FDA approved the first CRISPR therapy (sickle cell disease/ β -thalassaemia) in 2023.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Principles of Human Genetics” (recombinant DNA/RNA technology for therapeutic proteins, vaccines, siRNA; PCR,

FISH, NGS, mutational and prenatal analysis; CFTR/ Δ F508) and “Gene and Cell-Based Therapy in Clinical Medicine” (gene delivery vehicles/vectors, transduction, CRISPR/Cas9, approved gene/cell-therapy products including Strimvelis, Luxturna, Zolgensma, Zynteglo, Kymriah/Yescarta).

- **Coverage note:** Harrison 22e covers the *applications* of rDNA technology in depth but treats the **wet-lab cloning methodology only thinly** — the chapter explicitly states the detailed mutation-detection/molecular techniques were “discussed in previous versions of this chapter.” Accordingly, the enzyme toolkit, the step-wise cloning protocol, the cloning-vector capacity figures (plasmid/phage/cosmid/BAC/YAC), blue–white screening and the blotting/Sanger details are presented as **standard, universally accepted molecular biology** rather than verbatim Harrison content; the spec flags this topic as a known thin-coverage (gap) area. The viral-vector packaging limits and all gene-therapy product details are taken directly from Harrison 22e.



Stem Cell Therapy in Clinical Medicine

Asked in: Paper I Jul 2020 — RGUHS MD General Medicine

Definition / Introduction — A **stem cell** is an undifferentiated cell defined by two cardinal properties: *self-renewal* (the ability to divide while preserving an undifferentiated state) and *differentiation* (the capacity to generate the mature effector cells of a tissue). **Stem cell therapy** is the therapeutic exploitation of these properties to regenerate, replace, or genetically correct a diseased lymphohematopoietic or other tissue. In clinical practice today it spans three overlapping domains: (1) **hematopoietic cell transplantation (HCT)** — the dominant, well-established modality; (2) **gene-modified autologous stem-cell products** (ex vivo gene addition or gene editing); and (3) engineered immune effector cells (**CAR-T therapy**). Tens of thousands of lives are saved annually by stem-cell-based therapies.

Stem cell — properties and classification

- **Two cardinal functions** (Harrison, *Hematopoietic Stem Cells*): self-renewal sustains the stem-cell pool; differentiation produces mature cells. A dividing stem cell yields one of three outcomes — two stem cells, two differentiating cells (both *symmetric*), or one of each (*asymmetric division*).
- Self-renewal is regulated by **intrinsic factors** (Bmi-1, Gfi-1, PTEN, STAT5, p21, p18, HoxB4) and **extrinsic niche signals** (Notch, Wnt, Sonic hedgehog, angiogenin, Tie2/Ang-1).
- **Classification by potency**: *totipotent* (zygote → whole organism + placenta); *pluripotent* (embryonic stem cells, induced pluripotent stem cells [iPSC] → all three germ layers);

multipotent/adult (somatic) stem cells — e.g., hematopoietic stem cells (HSC), mesenchymal stem cells (MSC).

Stem-cell type	Source	Potency	Principal clinical role
Hematopoietic (HSC)	Marrow, mobilised blood, cord blood	Multipotent	Established — HCT, gene therapy vehicle
Embryonic (ESC)	Inner cell mass	Pluripotent	Investigational
Induced pluripotent (iPSC)	Reprogrammed somatic cells	Pluripotent	Investigational/disease modelling
Mesenchymal (MSC)	Marrow stroma, fat, cord	Multipotent	Investigational (immunomodulation)
Cancer stem-like cells	Tumours	—	Relapse source; therapeutic target

The hematopoietic stem cell — markers, niche and mobilisation

- ▶ The HSC sustains all blood and immune lineages plus tissue-fixed macrophages (Kupffer cells, alveolar macrophages, osteoclasts, microglia, Langerhans cells). The estimated stem-cell pool of **20,000–200,000 cells** produces hundreds of billions of blood cells daily.
- ▶ **Surface phenotype (mainly murine-derived):** CD34, Thy-1 (CD90), c-Kit (CD117), CD133, CD164, and c-Mpl (CD110, the thrombopoietin receptor).
- ▶ **Niche:** for most of life the HSC resides in the **bone-marrow perivascular/endosteal niche**, regulated by mesenchymal and endothelial cells producing **kit ligand** and **CXCL12 (SDF-1)**, plus sympathetic neurons, Schwann cells, osteoblasts and osteoclasts. The niche both nurtures and constrains stem-cell number.
- ▶ **Homing & mobilisation:** circulating HSCs roll on endothelial **P-/E-selectins** (via CD162/CD44), firmly adhere through **VLA-4/VCAM-1** integrins, and home via **CXCL12–CXCR4** signalling. Clinically, **G-CSF** and **plerixafor** (a CXCR4 antagonist) disrupt this retention to release stem cells into blood, enabling harvest by **leukapheresis** rather than marrow puncture.
- ▶ **Clonal dynamics:** HSCs acquire ~17 somatic mutations per year; expansion of clones bearing **DNMT3A**, **TET2**, or **ASXL1** mutations underlies **clonal hematopoiesis of indeterminate potential (CHIP)**, predisposing to myeloid malignancy and adverse inflammatory outcomes.

SOURCE & COVERAGE

- ▶ Sources of stem cells (Harrison, *Hematopoietic Cell Transplantation*):

Source	Collection	Engraftment	GVHD	Notes
Bone marrow	Iliac-crest aspiration (10–15)	Reference	Lowest with unrelated donors	Original source

	mL/kg); $1.5-5 \times 10^8$ nucleated cells/kg			
Peripheral blood (PBSC)	Leukapheresis after G-CSF $\pm$ plerixafor; aim $>2.5 \times 10^6$ CD34 ⁺ /kg	Fastest (~ 1 wk earlier)	More chronic GVHD (T-cell content)	Most commonly used
Umbilical cord blood	Cryopreserved units	~ 1 wk slower	Lowest (few T cells)	Tolerates HLA mismatch; double-cord units for adults

► **Categories by donor relationship:**

- **Autologous** — patient's own stored stem cells re-infused after high-dose therapy; **no** GVHD/rejection but **no graft-versus-tumour (GVT) effect** and risk of tumour-cell contamination.
- **Syngeneic** — identical twin ($\sim 1\%$ of cases); no GVHD, no tumour contamination.
- **Allogeneic** — genetically non-identical donor; provides a **GVT effect** but risks GVHD and graft rejection.

- **HLA matching** (genes HLA-A, -B, -C, -D): odds that a full sibling matches = $\frac{1}{4}$; probability of an HLA-identical sibling = $1 - (0.75)^n$ (n = number of siblings). Matched unrelated donors are found for $\sim 60\%$ of patients via registries (>40 million donors). With HLA-identical siblings, graft rejection is $1-3\%$ and severe acute GVHD $\sim 15\%$. **Post-transplant high-dose cyclophosphamide** now permits **haploidentical** (single-haplotype-shared) transplantation.

Conditioning regimens and the transplant procedure

- The **preparative (conditioning) regimen** eradicates underlying disease and immunosuppresses the host to prevent graft rejection.
- **Myeloablative:** combinations of busulfan, cyclophosphamide, melphalan, thiotepa, carmustine, etoposide, total-body irradiation (TBI).
 - **Reduced-intensity:** e.g., fludarabine + melphalan — significant but non-lethal myelosuppression; favoured in older/comorbid patients.
 - **Nonmyeloablative:** e.g., fludarabine + 200 cGy TBI — relies on the GVT effect.
- Disease-specific examples: SCID with a matched sibling needs **no conditioning**; aplastic anaemia — cyclophosphamide + antithymocyte globulin (ATG); thalassaemia/sickle cell — busulfan + cyclophosphamide.

- **Engraftment:** marrow grafts reach 500 granulocytes/ μL by **~day 22** (PBSC ~1 week faster, cord blood ~1 week slower). Innate immunity recovers in weeks; **adaptive (T- and B-cell) immunity takes 1–2 years**. Donor chimerism is documented by sex-chromosome FISH or short-tandem-repeat analysis.

Clinical indications for stem cell transplantation

- **Non-malignant:** severe combined immunodeficiency (cure >90%), aplastic anaemia, β -thalassaemia major and sickle cell anaemia (HLA-identical sibling cure 80–90%), congenital marrow-failure and phagocyte disorders (Kostmann, chronic granulomatous disease, Wiskott-Aldrich, Chédiak-Higashi), osteopetrosis, selected storage diseases (Hurler, Gaucher), and increasingly **severe autoimmune disease** (a randomised trial showed survival benefit of HCT in severe scleroderma; trials ongoing in multiple sclerosis).
- **Malignant:** acute leukaemias (AML/ALL — allogeneic, guided by remission status and measurable residual disease), CML failing ≥ 2 tyrosine-kinase inhibitors, myelodysplasia (IPSS Int-2/high), myelofibrosis, lymphomas and Hodgkin disease (usually **autologous**), **multiple myeloma** (autologous as part of initial therapy), and **relapsed testicular germ-cell tumour** (autologous high-dose chemotherapy).

Disease	Allogeneic 3-yr survival	Autologous
Severe combined immunodeficiency	95%	—
Aplastic anaemia	98%	—
Thalassaemia	95%	—
AML (first remission)	57%	—
Multiple myeloma (initial)	—	80%
Hodgkin disease (2nd remission)	68%	89%

Complications of transplantation

- **Acute GVHD** (first ~3 months; peak ~4 weeks): triad of **maculopapular skin rash**, **cholestatic liver injury** (rising bilirubin), and **secretory diarrhoea**, graded I–IV. Prophylaxis = **calcineurin inhibitor** (cyclosporine/tacrolimus) + **methotrexate**, often with a third agent (mycophenolate, abatacept, or post-transplant cyclophosphamide). Treatment = **prednisone 1–2 mg/kg**; steroid-refractory disease responds to the JAK inhibitor **ruxolitinib**.
- **Chronic GVHD** (3 months–2 years; 20–50%): autoimmune-like — malar rash, sicca, arthritis, obliterative bronchiolitis, cholestasis. Steroid-resistant disease: **ibrutinib**, **ruxolitinib**, **belumosudil** (kinase inhibitors).
- **Regimen-related toxicity:** mucositis, **sinusoidal obstruction syndrome (SOS / veno-occlusive disease)** — tender hepatomegaly, ascites, jaundice; treated with **defibrotide**; haemorrhagic

cystitis (prevent with MESNA); transplant-associated thrombotic microangiopathy (responds to **eculizumab**); late bronchiolitis obliterans, cataracts, infertility, hypothyroidism.

- ▶ **Infection** by phase: early neutropenic bacterial/Candida; intermediate **CMV**, **Aspergillus** (CMV prophylaxis with **letermovir** or pre-emptive ganciclovir); late encapsulated bacteria/VZV. Standard prophylaxis: levofloxacin, fluconazole/mould-active azole, **co-trimoxazole** for **Pneumocystis**, acyclovir.
- ▶ **Graft failure** and disease relapse — relapse after allograft may respond to **donor lymphocyte infusions** (CML response up to 75%).

Gene- and cell-based stem cell therapies (the modern frontier)

- ▶ **Why HSCs are the ideal gene-therapy target** (Harrison, *Gene and Cell-Based Therapy*): they persist for life, so genetic modification of autologous HSCs gives a durable, **HLA-matching-free**, **GVHD-free** cure. Transgene must integrate (lentiviral) or the target locus be edited; myeloablative conditioning is still needed.
- ▶ **Ex vivo gene-addition products (autologous HSCs)**: *Strimvelis* (retroviral, ADA-SCID), *Zynteglo* (lentiviral β^A -T87Q globin, transfusion-dependent β -thalassaemia/sickle cell disease), *Skysona* (cerebral adrenoleukodystrophy, ABCD1), *Libmeldy* (metachromatic leukodystrophy, ARSA). The **X-linked SCID** trials proved gene therapy could cure but revealed **insertional mutagenesis** (LMO-2 activation $\rightarrow$ T-ALL in 5/20 children), prompting the shift to safer **lentiviral vectors**.
- ▶ **Ex vivo gene editing**: *Casgevy* (exagamglogene autotemcel) — CRISPR/Cas9 inactivation of the **BCL11A** erythroid enhancer in autologous CD34⁺ cells, de-repressing **γ -globin/HbF** to treat sickle cell disease and β -thalassaemia ($\approx$ 29/31 patients free of vaso-occlusive crises).
- ▶ **CAR-T cell therapy**: autologous T cells engineered with a **chimeric antigen receptor** (antibody scFv + transmembrane + costimulatory **CD28 or 4-1BB** + CD3 ζ). Approved anti-**CD19** products (Kymriah, Yescarta, Tecartus, Breyanzi) for B-ALL and large-cell/mantle-cell lymphoma, and anti-**BCMA** products (Abecma, Carvykti) for myeloma — >80% complete-response rates in refractory B-ALL. Key toxicities: **cytokine release syndrome** (treat with **tocilizumab** $\pm$ steroids), **ICANS/neurotoxicity** (dexamethasone), B-cell aplasia/hypogammaglobulinaemia, and a boxed-warning risk of secondary T-cell malignancy.
- ▶ **Other cell therapies**: oncolytic virus *talimogene laherparepvec* (melanoma) and dendritic-cell vaccine (sipuleucel-T) for prostate cancer.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Hematopoietic hierarchy**: central Hematopoietic stem cell with a curved *self-renewal* arrow $\rightarrow$ **Multipotent progenitor** branching into **Common lymphoid progenitor** ($\rightarrow$ B cell, T cell, NK cell) and **Common myeloid progenitor** ($\rightarrow$ Granulocyte-monocyte progenitor

→ monocyte/granulocyte; → **Megakaryocyte-erythroid progenitor** → platelets, RBCs).

Annotate decreasing self-renewal and increasing proliferation/differentiation along the axis.

- ▶ **CAR vs native T-cell receptor:** label VH and VL (scFv antigen-binding domain), spacer, transmembrane (TM) domain, costimulatory domain (CD28 or 4-1BB), CD3ζ signalling chain; alongside a native TCR αβ chains recognising antigenic peptide–MHC I through the CD3 complex.

Clinical / Diagnostic significance

- ▶ Determine **HLA type early** in candidates (e.g., all AML patients) to enable timely donor search.
- ▶ **Autologous** transplant/gene therapy avoids GVHD and donor matching but lacks a GVT effect; **allogeneic** offers GVT at the cost of GVHD — the central therapeutic trade-off.
- ▶ Recognise and grade **GVHD** (skin/liver/gut) and monitor for **SOS, TMA, CMV reactivation, and PJP** — each has specific therapy (defibrotide, eculizumab, letermovir/ganciclovir, co-trimoxazole).
- ▶ Gene-edited and CAR-T recipients require **long-term surveillance** — lifelong monitoring for secondary malignancy after CAR-T, and 15-year insertion-site monitoring for integrating-vector HSC products.

High-yield exam pointers

- ▶ Two cardinal stem-cell properties: **self-renewal + differentiation**; achieved by **asymmetric division**.
- ▶ HSC markers: **CD34, CD90 (Thy-1), CD117 (c-Kit), CD133, CD110 (c-Mpl)**.
- ▶ Mobilisation = **G-CSF + plerixafor (CXCR4 antagonist)**; target autologous dose $>2.5 \times 10^6$ **CD34⁺ cells/kg**.
- ▶ HLA-identical sibling probability = $1 - (0.75)^n$; **post-transplant cyclophosphamide** enables **haploidentical** transplant.
- ▶ Conditioning intensity: myeloablative > reduced-intensity (**fludarabine + melphalan**) > nonmyeloablative (**fludarabine + 200 cGy TBI**).
- ▶ Acute GVHD = **skin + liver + gut**; first-line **prednisone**, steroid-refractory **ruxolitinib**. Chronic GVHD steroid-refractory: **ibrutinib/ruxolitinib/belumosudil**.
- ▶ **SOS** → **defibrotide**; **TMA** → **eculizumab**; **CMV** → **letermovir/ganciclovir**.
- ▶ **Casgevy** edits **BCL11A** to raise HbF in sickle cell disease/β-thalassaemia; X-linked SCID trial caused **LMO-2 insertional T-ALL**.
- ▶ CAR-T costimulatory domains = **CD28 or 4-1BB**; CRS treated with **tocilizumab**.

SOURCE & COVERAGE

- ▶ Harrison's Principles of Internal Medicine, 22e — "Hematopoietic Stem Cells" (David T. Scadden, Dan L. Longo); "Hematopoietic Cell Transplantation" (Frederick R. Appelbaum); "Gene and Cell-Based Therapy in Clinical Medicine" (Katherine A. High, Marcela V. Maus).
- ▶ *Coverage note:* The Harrison corpus covers HSC biology, hematopoietic cell transplantation, and gene-/cell-based (CAR-T, gene-editing) therapy in depth. Coverage of **embryonic stem cell, iPSC, and mesenchymal stem cell** therapeutics is limited, as these remain largely investigational; the classification of stem cells by potency given above is standard, universally accepted textbook medicine. No dedicated specialty text or CMDT chapter was specified for this topic.



Steps of practicing evidence-based medicine

Asked in: Paper I May 2019 — RGUHS MD General Medicine

Definition / Introduction — Evidence-based medicine (EBM) is the conscientious, explicit and judicious integration of the **best available external clinical research evidence** with **individual clinical expertise** and the **patient's values and preferences** to make decisions about the care of individual patients. It updates the traditional model of clinical medicine (knowledge + intuition + judgement) by placing far greater emphasis on the *processes* by which clinicians obtain the most up-to-date and relevant research to determine for themselves whether an intervention alters disease course or improves length/quality of life. As described by its founding proponents at *McMaster University* in the early 1990s, EBM is practised as a structured, repeatable cycle of well-defined steps — classically summarised as the "5 A's" (Ask, Acquire, Appraise, Apply, Assess).

The EBM cycle — the five steps ("5 A's")

Step	"A"	Core task	Key tools
1	Ask	Convert the clinical problem into a focused, answerable question	PICO / PICOT framework
2	Acquire	Search the literature/online databases efficiently for the best external evidence	MEDLINE, EMBASE, Cochrane Library, DARE
3	Appraise	Critically appraise the evidence for validity ,	Risk-of-bias checks, AMSTAR2, levels of evidence

Step	“A”	Core task	Key tools
		importance (magnitude) and applicability	
4	Apply	Integrate the appraisal with clinical expertise and the patient’s unique features and preferences	Shared decision-making, NNT/ARR
5	Assess	Evaluate one’s own performance/outcome and record for future use (audit)	Audit, reflective record-keeping

- ▶ Harrison frames the cycle as **four key steps** (formulate the question → search literature/databases → appraise validity & relevance → integrate with the unique patient and their preferences); the widely taught **fifth step** (self-audit / “Assess” / recording for future use) completes the loop. Both framings are reproduced below.

Step 1 — ASK: frame an answerable clinical question

- ▶ Asking a **well-built clinical question** generated from a real patient encounter is arguably the **single most important step** — a sharp question makes searching and appraisal far easier and forces the clinician to define the patient, intervention and outcomes precisely.
- ▶ Use the **PICO** acronym (a fifth element, *Time-frame*, gives **PICOT**):
 - **P** — *Patient / Problem* (e.g., immunocompetent child with cutaneous warts).
 - **I** — *Intervention* (the test, drug or exposure of interest).
 - **C** — *Comparator* (placebo/vehicle or an alternative; optional).
 - **O** — *Outcome* (a clinically important, patient-relevant endpoint).
 - **T** — *Time-frame* over which the outcome is judged.
- ▶ Questions are categorised by domain — **therapy, diagnosis, prognosis, aetiology/harm, and prevention** — because the question type dictates which study design is the “best evidence.”

Step 2 — ACQUIRE: search for the best external evidence

- ▶ Conduct a **predefined, reproducible, explicit search** of the literature and online databases (MEDLINE, EMBASE, the **Cochrane Database of Systematic Reviews**, DARE) rather than relying on memory or a single textbook.
- ▶ Searching the world’s literature and appraising it is time-consuming and demands skills most busy clinicians lack; hence the pragmatic shortcut of seeking a recent, high-quality **systematic review** that has already synthesised the primary studies (the *Cochrane* reviews are the prototype).

- Pre-appraised, pre-synthesised resources (systematic reviews, guidelines, evidence summaries) sit at the top of the practical search strategy.

Step 3 — APPRAISE: critically appraise the evidence

Appraisal asks three questions: **Are the results valid?** **What are the results (importance/magnitude)?** **Will they help my patient (applicability)?** This rests on the **hierarchy of evidence**, where the strength of evidence depends on the *type of question* asked.

Level	Therapy / harm question — best evidence
1a	Systematic review of multiple RCTs with homogeneity
1b	Individual RCT with narrow confidence intervals
1c	“ All-or-none ” effect (e.g., streptomycin for TB meningitis, insulin for diabetes)
2a/2b	Cohort studies (with homogeneity / individual cohort or low-quality RCT)
2c	“ Outcomes ” research (cost–benefit, cost–effectiveness, cost–utility)
3a/3b	Case–control studies
4	Case series (and poor-quality cohort/case–control studies)
5	Expert opinion without explicit appraisal; bench research; logical deduction

- (*Oxford Centre for Evidence-Based Medicine levels.*) For **diagnosis** questions, the best evidence is an **independent, blind comparison** of an appropriate spectrum of consecutive patients against a reference (“gold”) standard; for **rare harms**, cohort/case–control studies, post-marketing surveillance and pharmacovigilance are most useful.
- **Study quality outranks design label**: a well-conducted cohort study can be more reliable than a small, poorly conducted RCT. The best therapeutic evidence comes from large, fully masked RCTs with **concealed allocation** and **intention-to-treat** analysis.
- **Systematic reviews & meta-analysis** are regarded by many as the apex of the hierarchy because they comprehensively and reproducibly summarise the evidence; meta-analysis can reveal a true benefit that individually underpowered trials missed (classically, the benefit of **streptokinase/thrombolysis in acute MI** was evident by cumulative meta-analysis a decade before large trials/guidelines confirmed it). They are *not* infallible — they cannot remedy deficient primary data and should include **unpublished trials** to avoid **publication bias**; tools such as **AMSTAR2** appraise their quality.

Tools of appraisal — quantifying test performance and treatment effect

- ▶ **Diagnostic test metrics** — *sensitivity* (detection of diseased), *specificity* (detection of non-diseased), and ROC curves illustrating their trade-off.
- ▶ **Bayes' rule / post-test probability** — the post-test probability of disease is derived from the **pre-test probability** (prevalence/clinical context), **sensitivity** and **specificity**, summarised by the **likelihood ratio (LR)**:
 - $\text{LR positive} = \text{sensitivity} / (1 - \text{specificity})$; $\text{LR negative} = (1 - \text{sensitivity}) / \text{specificity}$.
 - An $\text{LR+} > 10$ markedly raises (rules *in*) the probability of disease; a very low LR- rules it *out*. The **Bayes nomogram** (Fig. 4-2) connects pre-test probability + LR to read off post-test probability.
- ▶ **Treatment-effect metrics** (essential for the “Apply” step):
 - **Absolute Risk Reduction (ARR)** = control event rate – treatment event rate.
 - **Relative Risk Reduction (RRR)** = $\text{ARR} \div \text{control event rate}$.
 - **Number Needed to Treat (NNT)** = $1 / \text{ARR}$ — e.g., a therapy cutting 5-year mortality from 12% → 8% gives $\text{ARR} = 4\%$ and $\text{NNT} = 25$. The same relative benefit applied to a lower-risk group (6% → 4%) gives $\text{ARR} 2\%$ and $\text{NNT} 50$ — illustrating that absolute benefit falls as baseline risk falls.
 - **Odds ratio / relative risk** are the usual summary measures of relative benefit; clinicians must always also examine the *absolute* benefit and harms.

Step 4 — APPLY: integrate evidence with expertise and patient values

- ▶ Integrate the appraised evidence with the **clinician's own expertise** and the **individual patient's circumstances, comorbidities and preferences** — the “average” trial patient may not resemble the patient in front of you (external validity/generalisability).
- ▶ Ask: *Can these results be applied to my patient? Were all clinically important outcomes considered? Do the benefits outweigh the harms and costs?*
- ▶ **Clinical practice guidelines** (Institute of Medicine 1990: “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances”) operationalise EBM but are meant to **assist, not dictate** — guideline-level evidence alone is never sufficient for an individual decision (notably, <15% of cardiovascular guideline recommendations rest on the highest level of trial evidence). This is the locus of **shared decision-making**.

Step 5 — ASSESS: audit and record

- ▶ **Evaluate your own performance** in executing steps 1–4 and the patient's outcome; **record the information for future use** so the appraised answer can be reused efficiently. This closes the loop and underpins clinical **audit and quality improvement** — guideline-derived “best practices”

become **quality indicators** (e.g., proportion of acute-MI patients given aspirin on admission; proportion of HFrEF patients on an ACE inhibitor).

Limitations and threats to EBM (examiner favourites)

- ▶ **Limitations:** publication bias; poor methodological quality of many trials; lack of evidence in many areas; reliance on **summary (group) statistics** that mask individual responses.
- ▶ **Threats:** data-driven and sponsor-funded systematic reviews, selective outcome reporting, non-publication of negative trials, “spin,” ghost-writing.
- ▶ EBM is an **ideal, not a finished tool**: most clinical problems will never be tested in an RCT, so excellent clinical reasoning plus respect for patient preferences remain paramount.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Evidence pyramid (hierarchy of evidence):** a triangle, broad base to narrow apex labelled bottom-to-top — *In-vitro/bench research* → *Animal research* → *Ideas/editorials/expert opinion* → *Case reports* → *Case series* → *Case-control studies* → *Cohort studies* → *Randomised controlled trials* → *Systematic reviews & meta-analyses (apex)*.
- ▶ **The EBM cycle (5 A's):** a circular loop of five boxes with arrows returning to the start — *Ask (PICO)* → *Acquire (search)* → *Appraise (validity, importance, applicability)* → *Apply (integrate with expertise + patient values)* → *Assess (audit/record)* → *back to Ask*.

Clinical / Diagnostic significance

- ▶ Provides a **reproducible, teachable framework** for translating a bedside problem into an evidence-supported decision, reducing reliance on anecdote and cognitive bias (anchoring, premature closure).
- ▶ Quantitative outputs (LR, post-test probability, NNT/ARR) let clinicians **calibrate testing and treatment thresholds** to an individual's baseline risk and to weigh benefit against harm and cost.
- ▶ Anchors **guideline development, clinical audit and quality indicators**, and frames **shared decision-making** by making the strength and limits of evidence explicit to the patient.

High-yield exam pointers

- ▶ EBM = **best external evidence + clinical expertise + patient values/preferences**; originated at *McMaster University*, early 1990s.
- ▶ Remember the 5 A's: **Ask** → **Acquire** → **Appraise** → **Apply** → **Assess** (Harrison lists the first four; the fifth is self-audit/recording).
- ▶ Step 1 question structured as **PICO(T)**; categorise by therapy/diagnosis/prognosis/harm/prevention.
- ▶ Hierarchy/best design by question: **therapy** → **RCT**; **diagnosis** → **cross-sectional study vs gold standard**; **prognosis** → **cohort**; **rare harm** → **case-control / pharmacovigilance**.

- ▶ **Systematic review/meta-analysis** = **apex**; *Cochrane* is the prototype; beware **publication bias** (include unpublished/negative trials); appraise with **AMSTAR2**.
- ▶ **NNT** = $1/ARR$; **LR+** = $\text{sensitivity}/(1 - \text{specificity})$, **LR+** >10 strongly rules in disease; use the **Bayes nomogram** for post-test probability.
- ▶ Quality can trump design: a good cohort study may beat a poor RCT; demand **concealed allocation + intention-to-treat**.
- ▶ Guidelines (IOM 1990 definition) **assist, not dictate**; <15% of CV recommendations rest on top-level evidence — individualise.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Decision-Making in Clinical Medicine” (the four key EBM steps; sources of evidence — clinical trials, registries, RCTs, meta-analysis; Bayes' rule, sensitivity/specificity, likelihood ratios, post-test probability; ARR/NNT; clinical practice guidelines and quality indicators).
- ▶ **Rook's Textbook of Dermatology, 10e** — “Principles of Evidence-based Dermatology” (used for the general EBM framework: the explicit **five-step cycle**, **PICO/PICOT**, the **hierarchy/levels of evidence** (Oxford CEBM), **NNT**, **AMSTAR2**, and the limitations/threats to EBM — these principles are generic to internal medicine).
- ▶ **Coverage note:** The RGUHS-suggested Harrison chapter covers the **content** of EBM richly but presents the cycle as **four steps** rather than the canonical **five-step** “5 A's”; the five-step structure and PICO/levels-of-evidence detail were grounded in Rook's general EBM chapter. The “5 A's” labelling (Ask/Acquire/Appraise/Apply/Assess) and **GRADE-style certainty rating** are universally accepted standard EBM terminology used here to organise the answer.



Structure of Internal Capsule and its blood supply

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — The **internal capsule** is a thick, compact, V-shaped (boomerang-shaped) sheet of **projection white matter** that carries virtually all the afferent (thalamocortical) and efferent (corticofugal) fibres travelling between the cerebral cortex and the brainstem/spinal cord. On a horizontal section it lies wedged between the **caudate nucleus and thalamus medially** and the **lentiform nucleus (putamen + globus pallidus) laterally**, with its apex (genu) pointing medially. Superiorly it fans out into the **corona radiata**; inferiorly it condenses into the **crus cerebri (cerebral peduncle)**. Because an enormous volume of motor and sensory traffic is funnelled through a small territory fed by tiny perforating end-arteries, a lesion barely a few millimetres across (a *lacune*) can produce a dense contralateral hemiplegia — making this anatomy of major clinical importance.

Gross anatomy, relations and subdivisions

- ▶ **Course:** continuous above with the **corona radiata** (subcortical white matter) and below with the **crus cerebri**; medially it borders the diencephalon, laterally the basal ganglia.
- ▶ On a horizontal (axial) section the capsule has five named parts; on a sagittal view the retrolenticular and sublenticular components are best appreciated:
 - **Anterior limb** — lies between the **head of the caudate** (medially) and the **lentiform nucleus** (laterally).
 - **Genu** — the bend/apex; relates to the lateral wall of the third ventricle; abuts the ICA-derived perforators.
 - **Posterior limb** — lies between the **thalamus** (medially) and the **lentiform nucleus** (laterally); the largest and clinically most important segment.
 - **Retrolenticular part** — fibres lying *behind* the lentiform nucleus.
 - **Sublenticular part** — fibres passing *beneath* the lentiform nucleus toward the temporal lobe.

Fibre content of each part

Part	Principal fibre tracts	Functional traffic
Anterior limb	Anterior (frontal) thalamic radiation; frontopontine fibres	Prefrontal–dorsomedial/anterior thalamic loops; frontal → pontine relay
Genu	Corticobulbar (corticonuclear) fibres; corticopontine fibres to facial & hypoglossal nuclei	Supranuclear control of bulbar/cranial-nerve motor nuclei
Posterior limb	Corticospinal (pyramidal) fibres, somatotopically arranged; superior thalamic radiation (sensory); corticorubral, corticoreticular fibres	Voluntary limb movement; thalamocortical somatosensory relay
Retrolenticular part	Optic radiation (geniculocalcarine fibres); posterior thalamic radiation	Vision (LGB → calcarine cortex)
Sublenticular part	Auditory (acoustic) radiation ; temporopontine fibres	Hearing (MGB → Heschl's gyrus)

- ▶ *Brazis* confirms the corpus-derived correlates: **corticospinal fibres run in the posterior limb**, the **corticobulbar/corticopontine fibres to facial and hypoglossal nuclei are concentrated in the genu**, the **superior thalamic radiation** (light-touch/pin sensation) travels in the posterior limb, and the **geniculocalcarine (optic) fibres lie in the retrolenticular white matter**.

Blood supply

The capsule is perfused almost entirely by small, deep **perforating (penetrating) end-arteries** with little collateral overlap — hence its vulnerability to lacunar infarction in hypertension and small-vessel disease.

Part of capsule	Arterial supply (parent vessel)
Anterior limb	Medial lenticulostriate branches / recurrent artery of Heubner from the A1 (precommunal) segment of the ACA; deep A1 perforators
Genu	Penetrating lenticulostriate perforators (single-vessel occlusion → <i>capsular genu syndrome</i>); classically also direct small branches of the internal carotid artery
Posterior limb	Superior part — lateral lenticulostriate arteries from the M1 segment of the MCA; inferior/main part — anterior choroidal artery (branch of the ICA)
Retrolenticular part	Anterior choroidal artery (with contribution from the posterior choroidal artery of the PCA)
Sublenticular part	Anterior choroidal artery

- ▶ **Recurrent artery of Heubner (medial striate artery):** arises from the lateral aspect of the ACA (A1/proximal A2) and supplies the **anteroinferior limb of the internal capsule, anterior putamen and caudate, and the tip of the outer globus pallidus**. (Harrison: A1 deep penetrators supply the anterior limb, anterior perforated substance, amygdala, anterior hypothalamus and inferior head of caudate.)
- ▶ **Lateral lenticulostriate arteries:** penetrating branches of the proximal MCA (M1) supply the putamen, outer globus pallidus, posterior limb of the internal capsule, adjacent corona radiata and most of the caudate; *Brazis* adds that they feed the superior portion of both the anterior and posterior limbs.
- ▶ **Anterior choroidal artery (AChA):** arises from the internal carotid artery distal to the posterior communicating artery; supplies the posterior limb of the internal capsule, the retrolenticular white matter (through which the geniculocalcarine fibres pass), the optic tract, lateral geniculate body, midbrain and choroid plexus of the temporal horn. It is vulnerable to iatrogenic occlusion during clipping of ICA aneurysms.

Somatotopic organisation (high-yield)

- ▶ Corticospinal fibres in the **posterior limb** are arranged **antero-posteriorly: face → arm → trunk → leg**.
- ▶ *Harrison*: ischaemia at the **genu** causes **facial weakness first**, then arm, then leg, as the infarct extends **posteriorly** within the capsule.

- ▶ *Brazis*: at superior capsular levels the **face/bulbar muscles** are affected by lesions of the **genu** or **anterior posterior limb**, whereas **more posterior lesions** cause **arm and leg weakness**.
- ▶ A “**parathalamic rim**” of the posterior limb carries the sensory tracts; small lacunes that spare this rim produce a **pure motor** deficit.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Horizontal (axial) section of internal capsule** (lentiform nucleus, caudate head, thalamus drawn around a V-shaped capsule). Label: *Anterior limb, Genu, Posterior limb, Retrolenticular part, Sublenticular part; Head of caudate nucleus, Putamen, Globus pallidus (lentiform), Thalamus; fibre content — frontopontine/anterior thalamic radiation (anterior limb), corticobulbar (genu), corticospinal + superior thalamic radiation (posterior limb), optic radiation (retrolenticular), auditory radiation (sublenticular); somatotopy face→arm→leg in posterior limb.*
- ▶ **Diagram 2 — Blood supply / coronal vascular territory**. Label: *Anterior limb → recurrent artery of Heubner (ACA-A1) + medial lenticulostriates; Genu → lenticulostriates/ICA branches; Posterior limb (superior) → lateral lenticulostriates (MCA-M1); Posterior limb (inferior) + retrolenticular → anterior choroidal artery (ICA).*

Clinical / Diagnostic significance

- ▶ **Pure motor hemiparesis** — the commonest lacunar syndrome; infarct in the **posterior limb of the internal capsule** (or corona radiata/basis pontis) → contralateral face-arm-leg weakness with little/no sensory loss (*Harrison, Brazis*).
- ▶ **Ataxic hemiparesis and dysarthria-clumsy hand syndrome** — lacunes of the **posterior limb** or **genu/anterior limb** (or basis pontis) respectively.
- ▶ **Sensorimotor stroke** — posteroventral thalamus + adjacent **posterior limb**.
- ▶ **Capsular genu syndrome** — contralateral facial and lingual paresis with dysarthria, mastication-palatal-pharyngeal weakness; bilateral genu lesions may cause cognitive/behavioural change.
- ▶ **Capsular warning syndrome** — clustering TIAs affecting face, arm and leg from threatened occlusion of a **single lenticulostriate artery**, heralding a completed capsular infarct.
- ▶ **Anterior choroidal artery syndrome (Foix)** — the classic triad of contralateral **hemiplegia** (posterior-limb corticospinal interruption), **hemianaesthesia** (superior thalamic radiation), and **homonymous hemianopia** (optic tract/LGB/optic radiation), often with macular/horizontal-meridian sparing.
- ▶ **Artery of Heubner infarction** — contralateral **face and arm weakness without sensory loss** (anterior-limb + anterior putamen).

- ▶ **Investigation:** MRI with diffusion-weighted imaging (DWI) is the most sensitive for acute lacunes; perforators are too small to be seen on CT/CT-angiography. Hypertension and age are the principal risk factors (lipohyalinosis/microatheroma of penetrators).

High-yield exam pointers

- ▶ Internal capsule = compact **projection fibres**, continuous above with **corona radiata**, below with **crus cerebri**; five parts — anterior limb, **genu**, posterior limb, retrolenticular, sublenticular.
- ▶ Corticospinal fibres → posterior limb; corticobulbar → genu; optic radiation → retrolenticular; auditory radiation → sublenticular.
- ▶ Somatotopy of posterior limb: face (anterior) → arm → leg (posterior).
- ▶ Blood supply summary: Anterior limb = recurrent artery of Heubner (ACA); Posterior limb = lateral lenticulostriates (MCA) + anterior choroidal artery (ICA); Retrolenticular/sublenticular = anterior choroidal artery.
- ▶ A tiny lacune in the posterior limb can cause a **dense hemiplegia** — disproportionate deficit for lesion size.
- ▶ **Pure motor hemiparesis** = the signature capsular lacunar syndrome; lenticulostriate occlusion.
- ▶ **Anterior choroidal artery triad** = **hemiplegia** + **hemianaesthesia** + **hemianopia**; high risk of iatrogenic occlusion during ICA aneurysm clipping.
- ▶ These are **perforating end-arteries** with poor collaterals → **hypertension/age** drive lacunar disease; DWI-MRI is the key test.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Introduction to Cerebrovascular Diseases” (lenticulostriate territory; ACA-A1, MCA-M1 and anterior choroidal artery supply of the internal-capsule limbs) and “Ischemic Stroke” (lacunar/small-vessel syndromes; posterior-limb and genu correlations).
- ▶ **Brazis, Masdeu & Biller — Localization in Clinical Neurology**** — “Vascular Syndromes of the Forebrain, Brainstem, and Cerebellum” (recurrent artery of Heubner, anterior choroidal artery, lenticulostriate territories, capsular genu and anterior-choroidal syndromes, lacunar-infarction table) and “Localization of Lesions Affecting the Cerebral Hemispheres” (capsular somatotopy, parathalamic sensory rim, corticobulbar/corticospinal fibre course).

Coverage note: The corpus (Harrison + Brazis) covers the **blood supply, fibre correlates and lacunar/clinical syndromes** in depth and is the primary grounding here. The fine **descriptive neuroanatomy of fibre content** (anterior thalamic radiation, frontopontine, auditory radiation in the sublenticular part) is given as **universally accepted standard neuroanatomy** (Gray's/Snell), consistent with and partly confirmed by the Brazis text; no specifics have been fabricated.



Temperature regulation

Asked in: Paper I Dec 2023 — RGUHS MD General Medicine

Definition / Introduction — Thermoregulation is the homeostatic process by which the body maintains its **core temperature** within a narrow physiological range (36.5–37.5°C / 97.7–99.5°F) despite wide swings in environmental temperature and metabolic activity. It is governed by the **hypothalamus**, which acts as a biological thermostat with a defined “**set point**,” balancing **heat production** against **heat loss**. A regulated upward shift of this set point produces **fever**, whereas failure of heat dissipation with an *unchanged* set point produces **hyperthermia** — a distinction that is clinically and therapeutically pivotal.

Normal body temperature, variation and measurement

- ▶ **Normal core range:** 36.5–37.5°C; mean oral temperature 36.6°C (95% CI 35.7–37.3°C) in a study of >35,000 adults. A temperature >37.7°C (>99.9°F) — the 99th percentile for healthy individuals — defines **fever**.
- ▶ **Diurnal rhythm:** lowest at 8 a.m., highest at 4 p.m.; also lower in summer, higher in winter.
- ▶ **Physiological modifiers:** temperature falls ~0.02°C per 10-year increase in age; African-American women run 0.052°C **higher** than white men; cancer raises baseline ~0.02°C, hypothyroidism lowers it ~0.01°C.
- ▶ **Menstrual cycle:** a.m. temperature is low for the 2 weeks before ovulation, then rises ~0.6°C (1°F) at **ovulation** and stays elevated through the luteal phase until menses.
- ▶ **Site corrections (high-yield):**

Site	Relationship to oral / core
Oral	Reference; lower if mouth-breathing (tachypnoea)
Rectal	~0.4°C (0.7°F) higher than oral
Lower oesophageal	Closely reflects true core temperature
Tympanic membrane (unadjusted mode)	~0.8°C (1.6°F) lower than rectal; more variable

Hypothalamic control and the “set-point” model

- ▶ The **preoptic anterior hypothalamus** and **posterior hypothalamus** integrate two afferent inputs: (1) **peripheral** signals from cutaneous **warmth/cold receptors** via peripheral nerves, and (2) **central** signals from the **temperature of blood** bathing the hypothalamic neurons.
- ▶ The **thermoregulatory centre** compares these inputs against the **set point** and drives efferent responses to keep blood temperature matched to that setting — analogous to a **home thermostat**.

- ▶ In a thermoneutral environment, basal **metabolism produces more heat than is needed**; the hypothalamus continuously balances this excess heat production (muscle, liver) against dissipation (skin, lungs).
- ▶ A standing concept: a natural “**thermal ceiling**” (~106°F) appears to be defended by central **antipyretic neuropeptides**, so most infective fevers rarely exceed this without CNS involvement.

Heat balance — production vs loss (effector mechanisms)

- ▶ **Heat-gain / conservation effectors** (triggered when actual temperature is *below* set point, i.e., the chill/rigor phase of rising fever):
 - **Cutaneous vasoconstriction** — vasomotor-centre neurons shunt blood from skin of hands/feet to the core, reducing radiant loss; the patient *feels cold*.
 - **Shivering thermogenesis** — increased heat production from skeletal muscle.
 - **Non-shivering thermogenesis** — increased metabolic heat from the **liver** (and, in standard physiology, brown adipose tissue — see Coverage note).
 - **Behavioural** — putting on clothing/bedding to reduce heat loss.
- ▶ **Heat-loss effectors** (triggered when actual temperature is *above* set point — e.g., when the set point is reset downward by antipyretics, the defervescence/flush phase):
 - **Cutaneous vasodilation and sweating** (evaporative loss).
 - **Behavioural** — removal of clothing.
- ▶ During fever, body temperature typically rises by 1–2°C; these conservation and production processes continue until blood temperature reaches the new febrile “thermostat setting,” then are held there by normal afebrile balance mechanisms.

Fever versus hyperthermia (must distinguish)

Feature	Fever	Hyperthermia
Hypothalamic set point	Raised (e.g., 37→39°C)	Unchanged / normal
Mechanism	Pyrogen-driven; regulated rise	Uncontrolled rise exceeding heat-loss capacity
Pyrogenic molecules	Present (cytokines, PGE2)	Absent
Typical cause	Infection, inflammation, malignancy	Exogenous heat exposure / excess endogenous heat production (exertion, drugs blocking sweating, heat stroke)
Skin	May be cold (vasoconstriction)	Hot but characteristically dry (in heat stroke / anhidrotic drugs)
Response to antipyretics	Responds (aspirin/acetaminophen lower it)	Does NOT respond

Feature	Fever	Hyperthermia
Urgency	Usually benign, self-limited	Can be rapidly fatal

- ▶ **Hyperpyrexia:** fever $>41.5^{\circ}\text{C}$ ($>106.7^{\circ}\text{F}$) — seen in severe infection and especially CNS haemorrhage.
- ▶ **Hypothalamic fever:** rare regulated set-point elevation from local **trauma, haemorrhage, tumour, or intrinsic hypothalamic malfunction** — but most patients with hypothalamic damage are paradoxically **subnormal**, not supranormal.

Pathogenesis of fever — resetting the set point upward

- ▶ **Exogenous pyrogens:** microbial products/toxins. Classic example is **lipopolysaccharide (endotoxin)** of gram-negative bacteria (fever at 2–3 ng/kg IV in humans). Gram-positive toxins act as **superantigens** (e.g., TSST-1, staphylococcal enterotoxins, streptococcal pyrogenic exotoxins; fever at 1–10 µg/kg).
- ▶ **Pyrogenic cytokines** (formerly “endogenous pyrogens”): small proteins (10–20 kDa) — IL-1, IL-6, TNF, interferons, ciliary neurotropic factor — released from **monocytes/macrophages and endothelial cells**. IL-1 and TNF produce fever at 10–100 ng/kg; IL-6 requires 1–10 µg/kg. Fever can also arise *without* infection (pericarditis, trauma, stroke, immunisation).
- ▶ **Final common pathway** — PGE₂: cytokines (and direct **Toll-like receptor/IL-1 receptor** activation) act on the **hypothalamic endothelium** near the **circumventricular organ — organum vasculosum of the lamina terminalis** — raising **prostaglandin E₂ (PGE₂)**. PGE₂ (chiefly via the **EP-3 receptor**, essential for fever) stimulates glial release of **cyclic AMP**, which acts as the neurotransmitter that **elevates the thermoregulatory set point**.
- ▶ Peripheral PGE₂ induced in tissues accounts for the **myalgias and arthralgias** of fever.

Antipyresis — restoring the set point downward

- ▶ Fever is reduced by lowering the elevated set point, achieved by **reducing hypothalamic PGE₂**.
- ▶ **Cyclooxygenase (COX) inhibitors** are the principal antipyretics; potency correlates with inhibition of **brain COX**. **Aspirin and acetaminophen** are equally effective; NSAIDs (**ibuprofen**) and COX-2 inhibitors are also excellent antipyretics.
- ▶ **Acetaminophen** is a poor peripheral COX inhibitor (minimal anti-inflammatory action) but in the brain is oxidised by **cytochrome P450** to an active COX-inhibiting form (with proposed **COX-3 inhibition**); it is the **preferred** antipyretic given the platelet/GI effects of aspirin and NSAIDs.
- ▶ **In children**, use **acetaminophen or ibuprofen** — aspirin risks **Reye syndrome** with certain viral infections.
- ▶ **Glucocorticoids** act at two levels: inhibit **phospholipase A₂** (less arachidonic-acid substrate for PGE₂) and block **transcription of pyrogenic cytokine mRNA**.

- ▶ Chronic high-dose antipyretics do **not** lower *normal* core temperature — confirming PGE2 has no role in normal thermoregulation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — “Chronology of fever induction”** (Harrison Fig 20-1): vertical flow with labels — *Infection, microbial toxins, mediators of inflammation, immune reactions* → *Monocytes/macrophages, endothelial cells* → *Pyrogenic cytokines (IL-1, IL-6, TNF, IFN)* → *Circulation* → *Hypothalamic endothelium* → *PGE2* → *cyclic AMP* → *Elevated thermoregulatory set point* → *Heat conservation, heat production* → *Fever*.
- ▶ **Diagram 2 — Hypothalamic “thermostat” balance:** central box *Hypothalamic set point* with afferents labelled *Skin warmth/cold receptors* and *Temperature of blood*; left arm *Heat production / conservation* (labels: *vasoconstriction, shivering, non-shivering thermogenesis, behaviour*); right arm *Heat loss* (labels: *vasodilation, sweating, behaviour*). Show set point shifting up = **fever**, set point normal but load > loss = **hyperthermia**.

Clinical / Diagnostic significance

- ▶ **Therapeutic crux:** confirm fever vs hyperthermia — hyperthermia (heat stroke, neuroleptic malignant/serotonin syndrome, malignant hyperthermia) is an emergency, does **not** respond to antipyretics, and needs **physical/external cooling** rather than COX inhibitors.
- ▶ **Metabolic cost:** every 1°C above 37°C raises **oxygen consumption** by ~13% — hence the rationale to treat fever in cardiac, pulmonary or neurologically compromised patients.
- ▶ **Temperature–pulse dissociation (relative bradycardia):** typhoid, brucellosis, leptospirosis, drug fever, factitious fever.
- ▶ **Blunted febrile response** (may have serious infection *without* fever): neonates, elderly, chronic liver/renal failure, and patients on **glucocorticoids or anticytokine therapy** — septic shock may even cause **hypothermia**.
- ▶ **Investigations:** CBC with manual differential (band forms, toxic granulations, Döhle bodies suggest bacterial infection), CRP and ESR for occult inflammation; circulating cytokine levels are not clinically useful.

High-yield exam pointers

- ▶ Control centre = **hypothalamus**: preoptic anterior (heat-loss) + posterior hypothalamus integrating **skin receptor** and **blood-temperature** inputs against a **set point**.
- ▶ Normal core 36.5–37.5°C; fever >37.7°C; hyperpyrexia >41.5°C.
- ▶ Rectal +0.4°C over oral; tympanic (unadjusted) –0.8°C below rectal; oesophageal ≈ core.
- ▶ Fever = **raised set point**; hyperthermia = **normal set point, failed heat loss** — only fever responds to antipyretics.

- ▶ Final mediator of fever = **PGE2** acting via **EP-3 receptor** near the **OVL**T; COX inhibitors are antipyretic.
- ▶ Rising fever = **vasoconstriction + shivering** (feels cold); defervescence = **vasodilation + sweating** (flush).
- ▶ **Acetaminophen preferred**; aspirin avoided in children (**Reye syndrome**); glucocorticoids inhibit **PLA2** + cytokine transcription.
- ▶ **+13% O₂ consumption per 1°C**; relative bradycardia in typhoid/brucellosis/leptospirosis.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 20 "Fever"** (Dinarello & Surana): thermoregulation, hypothalamic set-point, normal temperatures and measurement, fever vs hyperthermia, pyrogen/cytokine/PGE2 pathogenesis, and antipyretic pharmacology.

Coverage note (gap flagged): Ch 20 is fever-centric; *pure thermoregulatory physiology* is covered only insofar as it underlies fever. The four physical mechanisms of heat exchange (**radiation, conduction, convection, evaporation**) and **brown adipose tissue** as the dedicated organ of non-shivering thermogenesis are universally accepted standard physiology but are **not detailed in Ch 20** (which cites skin/lung dissipation and hepatic non-shivering thermogenesis) — included here only as standard textbook physiology. Detailed hyperthermia syndromes and heat-stroke management belong to Harrison Ch 478 (referenced by Ch 20 but not provided for this answer).



Teratogenesis: Mechanism, Risk Factors and Prevention

Asked in: Paper I Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — A **teratogen** is any agent (drug, chemical, physical factor, infectious organism or maternal metabolic state) that, acting during embryonic or fetal development, causes a permanent structural or functional abnormality in the conceptus. **Teratogenesis** is the process by which such abnormal development is initiated; the four classic manifestations are **death (abortion/stillbirth), structural malformation, intrauterine growth restriction (IUGR) and functional/behavioural deficit**. Only ~2–3% of major congenital anomalies are attributable to recognised drug/chemical teratogens, yet these are among the most *preventable* causes of birth defects, making preconception counselling a core internal-medicine responsibility for women of reproductive age.

Wilson's principles and the critical periods of development

The internist must grasp *when, to whom* and *how much* exposure produces harm — encapsulated in Wilson's six principles of teratology:

- ▶ **Genotype-dependence** — susceptibility depends on the genotype of the conceptus and how it interacts with the environment (e.g., slow vs fast hydroxylators, *MTHFR* polymorphisms).
- ▶ **Timing (developmental stage)** — susceptibility varies sharply with the stage of development at exposure (see critical periods below).
- ▶ **Mechanism-specific action** — each agent acts through a specific pathogenetic mechanism on developing cells/tissues.
- ▶ **Access depends on the agent** — manifestation requires the agent (or its metabolite) to reach the conceptus; this is governed by maternal absorption/metabolism and placental transfer (favoured by low molecular weight, lipid solubility, non-ionisation, low protein binding).
- ▶ **Four end-points** — the manifestations are *death, malformation, growth retardation and functional deficit*.
- ▶ **Dose-response** — severity and frequency rise with dose, from a *no-effect threshold* up to a wholly lethal level.

Critical periods (timing of exposure):

Stage	Timing (post-conception)	Dominant effect
Pre-implantation / blastogenesis	0–2 weeks	“All-or-none” — embryonic death and resorption, <i>or</i> complete recovery; structural defects uncommon
Embryonic period (organogenesis)	3–8 weeks	Maximum vulnerability to major structural malformations — organ-specific defects depending on what is forming
Fetal period	9 weeks–term	Functional deficits, growth restriction, minor anomalies (CNS, palate, teeth, external genitalia remain vulnerable)

This is why poor periconceptional glycaemic control in diabetes acts during the **critical first 5–8 weeks of embryonic growth**, increasing spontaneous abortion and congenital malformation, and why cytotoxic chemotherapy is *virtually never* given in the first trimester.

Mechanisms of teratogenesis

Teratogens converge on a limited number of cellular/molecular pathways:

- ▶ **Folate antagonism / impaired one-carbon metabolism** — antifolate and antiepileptic drugs (methotrexate, valproate, carbamazepine, phenytoin, trimethoprim) impair DNA synthesis and neural-tube closure → neural tube defects (NTDs) and orofacial clefts.
- ▶ **Disruption of the morphogen/retinoic-acid signalling pathway** — retinoids (isotretinoin) deregulate neural-crest migration → craniofacial, cardiac, thymic and CNS defects.

- ▶ **Neural-crest cell disruption** — impaired migration/apoptosis of crest cells underlies many craniofacial and conotruncal cardiac malformations (e.g., retinoids, alcohol).
- ▶ **Vascular disruption / hypoxia–ischaemia** — vasoconstriction or thrombosis interrupts blood supply to developing structures (limb-reduction and bowel-atresia patterns; cocaine, misoprostol).
- ▶ **Oxidative stress and free-radical injury** — reactive intermediates (e.g., of phenytoin, alcohol) damage embryonic macromolecules.
- ▶ **Receptor- or enzyme-mediated and endocrine disruption** — ACE-inhibitor/ARB blockade of the fetal renin–angiotensin system → renal tubular dysgenesis and oligohydramnios; androgens → virilisation; antithyroid drugs → fetal goitre/aplasia cutis.
- ▶ **Inhibition of cell proliferation / programmed cell death and impaired DNA synthesis** — cytotoxic chemotherapy, ionizing radiation.
- ▶ **Direct cytotoxic and tissue-tropic effects** — tetracycline chelates calcium in mineralising tissues (teeth, bone); aminoglycosides are cochleo-vestibulotoxic; intrauterine infection (e.g., rubella, CMV, Zika) directly destroys fetal tissue.

Major teratogenic agents and their characteristic effects

Agent	Characteristic effect on conceptus
ACE inhibitors / ARBs	Renal tubular dysgenesis, oligohydramnios, calvarial hypoplasia, IUGR, stillbirth and congenital anomalies — <i>contraindicated</i> in pregnancy
Warfarin	Fetal warfarin syndrome — <i>chondrodysplasia (chondromalacia) punctata</i> , nasal hypoplasia, stippled epiphyses; CNS injury and neonatal bleeding; avoid in 1st trimester (used only for mechanical valves; bridge to heparin at 36 weeks)
Valproate / other antiseizure drugs	NTDs (spina bifida), orofacial clefts, neurodevelopmental impairment — <i>discontinue before conception</i> ; prefer lamotrigine/levetiracetam
Phenytoin	<i>Fetal hydantoin syndrome</i> — digital/nail hypoplasia, facial dysmorphism, growth/cognitive deficit
Methimazole / carbimazole	<i>Aplasia cutis</i> , choanal/oesophageal atresia (crosses placenta more than PTU)
Isotretinoin / systemic retinoids	Retinoic-acid embryopathy — CNS, craniofacial (ear), cardiac and thymic defects; strict pregnancy-prevention programme
Methotrexate / aminopterin	Cranial dysostosis, limb defects, IUGR (aminopterin syndrome)
Lithium	Cardiac defects, classically <i>Ebstein's anomaly</i>

Agent	Characteristic effect on conceptus
Tetracyclines	Deciduous-tooth discoloration and bone-growth inhibition (2nd–3rd trimester)
Aminoglycosides (streptomycin)	Eighth-nerve (cochleo-vestibular) ototoxicity, may be irreversible
Thalidomide	Limb-reduction defects — <i>phocomelia/amelia</i> (historical prototype teratogen)
Diethylstilbestrol (prenatal)	Vaginal clear-cell adenocarcinoma and genital-tract anomalies in exposed daughters
Alcohol	Fetal alcohol spectrum disorder — IUGR, microcephaly, characteristic facies, intellectual disability
Cytotoxic chemotherapy / ionizing radiation	First-trimester exposure → abortion and malformation; both generally avoided
Infections (TORCH)	<i>Rubella</i> (cataract, cardiac, deafness), <i>CMV</i> (microcephaly, intracranial calcification, chorioretinitis), <i>Zika</i> (severe microcephaly, CNS malformation, fetal death), toxoplasma, syphilis, VZV, HSV

Risk factors for teratogenesis

- ▶ **Drug/medication exposure** — particularly the high-risk drugs above; polypharmacy and self-medication in early, often unrecognised, pregnancy.
- ▶ **Maternal disease/metabolic state** — *pregestational diabetes* with poor periconceptional control, *obesity*, untreated maternal PKU, and thyroid disease all raise the malformation rate.
- ▶ **Maternal infection** — primary first-trimester rubella, CMV, Zika, toxoplasmosis, syphilis.
- ▶ **Physical agents** — therapeutic/diagnostic *ionizing radiation* and sustained maternal *hyperthermia*.
- ▶ **Environmental/recreational toxins** — alcohol, tobacco, organic mercury (Minamata), lead, certain solvents.
- ▶ **Nutritional deficiency** — periconceptional *folate deficiency* (and antifolate drug use) — the lower the maternal folate, the greater the NTD risk.
- ▶ **Genetic susceptibility of the conceptus and timing/dose of exposure** (per Wilson's principles).
- ▶ **Advanced maternal age** — chiefly increases chromosomal (aneuploidy) risk rather than environmental teratogenesis.

Prevention and preconception counselling

Prevention is overwhelmingly *preconceptional and primary*:

- ▶ **Periconceptional folic acid** — 0.4 mg/day before and at conception (continued through the first 12 weeks) reduces NTDs (anencephaly, meningomyelocele, encephalocele, spina bifida) by ~80% and also lowers cleft-palate/lip risk; **high-risk women** (previous NTD-affected fetus, diabetes, sickle-cell disease, on antiepileptic drugs) need 4–5 mg/day. Population-level **food fortification** addresses poor supplement compliance.
- ▶ **Preconception optimisation of maternal disease** — tight glycaemic control before conception in diabetes; review and *switch teratogenic drugs* (stop ACE-I/ARB, valproate, warfarin, isotretinoin, statins; substitute pregnancy-compatible agents) ideally before conception.
- ▶ **Rational, lowest-effective-dose prescribing** in any woman of reproductive potential; treat the mother adequately (untreated maternal disease may itself harm the fetus).
- ▶ **Pregnancy-prevention programmes** for proven teratogens — e.g., the regulated isotretinoin programme: two negative pregnancy tests before initiation and a negative test before every refill, with mandated contraception.
- ▶ **Drug-safety classification** — the former FDA pregnancy categories A, B, C, D, X (X = contraindicated) have largely been replaced by the 2015 Pregnancy & Lactation Labeling Rule (PLLR) narrative format.
- ▶ **Immunisation** — ensure rubella and varicella immunity *before* pregnancy (MMR ≥3 months pre-conception); give influenza, COVID-19 and Tdap in pregnancy. Antenatal screening for rubella, syphilis, hepatitis B/C, HIV.
- ▶ **Avoid teratogenic exposures** — abstain from alcohol/tobacco; minimise diagnostic ionizing radiation; counsel on travel to Zika-endemic areas.
- ▶ **Antenatal surveillance** — maternal serum screening, detailed anomaly ultrasound (and fetal echocardiography in high-risk groups) for early detection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **“Critical periods of human development” timeline** — a horizontal bar from fertilisation to term divided into: *Weeks 0–2 (pre-implantation = “all-or-none”), Weeks 3–8 (embryonic period = organogenesis = maximal structural-malformation risk, shown as solid red bars), Weeks 9–38 (fetal period = functional defects/growth restriction, shown as lighter bars)*. Add organ-specific sensitivity bars labelled *CNS, heart, limbs, eyes, ears, teeth, palate, external genitalia*.
- ▶ **Wilson’s-principles concept map** — central box “*TERATOGEN*” with arrows to the four outcome labels: *Death, Malformation, Growth retardation, Functional deficit*, and side labels *Genotype, Timing, Mechanism, Access/Placental transfer, Dose-response*.

Clinical / Diagnostic significance

- ▶ Establishing teratogenic causation requires consistent exposure during the relevant critical window, a recognisable pattern of anomalies, and a biologically plausible mechanism.
- ▶ A drug history must be taken in *every* woman of reproductive age; the highest-risk window (organogenesis) often precedes recognition of the pregnancy — hence preconception, not antenatal, intervention.
- ▶ Detection: maternal serum markers, **anomaly ultrasound**, fetal echocardiography, and amniocentesis/cordocentesis where indicated; congenital rubella confirmed by IgM on fetal blood, CMV/Zika by maternal serology/NAAT with serial ultrasound.
- ▶ Management pearls: substitute pregnancy-safe alternatives (labetalol/nifedipine for hypertension instead of ACE-I/ARB; LMWH instead of warfarin except mechanical valves; PTU in the first trimester for hyperthyroidism); supplement folic acid 4 mg/day with antiepileptic drugs; counsel on the option of therapeutic termination after high-risk first-trimester exposure.

High-yield exam pointers

- ▶ **Teratogen** = agent causing permanent structural/functional fetal abnormality; four end-points = *death, malformation, growth retardation, functional deficit*.
- ▶ **Organogenesis (weeks 3–8 post-conception) = period of maximum structural-malformation risk**; weeks 0–2 = “all-or-none”; fetal period = functional/growth effects.
- ▶ **Wilson’s six principles**: genotype, timing, mechanism, access, four end-points, dose–response.
- ▶ **ACE-I/ARB** → renal dysgenesis/oligohydramnios/stillbirth; **warfarin** → chondrodysplasia punctata + nasal hypoplasia; **valproate** → NTDs; **isotretinoin** → retinoic-acid embryopathy; **lithium** → Ebstein’s anomaly; **thalidomide** → phocomelia; **DES** → vaginal clear-cell adenocarcinoma; **tetracycline** → stained teeth; **aminoglycoside** → VIII-nerve deafness; **methimazole** → aplasia cutis.
- ▶ **Folic acid 0.4 mg/day** (high-risk **4–5 mg/day**) periconceptionally cuts NTDs ~80%.
- ▶ Prevention is *preconceptional*: optimise maternal disease, switch teratogenic drugs, ensure rubella/varicella immunity, avoid alcohol and unnecessary radiation.
- ▶ Old FDA categories **A–B–C–D–X** superseded by the **PLLR (2015)** narrative labelling.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Medical Disorders During Pregnancy” (drug management in pregnancy: ACE-I/ARB, warfarin, antithyroid drugs, valproate/antiseizure drugs, chemotherapy/radiation, TORCH infections, diabetes and obesity in pregnancy); “Megaloblastic Anemias / Vitamin B12 and Folic Acid” (folic acid and NTD prevention); “Disorders of the Skin” (isotretinoin teratogenicity and pregnancy-prevention programme); “Treatment and Prophylaxis of Bacterial Infections / antimicrobials in pregnancy” (tetracyclines, aminoglycosides); “Approach to the Patient

with Cancer / cancer prevention” (diethylstilbestrol → vaginal clear-cell carcinoma; folic acid in prevention).

- ▶ **Coverage note:** Harrison 22e covers individual agent-specific teratogens and pregnancy drug-management well but does **not** contain a dedicated account of teratogenesis *mechanisms*, **Wilson’s principles of teratology**, the formal **critical-period framework**, or the named dysmorphic syndromes (fetal hydantoin/warfarin syndromes, FAS, Ebstein with lithium, aminopterin syndrome, thalidomide-phocomelia) and the FDA category/PLLR scheme — these are presented from **universally accepted standard internal-medicine/teratology** and are flagged here for transparency. No specialty teratology textbook was listed in the spec corpus.



Therapeutic Index

Asked in: Paper I Nov 2020 — RGUHS MD General Medicine

Definition / Introduction — The **therapeutic index (TI)** — also called the **therapeutic ratio** or, when expressed as a concentration range, the **therapeutic window** — is a quantitative measure of the *safety* of a drug. It expresses the separation between the dose (or plasma concentration) that produces the **desired therapeutic effect** and the dose (or concentration) that produces **toxicity**. A drug is “well-tolerated” when there is a **wide margin** between these two dose–response relations; conversely, when the curves lie close together the drug has a **narrow therapeutic index** and even small dosage increments may sharply increase the likelihood of harm. The concept therefore underpins rational dose selection, safety monitoring and the practice of therapeutic drug monitoring (TDM).

Quantitative basis — definitions and formulae

- ▶ Drug effects (both beneficial and adverse) follow a series of **quantal dose–response (cumulative frequency) curves**, where the proportion of a population showing a defined response is plotted against log dose/concentration (Fig. 71-1, Harrison).
- ▶ Three reference doses are read from these sigmoid curves:
 - **ED₅₀** (median *effective* dose) — dose producing the specified therapeutic effect in 50% of the population.
 - **TD₅₀** (median *toxic* dose) — dose producing a defined toxic effect in 50%.
 - **LD₅₀** (median *lethal* dose) — dose killing 50% (derived from animal/preclinical data).

Index	Formula	Meaning / use
Therapeutic Index (clinical)	$TI = TD_{50} / ED_{50}$	Higher ratio = safer drug

Index	Formula	Meaning / use
Therapeutic Index (preclinical)	$TI = LD_{50} / ED_{50}$	Animal data during drug development
Certain Safety Factor / Margin of Safety	$CSF = LD_1 / ED_{99}$ (or TD_1/ED_{99})	More reliable than TI; accounts for curve <i>slope</i> and overlap of extremes
Standard Safety Margin	$[(LD_1 - ED_{99})/ED_{99}] \times 100$	% dose increase from near-maximal efficacy to onset of lethality

- ▶ The TI is a **ratio with no units**; the larger the value, the greater the cushion between efficacy and toxicity.
- ▶ The plain TI (TD_{50}/ED_{50}) can be **misleading** when the two curves are not parallel, because it ignores the extremes of the population. The **certain safety factor** (LD_1/ED_{99}) corrects for this by comparing the dose that *just begins* to be toxic with the dose giving *near-maximal* benefit, and is the more clinically meaningful safety index.

Graphical representation (wide vs narrow ratio)

- ▶ **Wide therapeutic ratio:** the desired-effect and adverse-effect curves are **widely separated** — therapeutic doses carry a low probability of toxicity (e.g., penicillins, most modern antimicrobials).
- ▶ **Narrow therapeutic ratio:** the curves are **close / overlapping**, so the chance of toxicity at therapeutic doses is high; a **steep dose–response curve for adverse effects** is especially dangerous because a small dosage increment produces a large jump in toxicity risk.
- ▶ When a reproducible **concentration–effect** relationship exists, *plasma concentration* may be substituted for dose on the x-axis, which is the rationale for using measured drug levels (TDM) to steer therapy.

Narrow-therapeutic-index drugs and their target ranges

These agents require dose individualisation, level monitoring and caution with interactions/organ dysfunction.

Drug	Usual therapeutic range	Notes / monitoring caveat
Digoxin	HF 0.5–0.9 ng/mL; AF 0.5–2 ng/mL	Hypokalaemia potentiates toxicity; toxicity is a <i>clinical</i> diagnosis
Lithium	0.5–1.2 mmol/L	Thiazides/loop diuretics raise levels

Drug	Usual therapeutic range	Notes / monitoring caveat
Phenytoin	10–20 mg/L (5–10 in uraemia/hypoalbuminaemia); free target 0.5–2.0 mg/L	Capacity-limited (zero-order) kinetics; monitor <i>free</i> drug if low albumin/renal failure
Theophylline	5–15 mg/L (panic ≥ 30)	Clearance $\uparrow$ in smokers, $\downarrow$ in HF/cirrhosis
Valproic acid	50–100 mg/L (≤ 125 bipolar; panic > 150)	Concentration-dependent protein binding
Carbamazepine	4–12 mg/L	Auto-induces own metabolism
Gentamicin	Peak 4–8 mg/L, trough < 2 mg/L	Nephro-/oto-toxicity with high troughs
Vancomycin	Trough 10–20 mg/L	Trough-guided dosing; nephrotoxicity risk
Cyclosporine / Tacrolimus	CsA 100–300 ng/mL; Tac trough 8–12 ng/mL	Whole-blood (EDTA) trough; concentration-related nephrotoxicity
Warfarin	(INR-guided, not level)	Numerous CYP2C9/VKORC1 and drug interactions

Therapeutic window and therapeutic drug monitoring (TDM)

- ▶ The **therapeutic window** is the **concentration range** lying *above* the minimum effective concentration but *below* the toxic threshold; TDM aims to keep plasma levels within it.
- ▶ TDM is most valuable for drugs with: a **narrow therapeutic index**, a good **concentration–effect correlation**, **no easily measured clinical endpoint**, and **wide pharmacokinetic variability** — typically **anticonvulsants**, **antiarrhythmics**, **anti-rejection agents** and **certain antibiotics** (Harrison).
- ▶ **Timing matters**: for most maintenance dosing, sample at **trough** (just before the next dose at steady state) to confirm maintained efficacy — e.g., anticonvulsants and **vancomycin** (trough used because sustained high levels risk nephrotoxicity). When **peak**-related toxicity is the concern (e.g., QT prolongation with **sotalol/dofetilide**), the ECG/level is checked **~1–2 h post-dose** at steady state.
- ▶ **Steady state** is reached in **~4–5 elimination half-lives**; a level drawn before steady state under-reads the eventual value. A **loading dose** speeds attainment of effect but does *not* change the time to true steady state.
- ▶ **First- vs zero-order kinetics**: in first-order elimination, doubling the dose doubles the steady-state level (linear, predictable). For **zero-order (saturable)** drugs — **phenytoin**, **aspirin**,

fluoxetine, ethanol — a small dose increase causes a **disproportionate**, sometimes toxic, rise in concentration; this *functionally narrows* the therapeutic index and mandates small increments.

Factors that narrow or shift the therapeutic index

- ▶ **Altered clearance:** renal disease (digoxin, dofetilide, sotalolol → QT/arrhythmia), hepatic disease (↑ oral bioavailability of high first-pass drugs — morphine, midazolam, nifedipine), heart failure/shock (contracted volume of distribution → higher plasma/CNS levels).
- ▶ **Altered protein binding:** only free (unbound) drug is active; in renal/hepatic disease or hypoalbuminaemia a fall in binding from 99→98% **doubles** free drug — hence free-level monitoring for phenytoin/valproate.
- ▶ **Drug interactions:** CYP and P-glycoprotein **inhibitors** (amiodarone, azoles, macrolides, cimetidine) raise levels of narrow-index substrates (warfarin, digoxin, dabigatran), while **inducers** (rifampin, carbamazepine, phenytoin, St John's wort) lower them — both pushing the patient outside the window.
- ▶ **“High-risk pharmacokinetics”:** when an active narrow-index drug relies on a **single elimination pathway**, any genetic, disease or drug-interaction block of that pathway causes marked, sometimes toxic, accumulation.
- ▶ **Extremes of age & genetics:** the elderly (polypharmacy, reduced organ function) and pharmacogenomic variants (e.g., CYP2C9/VKORC1 for warfarin, TPMT for thiopurines) effectively shrink the safe margin.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Two stacked quantal dose–response graphs** (x-axis = *log dose/concentration*, y-axis = *cumulative % of population responding*). On EACH panel draw two sigmoid curves: a left “Desired/therapeutic effect” curve and a right “Adverse/toxic effect” curve.
 - **Top panel — Wide therapeutic ratio:** curves *widely separated*. Label ED_{50} and TD_{50} ; show the wide gap.
 - **Bottom panel — Narrow therapeutic ratio:** curves *close/overlapping* with a steep toxicity curve. Labels: ED_{50} , TD_{50} (or LD_{50}), **Therapeutic window/index** = TD_{50}/ED_{50} , **Margin of safety** = LD_1/ED_{99} , and arrows marking *minimum effective concentration* and *minimum toxic concentration*.

Clinical / Diagnostic significance

- ▶ **Drug selection & dosing:** prefer wide-TI drugs where possible; for narrow-TI agents, “start low, go slow,” use the smallest effective dose and titrate against levels or a clinical endpoint.
- ▶ **TDM** converts an abstract index into bedside practice — confirming adherence, diagnosing toxicity vs under-dosing, and guiding dose in renal/hepatic impairment.

- ▶ **Adverse drug reactions:** narrow-TI drugs are over-represented among the commonest culprits of ADR-related hospital admission (digoxin, warfarin, NSAIDs, opiates). **Type A** (dose-dependent, exaggerated pharmacology) reactions are the ones predicted by a low TI; **Type B** (idiosyncratic, dose-independent) reactions are *not* captured by the TI.
- ▶ **Drug development & regulation:** the preclinical LD_{50}/ED_{50} in animals is an early safety screen; a low TI demands tighter clinical-trial monitoring and may preclude approval.
- ▶ **Antidotes/rescue tied to the index:** digoxin-specific Fab (Digibind) for digoxin toxicity, leucovorin/glucarpidase rescue for methotrexate, and N-acetylcysteine for paracetamol all reflect the consequences of crossing a narrow window.

High-yield exam pointers

- ▶ $TI = TD_{50}/ED_{50}$ (clinical) or LD_{50}/ED_{50} (animal) — higher = safer; it is a **unitless ratio**.
- ▶ The **certain safety factor** (LD_1/ED_{99}) / standard safety margin is **more reliable** than TI because it accounts for curve slope and the extremes of the population.
- ▶ **Therapeutic window** = the *concentration range* above minimum effective and below toxic level; basis of TDM.
- ▶ Classic narrow-TI drugs: digoxin, lithium, warfarin, phenytoin, theophylline, aminoglycosides, vancomycin, cyclosporine/tacrolimus, antiarrhythmics, methotrexate.
- ▶ **Zero-order (saturable) kinetics** (phenytoin, aspirin, ethanol, fluoxetine) cause disproportionate level rises → behave as narrow-window drugs.
- ▶ Sample at **trough** for efficacy/most anticonvulsants and vancomycin; at **peak** (1–2 h) when peak toxicity (sotalol/dofetilide QT) is feared; interpret only at **steady state** (~4–5 half-lives).
- ▶ **Hypokalaemia worsens digoxin toxicity**; monitor **free phenytoin** in hypoalbuminaemia/renal failure; enzyme **inhibitors/inducers** and renal/hepatic disease shift the window.
- ▶ A **steep adverse-effect dose–response curve** is the single most dangerous feature — small dose rises cause large toxicity jumps.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Principles of Clinical Pharmacology” (Roden): therapeutic ratio/index/window concept and Fig. 71-1; dose–response relations; TDM, trough vs peak sampling (vancomycin, sotalol/dofetilide); first- vs zero-order kinetics; steady state and loading dose; high-risk pharmacokinetics; protein binding and free drug; Type A vs Type B ADRs; effects of renal/hepatic disease and drug interactions.
- ▶ **CMDT 2026** — Appendix: Therapeutic Drug Monitoring (Table e5–1): therapeutic concentration ranges, half-lives and monitoring caveats for digoxin, lithium, phenytoin, theophylline, valproate, carbamazepine, gentamicin, vancomycin, cyclosporine/tacrolimus and methotrexate.

- **Coverage note:** Harrison presents the therapeutic index *qualitatively* (therapeutic ratio/window with the dose–response figure). The *quantitative* formulae — $TI = TD_{50}/ED_{50}$ (or LD_{50}/ED_{50}), the certain safety factor = LD_1/ED_{99} and standard safety margin — are universally accepted standard pharmacology (Goodman & Gilman / KDT / Katzung) included here for completeness, as the corpus chapter does not state these ratios explicitly.



Transplant Organ Rejection: Types and Pathogenesis

Asked in: Paper I Nov 2021 — RGUHS MD General Medicine

Definition / Introduction — *Rejection* is the immune-mediated injury of a transplanted allograft caused by the recipient's recognition of donor **alloantigens** (chiefly mismatched **HLA** molecules) as foreign. It is classified by **tempo** (hyperacute, accelerated, acute, chronic) and by the **dominant effector arm** (T cell-mediated/cellular vs antibody-mediated/humoral). Understanding the pathogenesis underpins HLA matching, cross-matching, desensitization, and the entire framework of immunosuppression that has made transplantation the treatment of choice for end-stage organ failure.

Immunological basis — the alloimmune response

- **The target — HLA/MHC:** The major histocompatibility antigens are encoded on the short arm of **chromosome 6** (the HLA region). **Class I** (HLA-A, B, C) is expressed on all nucleated cells and presents to **CD8+** cells; **Class II** (HLA-DR, DQ, DP) is expressed on antigen-presenting cells (APCs) and presents to **CD4+** cells. HLA is highly **polymorphic**, so it becomes the principal immunologic target when mismatched. The number of mismatches at A, B and DR loci correlates with graft loss. ABO blood-group antigens and “minor” (non-HLA) antigens (e.g., endothelial antigens, the LIMS-1 locus) provide additional targets.
- **Allorecognition — two pathways (Fig. 325-1):**
 - **Direct pathway** — recipient T cells recognise *intact* donor MHC on **donor (passenger)** APCs: CD8 T cells recognise donor class I; CD4 T cells recognise donor class II. This drives **early, vigorous acute rejection**.
 - **Indirect pathway** — donor MHC is shed, processed and presented as **peptides** by **recipient (self)** APCs to CD4 T cells. This mirrors normal physiologic antigen recognition and sustains **chronic rejection** and **antibody production**.
- **Two-signal T-cell activation:** Signal 1 = TCR binding to alloantigen–MHC; **Signal 2** (costimulation) = CD28 on the T cell engaging CD80/CD86 on the APC. Both signals activate **calcineurin**, upregulating IL-2 and IFN- γ ; IL-2 acts via the **mTOR (target of rapamycin)**

pathway to drive clonal proliferation — the molecular targets of CNIs, belatacept and mTOR inhibitors respectively.

- **Two effector arms: T cell-mediated** (CD8 cytotoxic killing + CD4-driven cytokine inflammation) and **antibody-mediated** (follicular helper T cells [T_{fh}] → B-cell/plasma-cell differentiation → **donor-specific antibody [DSA]** → complement-dependent and -independent endothelial injury, marked by **C4d** deposition).

Classification of rejection by tempo and mechanism

Type	Onset	Dominant mechanism	Key pathology	Reversibility
Hyperacute	Minutes–hours	Preformed anti-donor antibody (ABO / anti-HLA class I) + complement	Vascular thrombosis, fibrinoid necrosis, cortical infarction	Irreversible — graft loss; prevent by cross-match
Accelerated	2–5 days	Anamnestic (memory) T-cell + antibody response in a sensitised recipient	Vascular + cellular injury	Often refractory to treatment
Acute — cellular (TCMR)	Days–weeks to months	Recipient CD4/CD8 T cells vs donor HLA	Interstitial mononuclear infiltrate, tubulitis, endothelialitis (Banff)	Usually reversible with steroids ± ATG
Acute — antibody-mediated (AMR)	Days–weeks	De novo / preformed DSA + complement	C4d+ peritubular capillaries, capillaritis, glomerulitis	Harder to treat; plasmapheresis, IVIG, rituximab
Chronic	Months–years	Combined indirect alloimmunity, chronic active AMR, non-immune injury	Interstitial fibrosis, tubular atrophy, vasculopathy (intimal proliferation), glomerulopathy	Largely irreversible ; slowly progressive

Pathogenesis of each type

- **Hyperacute rejection:** Caused by **preformed circulating antibodies** against donor antigens — natural anti-ABO isohaemagglutinins or **anti-HLA** antibodies from prior **transfusion**, **pregnancy**, **prior transplant**, or (rarely) vaccination/infection. Antibody binds graft endothelium, fixes complement, and triggers a fulminant **vasculitic thrombotic** event with immediate, irreversible graft loss. A **positive cytotoxic cross-match** (recipient serum + donor T

lymphocytes) predicts it and is **the only widely accepted absolute immunologic contraindication** to transplantation. Now largely *abolished* by routine ABO matching and cross-matching.

- ▶ **Accelerated rejection:** A rapid (2–5 day) anamnestic response in a **presensitised** recipient — secondary exposure to a previously primed antigen produces an immune response often **refractory to conventional treatment**. (A standard recognised category; Harrison emphasises the underlying mechanism of prior sensitisation rather than the eponymous label.)
- ▶ **Acute T cell-mediated (cellular) rejection (TCMR):** Recipient T cells respond to donor HLA. CD4+ cells recognise class II (HLA-DR) mismatch, proliferate and release proinflammatory cytokines; CD8+ cytotoxic cells recognise class I (HLA-A, -B) and lyse donor target cells via **perforin/granzyme B** and direct contact. Histology = immune-cell infiltration of the **interstitial, tubular and vascular** compartments (graded by the **Banff** classification). Clinically a **rise in serum creatinine** ± reduced urine output; treated with high-dose **methylprednisolone (0.5–1 g/day × 3 days)**, with ATG for steroid-resistant cases.
- ▶ **Acute antibody-mediated rejection (AMR):** Donor antigens drain to recipient lymph nodes, activating T_{fh} cells that drive B cells into **antibody-secreting plasma cells**. The resulting **DSA** (anti-HLA and non-HLA) deposit in the graft, injuring endothelium through complement-dependent and -independent routes. Diagnostic triad: (1) **C4d deposition** in peritubular capillaries/GBM, (2) **histologic microvascular injury** (capillaritis/glomerulitis), and (3) **circulating DSA**. Treatment is challenging — **plasmapheresis, IVIG, anti-CD20 (rituximab)** to deplete B cells, and **bortezomib** to target plasma cells.
- ▶ **Chronic rejection / chronic allograft dysfunction:** A slow, largely irreversible decline driven by **chronic active AMR**, indirect alloimmunity, and non-immune insults (CNI nephrotoxicity, hypertension, recurrent disease). Pathology = **interstitial fibrosis, tubular atrophy, transplant vasculopathy** (intimal proliferation, medial hypertrophy) and **glomerulopathy**. In the liver, the equivalent is **ductopenia** — the “**vanishing bile duct syndrome**” (progressive cholestasis, focal necrosis, vascular intimal fibrosis/foam cells), commoner after transplant for autoimmune liver disease and with limited reversibility.

Diagnosis and grading

- ▶ **Allograft biopsy is the gold standard** for distinguishing acute TCMR from AMR and from non-rejection causes (acute tubular injury, CNI toxicity, **BK polyomavirus** nephropathy, recurrent glomerular disease).
- ▶ **Banff classification** grades cellular rejection by the compartments infiltrated; **C4d immunostaining** of peritubular capillaries is the footprint of complement activation in AMR.
- ▶ **Immunologic work-up:** **Panel-reactive antibody (PRA)** quantifies sensitisation; **cytotoxic vs flow-cytometric cross-match** (more sensitive, detects anti-HLA IgG); **eplet matching** (especially class II DQ) refines risk.

- ▶ **Emerging non-invasive biomarkers:** donor-derived cell-free DNA, urinary chemokine CXCL9, urine exosome profiling — adjuncts to (not replacements for) biopsy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Allorecognition pathways (redraw Fig. 325-1):** Label — *Donor APC* (MHC I + MHC II), *Recipient (self) APC*, *Direct pathway* (CD8 T cell → donor MHC I; CD4 T cell → donor MHC II), *Indirect pathway* (self-APC presenting processed allopeptide on MHC II to CD4 T cell), *Th1/Th2/Th17, Tfh* → *naïve B cell* → *plasma cell* → *antibody-mediated rejection*, *Cytotoxic CD8 T cell* → *perforin/granzyme B* → *cellular rejection and organ damage*.
- ▶ **Timeline bar of rejection types:** a horizontal time axis labelled — *Minutes–hours* = *Hyperacute (preformed Ab)*, *2–5 days* = *Accelerated (sensitised)*, *Days–weeks–months* = *Acute (TCMR / AMR)*, *Months–years* = *Chronic (fibrosis, vasculopathy)*; annotate dominant mechanism and reversibility above each band.

Clinical / Diagnostic significance

- ▶ **Prevention starts before surgery:** ABO compatibility, HLA typing (now molecular/genomic), and a negative cross-match. **Desensitization** (plasmapheresis + IVIG ± rituximab) and **kidney paired donation** allow safe transplantation of sensitised candidates.
- ▶ **Immunosuppression** is lifelong (except identical twins). **Induction** = depleting (ATG, alemtuzumab/anti-CD52) or non-depleting (**basiliximab**, anti-IL-2R α) agents; **Maintenance** = a **calcineurin inhibitor** (tacrolimus/cyclosporine) + **antimetabolite** (mycophenolate) ± steroids, with **mTOR inhibitors** (sirolimus/everolimus) or **belatacept** (CTLA-4-Ig blocking CD28 costimulation; BENEFIT trial) as alternatives.
- ▶ **Treatment of established rejection:** TCMR → pulse methylprednisolone, then ATG if refractory; AMR → plasmapheresis + IVIG + rituximab ± bortezomib.
- ▶ **Complications of the immunosuppressed state:** time-dependent **opportunistic infection** (CMV, BK virus, *Pneumocystis*, fungal), and **malignancy** (skin/lip cancers, EBV-driven PTL) — the balance against rejection must always be weighed.
- ▶ **Contrast — graft-versus-host disease (GVHD):** the *reverse* of rejection. In allogeneic haematopoietic-stem-cell/bone-marrow transplantation, **immunocompetent donor T cells** **attack recipient (host) tissues** (skin, gut, liver), producing acute and chronic GVHD — host-versus-graft is rejection, graft-versus-host is GVHD.

High-yield exam pointers

- ▶ **Three classic types** = Hyperacute, Acute, Chronic; add Accelerated (sensitised) for completeness. Acute subdivides into **cellular** (TCMR) and **antibody-mediated** (AMR).

- ▶ **Hyperacute** = preformed antibody + positive cytotoxic cross-match = only absolute immunologic contraindication; occurs in minutes–hours; now largely abolished by cross-matching.
- ▶ **TCMR**: CD4 → class II, CD8 → class I; Banff-graded interstitial/tubular infiltrate; steroid-responsive.
- ▶ **AMR diagnostic triad**: C4d+ peritubular capillaries, microvascular injury, circulating DSA.
- ▶ **Direct allorecognition** drives early acute rejection; **indirect** drives chronic rejection and antibody formation.
- ▶ **Two-signal model**: TCR–MHC (signal 1) + CD28–CD80/86 (signal 2) → calcineurin → IL-2 → mTOR — the drug-target map.
- ▶ **Chronic rejection** = interstitial fibrosis, tubular atrophy, **transplant vasculopathy**; liver equivalent = **vanishing bile duct syndrome (ductopenia)**; largely irreversible.
- ▶ **HLA on chromosome 6**: class I = A, B, C; class II = DR, DQ, DP; mismatch number predicts graft survival.
- ▶ **GVHD is the mirror image of rejection** (donor T cells vs host), seen in allogeneic HSCT.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Kidney Transplantation” (Immunology of Rejection: hyperacute, T cell-mediated and antibody-mediated rejection, direct/indirect allorecognition, HLA matching, cross-matching, Banff/C4d/DSA, immunosuppression, chronic allograft injury); “Liver Transplantation” (allograft rejection — acute endothelialitis/bile-duct injury and chronic ductopenic *vanishing bile duct syndrome*); “Introduction to the Immune System” (type II cytotoxic and type IV delayed-type hypersensitivity mechanisms; MHC class I/II antigen presentation; GVHD references).

Coverage note: The corpus has **no single dedicated “transplantation immunology / rejection” chapter**; the richest, fully grounded source is the **Kidney Transplantation** chapter, supplemented by the **Liver Transplantation** and **immune-system** chapters. Specific *timings* (e.g., hyperacute minutes–hours, accelerated 2–5 days) and the **accelerated rejection** category are universally accepted standard internal-medicine teaching included to satisfy the full scope of the question; the chapters explicitly emphasise hyperacute, acute (cellular + AMR) and chronic rejection and the mechanism of prior sensitisation.



Genetic Testing in Pregnancy — Indications, Methods and Ethical Issues

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — **Prenatal genetic testing** is the application of cytogenetic, molecular and biochemical techniques during pregnancy to detect chromosomal abnormalities, single-gene (Mendelian) disorders and structural malformations in the fetus. It encompasses **screening** (population-level risk estimation: maternal serum markers, ultrasound, cell-free DNA) and **diagnostic** testing on fetal cells obtained by amniocentesis, chorionic villus sampling (CVS) or cordocentesis, plus **preimplantation genetic testing (PGT)** on IVF embryos. Because the information generated is sensitive, heritable and may inform decisions about continuation of pregnancy, it is inseparable from **genetic counselling** and a distinct set of **ethical, legal and social implications (ELSI)**.

Indications for genetic testing in pregnancy

Testing is offered when the *a priori* risk of a fetal genetic disorder is increased:

- ▶ **Advanced maternal age** (≥ 35 years) — rising risk of trisomies (21, 18, 13) with maternal age.
- ▶ **Abnormality of the fetus on ultrasound** — structural malformations or soft markers prompting karyotype/microarray.
- ▶ **Increased risk on the maternal serum screen** — an abnormal “quad” test (α -fetoprotein, β -human chorionic gonadotropin, inhibin-A, unconjugated estriol) or first-trimester combined screen.
- ▶ **Family history of a chromosomal abnormality** or a known **balanced parental translocation** (a recognised recurrence-risk situation, e.g. translocation Down syndrome).
- ▶ **A Mendelian disorder amenable to genetic testing** — known familial pathogenic variant (e.g. cystic fibrosis, thalassaemia/haemoglobinopathy, fragile-X, Duchenne muscular dystrophy, Marfan/FBN1, homocystinuria).
- ▶ **Positive carrier screening** in one or both parents, **consanguinity**, or membership of an at-risk ethnic group (e.g. founder mutations).
- ▶ **Recurrent pregnancy loss / previous affected child / infertility undergoing IVF** (overlap with adult and preconceptional indications).

Note: The corpus also lists postnatal indications (multiple congenital anomalies, developmental delay, intellectual disability, autism, short stature, dysmorphism, disorders of sexual development) — useful to contrast prenatal vs paediatric indications in the answer.

Methods I — Sampling techniques (when and how fetal material is obtained)

Method	Timing (gestation)	Technique	Material / typical analysis
Cell-free DNA (cfDNA) screen (NIPT)	from ~10 weeks	Maternal venous blood — non-invasive	Fetal + maternal cfDNA; screens common chromosomal

Method	Timing (gestation)	Technique	Material / typical analysis
			aneuploidies and fetal sex; a <i>screen</i> , not diagnostic
Maternal serum screen / ultrasound	1st–2nd trimester	Non-invasive	Quad markers, nuchal translucency, anomaly scan — risk estimation
Chorionic villus sampling (CVS)	weeks 9–12	Trans-cervical or trans-abdominal biopsy of chorion	Cytogenetic + mutational analysis; <i>earliest</i> diagnostic test — relevant when termination is a consideration
Amniocentesis	~16 weeks	Aspiration of amniotic fluid	Cultured amniocytes for karyotype , FISH , mutational analysis
Percutaneous umbilical blood sampling (PUBS / cordocentesis)	from ~18 weeks	Aspiration of fetal blood	Late-gestation diagnosis (rapid karyotype, fetal anaemia/infection work-up)
Preimplantation genetic testing (PGT)	pre-implantation	Single cell from 4- to 8-cell embryo, or first polar body of the oocyte (with IVF)	Avoids therapeutic abortion; costly and labour-intensive

- ▶ **Non-invasive (screening)** = cfDNA, serum markers, ultrasound — no procedure-related fetal loss; abnormal results require **confirmation** by an invasive diagnostic test.
- ▶ **Invasive (diagnostic)** = CVS, amniocentesis, PUBS — definitive but carry a procedure-related risk.

Methods II — Laboratory analytic techniques

Once fetal cells/DNA are obtained, the genome is interrogated at three levels:

- ▶ **Cytogenetics** — **chromosome level**: *karyotype* analysis (numerical and large structural abnormalities), **fluorescence in situ hybridisation (FISH)** for targeted aneuploidy/microdeletions.
- ▶ **Cytogenomics** — **sub-microscopic level**: **chromosomal microarray / array-based testing** for copy-number variants (deletions/duplications), and **multiplex ligation-dependent probe amplification (MLPA)** for single-exon deletions/duplications.
- ▶ **Molecular** — **sequence level**: PCR amplification from minute DNA samples, **direct (Sanger) DNA sequencing** for known single-gene disorders and prenatal diagnosis, and **next-generation /**

massively parallel sequencing — targeted gene panels, whole-exome sequencing (WES) and whole-genome sequencing (WGS) for undiagnosed syndromes.

- ▶ **Analysis of cfDNA (“liquid biopsy”)** from a maternal sample provides minimally invasive screening for fetal chromosomal abnormalities and sex.
- ▶ The optimal family strategy is to **test an affected family member first** to identify the pathogenic variant, then offer **targeted variant testing** to the fetus/at-risk relatives.

Ethical issues involved

Prenatal genetic testing raises ethical, legal and social concerns that the candidate must be able to enumerate:

- ▶ **Genetic privacy & non-discrimination:** Genetic data is sensitive and should not be accessed without **explicit consent**; disclosure risks **discrimination by insurers or employers**. The U.S. **Genetic Information Nondiscrimination Act (GINA, 2008)** protects *asymptomatic* individuals in health insurance and employment but **does not protect the symptomatic individual** and **does not cover disability, long-term-care or life insurance**; the Affordable Care Act (2014) partly fills this gap.
- ▶ **Informed consent & non-directive counselling:** Couples must understand what the test can and cannot determine, its limitations, the possibility of inconclusive results, and the implications for the fetus and other relatives. Counselling is **non-directive** and supports **reproductive autonomy** — the decision (including continuation vs termination of pregnancy) rests with the parents.
- ▶ **Termination of pregnancy:** Earlier diagnosis (CVS) is valued *because* it allows earlier decision-making; this links prenatal testing to the morally contested issue of **selective termination** and concerns about devaluing disability.
- ▶ **Incidental / secondary findings:** Comprehensive sequencing (WES/WGS) may reveal **medically actionable** conditions but also **untreatable** disorders and **variants of uncertain significance (VUS)** unrelated to the test indication — a recognised ethical dilemma causing anxiety.
- ▶ **Uncertainty & psychosocial harm:** “Excluding a specific disorder is never equivalent to the assurance of a normal child”; results generate **anxiety, despair and survivor guilt**, and most adult-onset results are only *predictive* of risk, not deterministic.
- ▶ **Testing of children for adult-onset disease:** Professional bodies caution against testing for adult-onset disorders in childhood where no childhood intervention exists, to preserve the **future child’s right to decide** (exceptions: MEN-2 → prophylactic thyroidectomy; FAP → colonoscopy from 10–15 yr).
- ▶ **Direct-to-consumer (DTC) testing:** Variable validity, inadequate counselling, confidentiality and **regulatory** concerns (CLIA/CAP accreditation; ACMG position statement).
- ▶ **Equity — the “genomics divide”:** High cost may widen global inequities; WHO initiatives aim to attenuate these.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — Prenatal testing timeline** (gestation in weeks on a horizontal axis). Labels: *cfDNA / NIPT (~10 wk)*, *CVS — chorionic villus sampling (9–12 wk, trans-cervical/trans-abdominal)*, *First-trimester combined screen (nuchal translucency)*, *Maternal serum “quad” screen (2nd trimester)*, *Amniocentesis (~16 wk, amniotic fluid)*, *Anomaly ultrasound (~18–20 wk)*, *PUBS / cordocentesis (≥ 18 wk, fetal blood)*; annotate **Non-invasive (screening)** vs **Invasive (diagnostic)**.
- ▶ **Diagram 2 — Three-tier methods pyramid**. Labels: base *Chromosome level: karyotype, FISH*; middle *Cytogenomic: chromosomal microarray (CNV), MLPA*; apex *Molecular: PCR, Sanger sequencing, NGS panels / WES / WGS, cfDNA*.

Clinical / Diagnostic significance

- ▶ Distinguishes a **screening** result (cfDNA, serum, ultrasound — gives a risk) from a **diagnostic** result (CVS/amniocentesis/PUBS — confirms or excludes) — abnormal screens **must** be confirmed invasively before irreversible decisions.
- ▶ **CVS earlier than amniocentesis** is decisive when termination is being considered; **PUBS** is reserved for late gestation and fetal blood disorders/infection.
- ▶ In **Down syndrome**, cytogenomic analysis is performed even with simple trisomy 21 to detect an **unbalanced translocation**, because a parent with a **balanced translocation** carries a substantial recurrence risk.
- ▶ **PGT with IVF** allows selection of unaffected embryos, avoiding therapeutic abortion, for couples with a known familial pathogenic variant.
- ▶ Every prenatal test must be wrapped in **pre-test counselling, informed consent and post-test counselling**, with the option of **DNA banking** and onward testing of relatives.

High-yield exam pointers

- ▶ **Amniocentesis ~16 wk; CVS weeks 9–12; PUBS/cordocentesis ≥ 18 wk; cfDNA from maternal blood (non-invasive).**
- ▶ **Quad test = AFP + β -hCG + inhibin-A + unconjugated estriol.**
- ▶ **Amniotic fluid cells $\rightarrow$ karyotype, FISH, mutational analysis.**
- ▶ **Three method tiers: karyotype/FISH $\rightarrow$ microarray/MLPA $\rightarrow$ PCR/Sanger/NGS (panel, WES, WGS).**
- ▶ **GINA (2008) protects asymptomatic people in health insurance/employment; not symptomatic, not life/disability/long-term-care insurance.**
- ▶ **Counselling is non-directive; respect reproductive autonomy; consent must cover incidental findings & VUS.**

- ▶ “Excluding a disorder ≠ guarantee of a normal child.”
- ▶ Test the **affected family member first** to find the variant, then do targeted fetal testing.
- ▶ PGT analyses a single cell from a 4–8-cell embryo or the first polar body.

SOURCE & COVERAGE

- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “Principles of Human Genetics” (indications for testing, amniocentesis/CVS/PUBS/cfDNA timing and technique, quad test, preimplantation/preconceptual diagnosis, mutational-analysis methods, GINA and ethical issues).
- ▶ **Harrison’s Principles of Internal Medicine, 22e** — “The Integration of Inherited Genetics into Clinical Practice” (methodologic approaches: karyotype/FISH/MLPA/microarray/PCR/NGS; pre- and post-test counselling, informed consent, DNA banking, testing children for adult-onset disease, DTC testing/ACMG, VUS, GINA limitations).
- ▶ **CMDT 2026** — “Genetic & Genomic Disorders” (Down syndrome: cytogenomic analysis to detect unbalanced translocation and recurrence risk; cfDNA for fetal sex-chromosome aneuploidy; prenatal diagnosis in single-gene disorders).

Coverage note: This is an internal-medicine corpus; it covers prenatal **methods and ethics** well but does not provide obstetric-grade detail (e.g. exact cfDNA/NIPT detection rates and false-positive rates, nuchal-translucency cut-offs, procedure-related miscarriage rates, or ACOG/ISPD screening protocols). Such figures should be drawn from a dedicated obstetrics/medical-genetics text. The principle that genetic counselling is **non-directive** is stated as universally accepted standard practice rather than verbatim from these chapters.



What are the indications for genetic counselling? List genetic conditions that can be tested and the interventions that can be instituted

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — **Genetic counselling** is the communication process by which trained professionals (clinical geneticists and genetic counsellors, working with the primary physician) help individuals and families understand the medical, psychological and familial implications of a genetic contribution to disease, the available testing options, and the risk of recurrence or transmission. It is **non-directive and consent-based**, and—because genetic information affects *entire families*—must precede any predictive genetic testing. Its goals are accurate risk assessment, informed reproductive and medical decision-making, and linkage to **risk-reducing interventions, surveillance and supportive services**.

Indications for genetic counselling and testing

The triggers span the entire life cycle (Harrison Table 479-4) and are best grouped as personal/family-history “red flags” plus stage-specific indications.

Family-history and clinical red flags (refer for counselling when present):

- ▶ **Two or more first-degree relatives** with the same or related condition (asthma, premature cardiovascular disease, type 2 diabetes, breast, colon or melanoma) — relative risk rises 2- to 5-fold.
- ▶ **Young age of disease onset** (e.g., a 30-year-old non-smoking woman with myocardial infarction; breast cancer < 50 years).
- ▶ **Unusual or “sentinel” diagnoses** — male breast cancer, medullary thyroid cancer, bilateral/multifocal tumours.
- ▶ **Multiple related primary cancers in one individual** (e.g., colon *and* endometrial cancer → Lynch syndrome).
- ▶ **Absence of expected non-hereditary risk factors** for a disease (e.g., unprovoked deep-vein thrombosis suggests inherited thrombophilia).
- ▶ **Physical clues** — xanthomas in youth (familial hypercholesterolaemia); trichilemmomas with breast cancer (Cowden/*PTEN*).
- ▶ **High-risk ethnicity** — ~2.5% of Ashkenazi Jews carry one of three founder *BRCA1/BRCA2* pathogenic variants.
- ▶ **A known pathogenic variant already identified in the family** (cascade testing of at-risk relatives).

Indications by life stage (Table 479-4):

Timing	Indications for testing/counselling
Prenatal	Advanced maternal age (> 35 yr); fetal abnormality on ultrasound; abnormal maternal serum/“quad” screen (α -fetoprotein, β -hCG, inhibin-A, unconjugated estriol); family history of chromosomal abnormality; Mendelian disorder amenable to testing
Neonatal & childhood	Multiple congenital anomalies; intellectual disability/developmental delay; autism spectrum disorder; dysmorphic features; failure to thrive; short stature; disorders of sexual development; known familial chromosomal alteration; childhood cancer
Adult	Infertility; recurrent miscarriage; familial cancer; suspected adult-onset Mendelian/cardiac/neurologic disorder; reproductive decision-making

- ▶ **Preconception/reproductive** counselling: carrier screening of couples, consanguinity, prior affected child, and consideration of **preimplantation genetic testing (PGT)** with IVF.
- ▶ **Pharmacogenetic** indications: before drugs with heritable toxicity (e.g., *TPMT*/thiopurines, *DPYD*/fluoropyrimidines).

Components and process of genetic counselling

- ▶ **Confirm the diagnosis first** — clinical, pathological or biochemical, since a precise phenotype directs gene selection.
- ▶ **Construct a three-generation pedigree** documenting first- and second-degree relatives, ages/age of onset, ethnicity, consanguinity and confirmed diagnoses (records, pathology reports, death certificates).
- ▶ **Pretest education and informed consent** — explain purpose, what the test can and cannot reveal, possible results (positive / true-negative / **uninformative negative** / **variant of uncertain significance**, VUS / secondary findings), limitations, and psychosocial, insurance and familial implications.
- ▶ **Optimal testing strategy** — test an **affected family member first**; if a pathogenic variant is found, offer **cascade testing** to relatives. A relative testing negative for a known familial variant reverts to **general-population risk**.
- ▶ **Post-test counselling** — disclose result in the context of personal/family history, formulate a management plan, and arrange follow-up.
- ▶ **Special situation** — **children**: testing for *adult-onset* disorders with no childhood intervention (e.g., Huntington's) is generally **deferred** to preserve future autonomy; but testing is offered when childhood intervention exists (MEN2 → prophylactic thyroidectomy; FAP → colonoscopy from age 10–15 yr).
- ▶ **Ethical/legal**: genetic privacy, the **Genetic Information Nondiscrimination Act (GINA, 2008)** protecting against health-insurance and employment discrimination (not life/disability/long-term-care insurance), and the option of **DNA banking**.

Genetic conditions that can be tested — gene, inheritance and intervention

Predictive testing is **presymptomatic** when a variant confers near-100% disease likelihood (e.g., Huntington's) and **predisposition** testing when risk is < 100% (e.g., hereditary colon cancer). Representative tractable disorders (Harrison Table 480-2):

System / disorder	Inheritance	Gene(s)	Key intervention(s)
Lynch syndrome (HNPCC)	AD	<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> (<i>EPCAM</i>)	Early/frequent colonoscopy; risk-reducing surgery; aspirin

System / disorder	Inheritance	Gene(s)	Key intervention(s)
Familial adenomatous polyposis	AD	<i>APC</i>	Colonoscopy from 10–15 yr; prophylactic colectomy; chemoprevention
Hereditary breast & ovarian cancer	AD	<i>BRCA1</i> , <i>BRCA2</i> (also <i>PALB2</i> , <i>CHEK2</i> , <i>ATM</i>)	Risk-reducing salpingo-oophorectomy; breast MRI surveillance; risk-reducing mastectomy; PARP inhibitors
Hereditary diffuse gastric cancer	AD	<i>CDH1</i>	Prophylactic gastrectomy; enhanced breast surveillance
Factor V Leiden	AD	<i>F5</i>	Avoid thrombogenic risk factors
Haemophilia A / B	X-linked	<i>F8</i> / <i>F9</i>	Factor VIII / IX replacement
G6PD deficiency	X-linked	<i>G6PD</i>	Avoid oxidant drugs and certain foods
Sickle cell disease	AR	<i>HBB</i>	Hydroxyurea; haematopoietic stem-cell transplant; gene therapy
Hypertrophic cardiomyopathy	AD	<i>MYBPC3</i> , <i>MYH7</i> , <i>TNNT2</i> , <i>TPM1</i>	Echo screening; beta blockers; myectomy; avoid strenuous exertion
Long QT syndrome	AD/AR	<i>KCNQ1</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i>	ECG screening; antiarrhythmics; ICD
Marfan syndrome	AD	<i>FBN1</i>	Beta blockers/ARBs; aortic monitoring; valve/root replacement
Familial Mediterranean fever	AR	<i>MEFV</i>	Colchicine
Hereditary haemochromatosis	AR	<i>HFE</i>	Therapeutic phlebotomy
α 1-antitrypsin deficiency	AR	<i>SERPINA1</i>	Avoid smoking/occupational toxins
Cystic fibrosis	AR	<i>CFTR</i>	Airway clearance; CFTR modulators ; lung transplant
MEN type 2	AD	<i>RET</i>	Prophylactic thyroidectomy; screen for pheochromocytoma/hyperparathyroidism
Familial hypocalciuric hypercalcaemia	AD	<i>CASR</i>	Avoid parathyroidectomy; calcimimetics

System / disorder	Inheritance	Gene(s)	Key intervention(s)
Polycystic kidney disease	AD/AR	<i>PKD1, PKD2, PKHD1</i>	BP control; treat UTIs; renal transplant
Nephrogenic diabetes insipidus	X-linked/AR	<i>AVPR2, AQP2</i>	Fluids; thiazides ± amiloride
Malignant hyperthermia	AD	<i>RYR1, CACNA1S</i>	Avoid precipitating anaesthetics
Duchenne muscular dystrophy	X-linked	<i>DMD</i>	Glucocorticoids; exon-skipping antisense oligonucleotides ; stop-codon readthrough
Wilson disease	AR	<i>ATP7B</i>	Zinc; trientine (chelation)
Huntington disease	AD	<i>HTT</i>	Supportive care; PT/OT; presymptomatic testing

Interventions that can be instituted after genetic risk identification

Harrison classifies post-test interventions into four categories, scaling with how “actionable” the disorder is:

- ▶ (1) **Surveillance / heightened awareness** — intensified, earlier or more frequent screening (e.g., breast MRI in *BRCA* carriers; colonoscopy in Lynch/FAP; echocardiography in HCM/Marfan; ECG in long QT).
- ▶ (2) **Specific medical/surgical intervention** —
 - *Chemoprevention*: aspirin (Lynch); tamoxifen/raloxifene/exemestane (*BRCA*).
 - *Risk-reducing surgery*: salpingo-oophorectomy ± mastectomy (*BRCA*); colectomy (FAP); gastrectomy (*CDH1*); prophylactic thyroidectomy (MEN2).
 - *Disease-modifying drugs*: phlebotomy (haemochromatosis); colchicine (FMF); zinc/trientine (Wilson); beta blockers/ARBs (Marfan); CFTR modulators (CF).
 - *Molecularly targeted/novel therapy*: **PARP inhibitors** for *BRCA1/2*- and *PALB2*-associated cancers; **transthyretin stabilisers** for TTR cardiac amyloid; **exon-skipping/readthrough agents** for DMD; **gene therapy/replacement** for spinal muscular atrophy and sickle cell disease (including CRISPR-Cas9-based therapy, FDA-approved 2023).
- ▶ (3) **Risk avoidance** — avoid oxidant drugs (G6PD); avoid triggering anaesthetics (malignant hyperthermia); avoid smoking (α 1-antitrypsin); avoid strenuous exercise/dehydration (HCM); diet modification (hyperkalaemic periodic paralysis).
- ▶ (4) **Referral to support services** — for disorders with limited treatment (e.g., Huntington’s): PT/OT, social work, support groups, and consideration of PGT/**prenatal diagnosis** for reproductive choices.

- ▶ **Pharmacogenetic interventions** individualise drug therapy and avoid toxicity — *TPMT* (thiopurines), *DPYD* (5-FU/capecitabine), *G6PD*, malignant hyperthermia, and *CYP2C9/VKORC1* (warfarin, though clinical-algorithm superiority is unproven).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Three-generation pedigree (Harrison Fig. 480-1 style)**: draw squares (males)/circles (females), a diagonal line for deceased, an *arrow* marking the **proband**, with affected individuals shaded and annotated with diagnosis + age (e.g., “Breast ca 44”, “Ovarian ca 54”); show paternal-side breast/ovarian clustering suggesting *BRCA1/2*. Labels: I–IV generations, proband arrow, key (breast cancer, ovarian cancer).
- ▶ **Algorithm “Approach to genetic testing” (Fig. 480-2)**: boxes — *Patient identified by clinical/family history* → *Pretest counselling + informed consent (multigene panel/WES)* → *Mutational analysis* → *Interpretation in context of personal/family history* → *Post-test counselling & treatment implications for patient and family* → *Return to primary-care follow-up*.

Clinical / Diagnostic significance

- ▶ **Methods of testing**: PCR-based DNA sequencing; cytogenetics/karyotype; FISH; MLPA for copy-number changes; **massively parallel (next-generation) sequencing** — multigene panels, **whole-exome (WES)** and whole-genome sequencing; immunohistochemistry for mismatch-repair proteins (universal Lynch screening).
- ▶ **Prenatal techniques**: **amniocentesis** (~16 weeks), **chorionic villus sampling** (9–12 weeks, earlier if termination considered), **percutaneous umbilical blood sampling/cordocentesis** (~18 weeks), and non-invasive **cell-free fetal DNA** from maternal blood.
- ▶ **Interpretation caveats**: an *uninformative negative* does not exclude disease; manage by personal/family history. A **VUS** should not drive management until reclassified. Beware **incidental/secondary findings** (ACMG SF actionable-gene list) and direct-to-consumer testing (variable quality; results “not for medical management”).
- ▶ **Population screening** (e.g., *BRCA*, Lynch, *LDLR*, *TTR*) is emerging but limited by penetrance, VUS handling and equity concerns.

High-yield exam pointers

- ▶ **Test the affected relative first**; then offer **cascade testing** — most informative and cost-effective strategy.
- ▶ **Genetic testing must never precede counselling and informed consent**.
- ▶ **Presymptomatic** (Huntington’s, ~100% risk) vs **predisposition** (hereditary colon cancer, < 100%) testing — know the distinction.

- ▶ **Quad test** = AFP + β -hCG + inhibin-A + unconjugated estriol; abnormal result is a prenatal indication.
- ▶ **Advanced maternal age** > 35 years is a classic amniocentesis indication.
- ▶ **MEN2** → **prophylactic thyroidectomy**; **FAP** → **colonoscopy from 10–15 yr** — the two paediatric exceptions to deferring adult-onset testing.
- ▶ **GINA (2008)** protects against health-insurance/employment (not life/disability) discrimination.
- ▶ **BRCA1/2**: risk-reducing salpingo-oophorectomy proven to reduce mortality; **PARP inhibitors** are the targeted therapy.
- ▶ Four intervention categories: **surveillance**, **specific medical/surgical therapy**, **risk avoidance**, **supportive referral**.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “The Integration of Inherited Genetics into Clinical Practice” (family history/pedigree, testing strategies, informed consent, follow-up care, Table 480-2 conditions–genes–interventions, GINA, presymptomatic vs predisposition testing, therapeutic interventions, pharmacogenetics) and “Principles of Human Genetics” (prenatal diagnosis—amniocentesis/CVS/PUBS/cfDNA, Table 479-4 indications across the life span, postnatal cytogenetic indications, ethical issues).

Coverage note: This topic is covered well by Harrison; the spec lists no dedicated subspecialty textbook and CMDT was not required, so the answer is grounded in Harrison 22e chapters 479–480. All genes, inheritance patterns, doses/timings (amniocentesis 16 wk, CVS 9–12 wk, PUBS ~18 wk) and interventions are verbatim from these chapters.



What are the pathways of complement system and the effector actions of each? Discuss how it impacts immunity

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — The **complement system** is a major soluble effector arm of *innate immunity*: a cascade of ~30 plasma and membrane proteins (predominantly **serine proteases**, regulators and receptors) that are activated sequentially, each cleaving and activating the next. Activation proceeds via **four pathways** — three initiating routes (**classical**, **lectin/MBL**, **alternative**) that converge on cleavage of C3, and a shared **terminal pathway** that assembles the lytic **membrane attack complex (MAC)**. Its three cardinal effector functions are **opsonisation**, generation of **inflammatory anaphylatoxins**, and **cytolysis**, and it forms the principal molecular bridge linking innate to adaptive immunity.

The three initiating pathways and the common terminal pathway

Feature	Classical pathway	Lectin (MBL) pathway	Alternative pathway
Trigger	Antigen–antibody immune complexes (IgM, IgG1, IgG2, IgG3) bound to C1q	Microbial surfaces bearing terminal mannose groups	Spontaneous C3 “tick-over”; C3b deposited directly on microbes / “altered self” (tumour cells) — <i>antibody-independent</i>
Recognition / initiating proteins	C1 complex = C1q–C1r–C1s	MBL (a collectin) + MASP-1 and MASP-2 (substitute for C1q, C1r, C1s)	Factor D, factor B, C3; stabilised by properdin (factor P)
Early activation	C1s cleaves C4 → C4a + C4b and C2 → C2a + C2b	MASPs cleave C4 and C2 (identical to classical from here on)	Factor D cleaves factor B (bound to C3b) → Bb
C3 convertase	C4b2a	C4b2a	C3bBb (properdin-stabilised)
C5 convertase	C4b2a3b	C4b2a3b	C3bBb3b
Immunological role	Links adaptive → innate immunity via specific antibody	Pattern-recognition of carbohydrate (true innate)	Powerful amplification loop for any C3b deposited by any pathway

- ▶ All three routes converge at **C3 cleavage** ($C3 \rightarrow C3a + C3b$) and then on the **terminal pathway**: the C5 convertase cleaves $C5 \rightarrow C5a + C5b$; C5b sequentially recruits C6, C7, C8 and multiple C9 (poly-C9) to form the MAC (C5b-9), which inserts into the lipid bilayer of bacteria or target cells and causes osmotic lysis.
- ▶ The cascade is *enzymatic and amplifying* — a single convertase cleaves many C3 molecules, so a small trigger produces a large effector response. The components are mostly serine proteases acting in a defined order.

Effector actions of complement

Effector molecule(s)	Action	Immunological consequence
C3b (and C4b, C1q, iC3b)	Opsonisation — coats microbe/target	Binds phagocyte complement receptors (CR1/CD35, CR3) → enhanced phagocytosis and clearance
C3a, C5a (also weak C4a)	Anaphylatoxins	Mast-cell/basophil degranulation, ↑ vascular permeability, smooth-muscle contraction; C5a is a potent neutrophil

Effector molecule(s)	Action	Immunological consequence
		chemoattractant and activator → acute inflammation
C5b-9 (MAC)	Cytolysis / membrane perturbation	Direct lysis of bacteria (esp. <i>Neisseria</i>) and of antibody-coated cells
C3b/C4b on immune complexes	Immune-complex solubilisation & clearance	ICs bound by erythrocyte CR1 (CD35) are ferried to liver/spleen reticulo-endothelial system for safe disposal
C3d-antigen on B cells	Immune adjuvant	C3d engages CR2 (CD21) on B cells, lowering the threshold for B-cell activation — couples innate sensing to antibody production

- In summary (Harrison): complement cleavage products **facilitate microbe/damaged-cell clearance** (C1q, C4, C3), **promote inflammation** (anaphylatoxins C3a, C5a), and **promote lysis** (MAC).

Regulation of complement (why self is spared)

Tight regulation prevents bystander injury to host tissue; loss of a regulator causes characteristic disease.

Regulator	Type	Function	Loss / dysfunction causes
C1 inhibitor (C1-INH)	Plasma serpin	Inactivates C1r/C1s, MASPs and kallikrein; limits bradykinin generation	Hereditary angioedema (↓C4, ↓C2)
Factor H	Plasma	Cofactor for factor I; decay of alternative C3 convertase	aHUS, C3 glomerulopathy; deficiency → haemolytic-uraemic syndrome
Factor I	Plasma protease	Cleaves/inactivates C3b and C4b	Pyogenic infections
DAF / CD55	GPI-anchored membrane	Accelerates decay of C3/C5 convertases; blocks C3-fragment binding	Lost in PNH

Regulator	Type	Function	Loss / dysfunction causes
CD59 (protectin)	GPI-anchored membrane	Blocks MAC (C9) insertion	Lost in PNH → intravascular haemolysis
MCP / CD46	Membrane	Cofactor for factor I	aHUS

Impact on immunity — how complement shapes host defence

- ▶ **Frontline innate defence:** lyses and opsonises pathogens within minutes of exposure, before antibody is available; the lectin and alternative pathways need no prior immunity (true pattern-recognition / innate arms).
- ▶ **Bridge to adaptive immunity:** classical-pathway activation via **immune-complex binding to C1q links innate and adaptive systems** through specific antibody; C3d-coated antigen amplifies B-cell responses (CR2/CD21), so complement is also an *adjuvant* for antibody production.
- ▶ **Inflammation & leukocyte recruitment:** C5a and C3a recruit and activate neutrophils, mast cells and basophils (which bear C3a/C5a receptors), orchestrating acute inflammation.
- ▶ **Immune-complex homeostasis:** efficient IC clearance prevents tissue deposition; *early* complement deficiency → defective clearance → **immune-complex disease** (SLE-like syndromes, glomerulonephritis, vasculitis).
- ▶ **A double-edged sword:** the same effectors that protect can injure host tissue when dysregulated — e.g. complement-fixing (C1-binding) IgM/IgG mediates **type II cytotoxic** reactions (transfusion haemolysis, Goodpasture's, pemphigus vulgaris) and contributes to **type III immune-complex injury**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Diagram 1 — The four pathways converging on C3 and the MAC.** Three parallel columns feeding a common stem. Labels: *Classical* (Ag-Ab complex → C1q-C1r-C1s → C4, C2 → C4b2a); *Lectin* (mannose → MBL + MASP-1/2 → C4, C2 → C4b2a); *Alternative* (microbial surface, C3 tick-over → factor B, factor D, properdin → C3bBb); arrows from all three to C3 → C3a + C3b; then C5 convertase → C5 → C5a + C5b → C6, C7, C8, C9 (poly-C9) = MAC (C5b-9) → cell lysis. Side annotations: C3a/C5a = **anaphylatoxins (inflammation)**, C3b = **opsonin (phagocytosis)**, MAC = **lysis**.
- ▶ **Diagram 2 — Membrane regulators in PNH.** RBC membrane with GPI-anchored CD55 (blocks C3 convertase) and CD59 (blocks MAC); show their loss after PIGA mutation → C3b deposition → MAC-mediated **intravascular haemolysis**; mark site of **eculizumab** (anti-C5) block.

Clinical / Diagnostic significance

- ▶ **Pattern of deficiency predicts the disease (Table 360-12):**
 - Early classical components (C1q, C1r, C1s, C4, C2) → immune-complex syndromes (SLE, SLE-like, GN, vasculitis) and pyogenic infection with encapsulated organisms (*S. pneumoniae*).
 - C3 / alternative pathway (C3, factor D) → severe pyogenic infections + immune-complex disease.
 - Properdin → invasive *Neisseria* infection; factor H/I → HUS / pyogenic infection.
 - Terminal/MAC components (C5–C8; rarely C9) → recurrent *Neisseria* (meningococcal) infections.
- ▶ **Acquired complement disorders:**
 - **Paroxysmal nocturnal haemoglobinuria (PNH):** acquired PIGA mutation blocks GPI-anchor synthesis → loss of CD55 + CD59 → MAC-mediated **intravascular haemolysis**, haemoglobinuria, thrombosis; Coombs-negative. Treated with **eculizumab/ravulizumab** (anti-C5); **pegcetacoplan** (anti-C3) also curbs C3d-mediated extravascular haemolysis.
 - **Hereditary angioedema:** C1-INH deficiency → unopposed kallikrein/bradykinin → recurrent **non-pruritic, non-urticarial angioedema** with GI involvement; complement screen shows low C4 (and C2).
- ▶ **Therapeutics targeting complement:** eculizumab/pezelimab (anti-C5) for PNH/aHUS/CHAPLE; C3-directed agents; recombinant C1-INH for HAE — illustrating complement as a druggable pathway.
- ▶ **Useful tests:** CH50 (screens the entire classical→terminal pathway; zero/very low suggests a complete component deficiency), AH50 (alternative pathway), and individual **C3/C4 levels** (low C4 with normal C3 favours classical-pathway/C1-INH problems; low C3 favours alternative-pathway activation).

High-yield exam pointers

- ▶ **Four pathways = classical + lectin + alternative (initiating) + terminal (common).** All converge on C3, then MAC (C5b-9).
- ▶ **C3 convertases:** classical/lectin = C4b2a; alternative = C3bBb (properdin-stabilised). C5 convertases: C4b2a3b and C3bBb3b.
- ▶ **Lectin pathway** uses MBL + MASP-1/MASP-2 in place of C1q/C1r/C1s; triggered by **mannose**.
- ▶ **Three effectors:** opsonisation (C3b), anaphylatoxins (C3a, C5a; C5a = chemotactic), lysis (MAC); plus **immune-complex clearance** (RBC CR1/CD35) and **B-cell adjuvant** (C3d–CR2/CD21).
- ▶ **Antibody isotypes fixing classical complement:** IgM (most potent) and IgG1, IgG2, IgG3 (via C1q); IgG4 and IgA do not fix classical complement.

- ▶ Early-component deficiency → SLE / immune-complex disease; terminal (MAC) deficiency → recurrent *Neisseria*.
- ▶ PNH = loss of GPI-anchored CD55 + CD59 (PIGA); treat with anti-C5 eculizumab.
- ▶ Hereditary angioedema = C1-INH deficiency, bradykinin-mediated, low C4, no urticaria.
- ▶ Complement is the key molecular bridge between innate and adaptive immunity.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Introduction to the Immune System” (four pathways, MASP/MBL, C3/C5 convertase convergence, MAC, anaphylatoxins, opsonisation, immune-complex clearance, Table 360-12 Complement Deficiencies and Associated Diseases, antibody complement-fixation); “Mechanisms of Regulation and Dysregulation of the Immune System” (complement-targeting biologics — eculizumab/pezelimab); “Hemolytic Anemias” (PNH — CD55/CD59, PIGA, eculizumab/pegcetacoplan); “Urticaria, Angioedema, and Allergic Rhinitis” (C1-INH deficiency / bradykinin-mediated hereditary angioedema, low C4/C2).
- ▶ **Coverage note:** The precise **convertase subunit formulae** (C4b2a, C3bBb, C4b2a3b, C3bBb3b), the **CR2/CD21–C3d** B-cell adjuvant link, properdin's *stabilising* role, and the laboratory screens **CH50/AH50** are universally accepted standard immunology (Janeway/Abbas) used to complete the answer; Harrison states the pathway proteins (C1/C4/C2; factor D/B/C3; MBL/MASP) and effector outcomes but does not spell out every convertase formula verbatim.



What is polymerase chain reaction? How is DNA sequencing done? Give examples of its use in diagnosis of disease conditions

Asked in: Paper I May 2025 — RGUHS MD General Medicine

Definition / Introduction — The **polymerase chain reaction (PCR)** is a *nucleic acid amplification test (NAAT)* that amplifies a specific region of DNA in vitro into millions of copies using sequence-specific oligonucleotide primers and a thermostable DNA polymerase. **DNA sequencing** is the determination of the precise order of nucleotide bases (A, T, G, C) in a DNA segment, performed historically by the *Sanger (dideoxy chain-termination)* method and now predominantly by *next-generation (massively parallel) sequencing*. Together these molecular tools underpin modern diagnosis of inherited, infectious and neoplastic disease, allowing genetic testing and mutational analysis from minute amounts of DNA extracted from leukocytes, buccal cells, or even single cells.

Principle, requirements and components of PCR

- ▶ **Principle** — *exponential, primer-directed enzymatic amplification* of a target sequence; each cycle theoretically doubles the template, so n cycles yield $\approx 2^n$ copies (25–40 cycles produce millions to billions of copies).
- ▶ **Template** — the double-stranded DNA containing the region of interest (genomic, plasmid, or, after reverse transcription, cDNA).
- ▶ **Primers** — a pair of short single-stranded oligonucleotides (~18–25 bp) complementary to sequences flanking the target; they define specificity. *Even a single base-pair mismatch, particularly near the 3' end of the primer, may abolish amplification* (Harrison).
- ▶ **Thermostable DNA polymerase** — *Taq polymerase* (from the thermophilic bacterium *Thermus aquaticus*), which survives repeated high-temperature denaturation.
- ▶ **dNTPs** (the four deoxynucleotide building blocks), **Mg²⁺-containing buffer**, and a programmable **thermal cycler**.
- ▶ A key strength is sensitivity: PCR enables genetic and mutational analysis with very small quantities of DNA, and **DNA sequencing can be performed directly on PCR products**.

The three steps of a PCR cycle

Step	Temperature (typical)	Event
1. Denaturation	~94–95 °C	Double-stranded template separates into two single strands
2. Annealing	~50–65 °C	Primers hybridise to their complementary flanking sequences
3. Extension (elongation)	~72 °C	<i>Taq</i> polymerase synthesises the new strand 5'→3' from each primer

- ▶ The cycle is repeated 25–40 times; an initial denaturation and a final extension flank the cycling. Product is detected by *agarose gel electrophoresis*, fluorescence (real-time PCR), or downstream sequencing.

Modifications / types of PCR

Variant	Key feature & use
Reverse-transcriptase PCR (RT-PCR)	RNA first converted to cDNA by reverse transcriptase, then amplified — used for RNA viruses (HIV, HCV, SARS-CoV-2, influenza) and fusion transcripts
Real-time / quantitative PCR (qPCR)	Fluorescent signal measured per cycle → <i>quantifies</i> template (e.g. HIV/HBV/HCV viral load); RT-qPCR combines both

Variant	Key feature & use
Multiplex PCR	Several primer sets in one reaction → <i>syndromic panels</i> (respiratory, gastroenteritis, meningoencephalitis) detecting many pathogens at once
Nested PCR	Two sequential amplifications with internal primers → increased sensitivity/specificity (standard molecular biology)
Isothermal amplification (e.g. LAMP)	Amplifies at a single temperature without thermal cycling → point-of-care/field and resource-limited settings

DNA sequencing — Sanger (first-generation) method

- ▶ **Principle: dideoxy chain termination.** The denatured template, a primer, DNA polymerase, normal dNTPs and a small proportion of fluorescently-labelled **dideoxynucleotides (ddNTPs)** are combined.
- ▶ Because ddNTPs lack the **3'-hydroxyl group**, their incorporation halts further chain elongation, generating a nested set of fragments terminating at every base position.
- ▶ Fragments are resolved by size on **capillary electrophoresis**; the fluorescent terminators are read off as a **chromatogram** (Harrison shows “*chromatograms of sequence analyses after amplification of genomic DNA by PCR*” — Fig. 479-10B).
- ▶ Sanger sequencing of PCR products remains the reference standard for *single-gene/targeted* mutation confirmation.

Next-generation (NGS) and third-generation sequencing

- ▶ **Next-generation / massively parallel sequencing** produces *millions of sequences concurrently*, far beyond the capacity of prior dye-terminator methods, with cost per genome falling steeply.
- ▶ Clinical formats:
 - **Targeted gene panels** — multiple candidate genes captured by hybridisation then deep-sequenced (locus-heterogeneous disorders, somatic tumour panels).
 - **Whole-exome sequencing (WES)** — all coding exons; used for undiagnosed/rare syndromes.
 - **Whole-genome sequencing (WGS)** — entire genome, including non-coding regions.
 - **RNA sequencing (RNA-Seq)** — gene fusions, aberrant expression.
- ▶ **16S ribosomal RNA gene sequencing** identifies fastidious/unculturable bacteria; **metagenomic** (“shotgun”) and **cell-free DNA sequencing** allow *unbiased* pathogen discovery (e.g. *Leptospira* DNA found in CSF → neuroleptospirosis confirmed by retrospective PCR). **Long-read (third-generation)** platforms resolve repeats, plasmids and structural variants.

- *Caveats*: NGS detects numerous **variants of uncertain significance (VUS)** and incidental (secondary) findings, demands heavy bioinformatics, and may miss copy-number variants if not specifically analysed.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — One PCR cycle**: draw double-stranded template; arrow to *Denaturation* (~94 °C) showing two separated single strands; *Annealing* (~55 °C) showing forward and reverse primers bound; *Extension* (~72 °C) with Taq polymerase synthesising new strands; loop arrow back labelled “repeat ×25–40 → exponential 2ⁿ amplification.” Label: **template, primers, Taq polymerase, dNTPs, 5'/3' ends.**
- **Diagram 2 — Sanger sequencing**: template + primer + DNA polymerase + dNTPs + labelled ddNTPs; show a ladder of chain-terminated fragments of increasing length; arrow to **capillary electrophoresis** and a four-colour **chromatogram** read 5'→3'. Label: **ddNTP (no 3'-OH), chain termination, fluorescent peaks A/T/G/C.**

Clinical / Diagnostic significance

- **Infectious disease (NAAT-based)**:
 - *Tuberculosis* — PCR amplification of the **rpoB gene** identifies *M. tuberculosis* directly in sputum and simultaneously detects **rifampicin resistance** (Xpert-type NAAT-R); CMDT: NAAT sensitivity/specificity 85–97% in smear-positive specimens, resistance-marker specificity > 98%.
 - *HIV* — **RT-qPCR viral load** for diagnosis/monitoring; **genotypic resistance testing** is standard before therapy (e.g. the **K103N** reverse-transcriptase mutation predicts efavirenz resistance).
 - *Hepatitis B/C, SARS-CoV-2, influenza* — PCR/RT-PCR for detection and treatment response; multiplex **respiratory viral panels**.
 - *Antibiotic resistance* — **mecA** (PBP2A) PCR for **MRSA**; **van** genes for **VRE**; multiplex carbapenemase PCR (**KPC, NDM, OXA-48, IMP1, VIM**).
- **Inherited single-gene disorders**: PCR-based mutation panels detect **CFTR ΔF508** (cystic fibrosis), **β-globin Glu6Val/E6V** (sickle cell), and **trinucleotide-repeat expansions** (fragile X, Huntington's CAG repeat), including premutation sizing. Used for carrier testing, **prenatal diagnosis** (amniocentesis/CVS with FISH + mutational analysis), and non-invasive prenatal **cfDNA** screening for aneuploidy/fetal sex.
- **Oncology / haematology**: RT-PCR for **BCR-ABL1 [t(9;22)]** diagnoses and monitors CML/Ph⁺ ALL minimal residual disease; tumour **mutational profiling/NGS** identifies *actionable driver mutations* guiding targeted therapy; **liquid-biopsy cfDNA** for minimally invasive diagnosis and surveillance; **BRCA1/BRCA2** testing for hereditary cancer risk.

- ▶ **Pharmacogenomics:** genotyping guides drug choice and dosing.
- ▶ **Pitfalls:** interpret NAAT against **pre-test probability** (a negative result in high-probability TB does not exclude disease); risk of **contamination/false positives**; detection of a microbial sequence alone does not prove causation (Koch's postulates); allelic heterogeneity means a negative targeted panel does not exclude a mutation elsewhere.

High-yield exam pointers

- ▶ PCR = in-vitro amplification needing **template, two primers, Taq polymerase (from Thermus aquaticus), dNTPs, Mg²⁺, thermal cycler**.
- ▶ Three steps: **Denaturation** (~94 °C) → **Annealing** (~55 °C) → **Extension** (~72 °C); ≈2ⁿ amplification over 25–40 cycles.
- ▶ RT-PCR for RNA (HIV, HCV, SARS-CoV-2); **qPCR** quantifies (viral load); **multiplex** = syndromic panels.
- ▶ **Sanger sequencing** uses **dideoxynucleotides (no 3'-OH)** → **chain termination**, read as a chromatogram; **NGS** = massively parallel (WES, WGS, panels).
- ▶ TB: **rpoB** PCR detects organism and **rifampicin resistance**; MRSA = **mecA**; VRE = **van** genes.
- ▶ Heme-onc: **BCR-ABL1** RT-PCR for CML/MRD; tumour NGS for **actionable mutations**; **cfDNA liquid biopsy**.
- ▶ Genetic: CFTR ΔF508, sickle E6V, fragile X / **Huntington repeat expansions**; prenatal cfDNA (NIPT).
- ▶ **16S rRNA / metagenomic / cfDNA sequencing** identifies culture-negative and novel pathogens.

SOURCE & COVERAGE

- ▶ **Harrison's Principles of Internal Medicine, 22e** — “Principles of Human Genetics” (mutational analysis, Sanger chromatograms after PCR amplification, NGS/WES/WGS, targeted panels, repeat-expansion and single-gene examples, prenatal diagnosis) and “Microbial Genomics and Infectious Disease” (NAAT/PCR definitions, RT-PCR, multiplex syndromic panels, 16S rRNA and metagenomic/cfDNA sequencing, rpoB/TB, HIV genotyping K103N, mecA/MRSA, van/VRE, carbapenemase panels, MALDI-TOF context).
- ▶ **CMDT 2026** — “Pulmonary Disorders” (NAAT-TB and resistance-marker performance characteristics for tuberculosis).
- ▶ *Coverage note:* The corpus covers PCR and DNA sequencing as laboratory techniques only thinly (spec gap = true). The **step-level mechanism of PCR** (denaturation/annealing/extension temperatures, *Taq*/Thermus aquaticus) and the **dideoxy chain-termination basis of Sanger sequencing** are not described in mechanistic detail in Harrison/CMDT; these are included as universally accepted standard molecular

biology. All disease examples, the rpoB/mecA/van/carbapenemase/HIV-genotype details, the NGS/16S/metagenomic content and the single-gene/repeat-expansion examples are directly grounded in the cited chapters.



When, Where and How Do You Monitor Drug Therapy? Illustrate with Examples

Asked in: Paper I 06 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Monitoring of drug therapy* is the systematic process of assessing whether a prescribed drug is producing the intended benefit while staying within a safe exposure range, so that the dose can be individualised. It is achieved by tracking **clinical endpoints**, **physiological/biochemical surrogate markers**, **direct plasma (serum/whole-blood) drug-concentration measurement** — *therapeutic drug monitoring (TDM)* — and increasingly by **pharmacogenomic testing**. The unifying rationale is the **therapeutic window** (therapeutic index/ratio): the separation between the concentration needed for efficacy and that producing toxicity. Where this window is narrow and a definable concentration–effect relationship exists, monitoring lets the clinician keep the drug above the minimum effective and below the toxic concentration.

Goals and the four modalities of monitoring (HOW)

- ▶ The desired goal of any drug therapy is to **maximise the likelihood of benefit while minimising the risk of adverse drug reactions (ADRs)**. Monitoring operationalises this for the individual patient, because outcome varies widely owing to pharmacokinetic and pharmacodynamic differences (genetics, organ dysfunction, drug interactions, adherence, age).
- ▶ **1. Clinical/symptomatic endpoints** — the simplest method: relief of pain or palpitations, seizure frequency, mood; the patient reports efficacy. Useful when effect is directly observable.
- ▶ **2. Physiological / biochemical surrogate markers** — objective, repeatable tests that track effect: blood pressure (antihypertensives), INR (warfarin), aPTT/anti-Xa (heparin), blood glucose and HbA1c (insulin/oral hypoglycaemics), TSH (levothyroxine), LDL cholesterol (statins), QT interval on ECG (sotalol, dofetilide).
- ▶ **3. Plasma drug-concentration measurement (TDM)** — quantifying the drug itself; reserved for agents where concentration predicts effect/toxicity but no easy clinical surrogate exists (anticonvulsants, antirejection agents, antiarrhythmics, antibiotics).
- ▶ **4. Toxicity surveillance and pharmacogenomic testing** — periodic organ-function/haematology checks to catch dose-dependent toxicity, plus pre-emptive genotyping to predict variant responders.

WHEN do you monitor — indications and timing

- ▶ **Patient-side (clinical) indications to measure a drug level:** narrow therapeutic index drug; suspected **toxicity** that mimics the underlying disease (e.g. digoxin, lithium, phenytoin); **failure of efficacy** (to detect non-adherence, an interaction, or use of expired/degraded drug); suspected **non-adherence**, especially in chronic disease (hypertension, HIV) and multi-dose regimens; after a **dose change**, or after starting/stopping an interacting drug; in **organ dysfunction** (renal/hepatic) and at extremes of age; and for drugs with **saturable (zero-order) kinetics** such as phenytoin, where small dose increments cause disproportionate rises.
- ▶ **Pharmacokinetic timing — sample at steady state:** steady state is reached after ~4–5 **elimination half-lives** following initiation or any dose change; levels drawn earlier underestimate the eventual concentration.
- ▶ **Trough vs peak:** for *efficacy and most chronic dosing*, draw a **trough** — the lowest concentration, **just before the next dose** at steady state (anticonvulsants, vancomycin, ciclosporin, tacrolimus). For drugs where **toxicity tracks the peak**, sample at the anticipated peak — e.g. evaluate the ECG/QT 1–2 h post-dose at steady state with sotalol/dofetilide; draw an **aminoglycoside peak** 30 min after the end of a 30–60 min infusion.
- ▶ **Drug-specific timing pitfalls:** digoxin must **not** be drawn within **6 h of an oral** (or 4 h of an IV) dose because distribution is incomplete; **lithium** is sampled at a standard **12 h post-dose**; **methotrexate** is checked at **48 h** to guide leucovorin rescue.

WHERE do you monitor — specimen, site and setting

- ▶ **Specimen/matrix:** most TDM uses **serum from a plain (red-top) tube**, drawn at trough. Two important exceptions are **ciclosporin and tacrolimus**, which partition into red cells and require **whole blood in an EDTA (lavender-top) tube**.
- ▶ **Free vs total drug:** only **unbound drug** is pharmacologically active. For highly protein-bound drugs in hypoalbuminaemia/uraemia (classically **phenytoin**, and **valproate**), measure the **free (unbound) concentration** — target free phenytoin 0.5–2 mg/L — because total levels mislead.
- ▶ **Sampling site of effect:** plasma concentration is only a surrogate for concentration at the target. Where tissue and plasma levels diverge (e.g. **P-glycoprotein** excluding drug from brain at the blood–brain barrier; drug acting outside plasma), plasma TDM is **not** a reliable guide and clinical/physiological monitoring is preferred.
- ▶ **Clinical setting:** ranges from the **ward/ICU** (vancomycin and aminoglycoside levels, lithium, antiepileptics, immunosuppressants, anticoagulation) to the **outpatient/anticoagulation clinic** (INR, HbA1c, TSH, BP) and **pharmacovigilance systems** (spontaneous ADR reporting, e.g. MedWatch) for population-level safety signals.

Which drugs need plasma-concentration monitoring (TDM) — criteria + ranges

A drug warrants plasma TDM when **most** of the following apply: narrow therapeutic index; good concentration–effect/toxicity correlation; wide inter-individual pharmacokinetic variability; **no easily measured clinical endpoint**; toxicity that resembles the disease being treated; or saturable kinetics. By contrast, drugs with a direct surrogate (warfarin→INR, heparin→aPTT, insulin→glucose) do **not** need level monitoring.

Drug	Effective (target) concentration	Sampling note
Digoxin	0.5–0.9 ng/mL (heart failure); 0.5–2 ng/mL (AF)	Trough; not within 6 h of oral dose; hypokalaemia potentiates toxicity
Lithium	0.5–1.2 mmol/L	12 h post-dose; thiazide/loop diuretics raise levels
Phenytoin	10–20 mg/L (5–10 in uraemia/hypoalbuminaemia); free 0.5–2 mg/L	Trough; zero-order (capacity-limited) kinetics
Valproate (total)	50–100 mg/L (50–125 for bipolar)	Total + free preferred in renal/liver disease
Carbamazepine	4–12 mg/L	Auto-induces own metabolism
Phenobarbital	10–40 mg/L	—
Theophylline	5–15 mg/L (panic ≥30)	Clearance ↑1.5–2× in smokers
Vancomycin	Trough 10–20 mg/L	Trough used for efficacy and to limit nephrotoxicity
Gentamicin / Tobramycin	Conventional peak 4–8 / 5–10 mg/L; trough <2 mg/L	Peak 30 min post-infusion; trough pre-dose
Amikacin	Peak 20–30 mg/L; trough <8 mg/L	Once-daily high-dose: peak ~60, trough <5
Ciclosporin	100–300 ng/mL (12-h trough)	Whole blood (EDTA)
Tacrolimus	Trough 8–12 ng/mL	Whole blood; CYP3A5-dependent dosing
Methotrexate	<0.1 µmol/L at 48 h	Higher → escalate leucovorin ; glucarpidase if renal failure

Surrogate monitoring, toxicity surveillance and pharmacogenomic (“pre-emptive”) monitoring

- Surrogate endpoints (no drug level needed): *warfarin* → INR (target ~2–3); *unfractionated heparin* → aPTT (~1.5–2.5×) or anti-Xa; *insulin* / *sulfonylureas* → capillary glucose and HbA1c; *antihypertensives* → BP; *levothyroxine* → TSH; *statins* → LDL-C for efficacy.

- ▶ **Toxicity surveillance (organ-function/haematology):** serum creatinine/eGFR with aminoglycosides, vancomycin and digoxin (and dose-reduce renally cleared dofetilide/sotalol to avoid QT prolongation); LFTs with valproate, methotrexate and anti-tubercular drugs; CBC with carbamazepine, methotrexate and clozapine; serum K^+ with digoxin (hypokalaemia potentiates toxicity).
- ▶ **Pharmacogenomic testing** identifies variant responders *before or during* therapy:

Gene	Drug	Why test / action
TPMT / NUDT15	Azathioprine, 6-mercaptopurine	Loss-of-function → life-threatening myelosuppression; reduce dose/avoid
*HLA-B1502**	Carbamazepine (Asian/Indian ancestry)	Avoid — risk of SJS/TEN
*HLA-B5701**	Abacavir	Avoid — hypersensitivity reaction
*HLA-B5801**	Allopurinol (Han Chinese/Korean/Thai)	Avoid — SJS/TEN
G6PD	Rasburicase, tafenoquine, primaquine	Deficiency → haemolysis/methaemoglobinaemia; use alternative
CYP2C19	Clopidogrel	Loss-of-function → poor bioactivation, more CV events
CYP2C9 / VKORC1	Warfarin	Predict lower maintenance dose (–1639G>A)
DPYD	5-FU, capecitabine	Deficiency → severe/fatal toxicity; reduce/avoid
*UGT1A128**	Irinotecan	Reduced glucuronidation → neutropenia, diarrhoea
SLCO1B1 (c.521T>C)	Simvastatin	↑ levels → statin myopathy

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **Therapeutic window curve** (after Harrison Fig. 71-1): two overlapping sigmoid dose/concentration–response curves on the same axes — label “*Desired (therapeutic) effect*” (left curve) and “*Adverse effect / toxicity*” (right curve); shade the gap between them as the “**Therapeutic window / index**”; mark the *Minimum effective concentration* and *Minimum toxic concentration*; draw a *narrow window* inset where the curves nearly overlap (e.g. digoxin, lithium).
- ▶ **Steady-state accumulation curve** (after Fig. 71-4): concentration (y-axis) vs time in half-lives (x-axis) showing step-wise rise to a plateau; label “*Steady state at ~4–5 half-lives*”,

Gene	Drug	Why test / action
		“Trough — sample here (pre-dose)”, “Peak”, and show a loading dose reaching the plateau sooner without changing the final steady state.

Clinical / Diagnostic significance

- ▶ Converts empirical prescribing into **individualised, dose-optimised therapy**, reducing both treatment failure and dose-dependent toxicity.
- ▶ For **first-order drugs**, the steady-state level is linearly proportional to dose — if you want to double the level, double the dose; this does **not** hold for **zero-order** drugs (phenytoin, aspirin, fluoxetine), where a small increment can produce a disproportionate, toxic rise.
- ▶ A measured level distinguishes the differential of a deteriorating patient: e.g. worsening features on **digoxin/lithium/phenytoin** may be toxicity rather than disease progression.
- ▶ **Failure of efficacy** with a sub-therapeutic level points to **non-adherence, a drug interaction, or degraded/expired drug** — a frequent, correctable problem in chronic disease.
- ▶ In **renal disease**, reduce dose of renally cleared drugs (digoxin, dofetilide, sotalol) and consider free phenytoin; in **hepatic disease/cirrhosis**, oral bioavailability of high first-pass drugs (morphine, midazolam, nifedipine) roughly doubles — start low.

High-yield exam pointers

- ▶ **TDM indications mnemonic:** narrow therapeutic index + good concentration–effect correlation + no clinical surrogate + wide PK variability + toxicity mimicking disease + saturable kinetics.
- ▶ **Sample at steady state** = ~4–5 half-lives; trough = just before the next dose; aminoglycoside **peak** 30 min post-infusion.
- ▶ **Specimen:** serum (plain red-top) for most; **whole blood EDTA** for ciclosporin and tacrolimus.
- ▶ **Free-drug monitoring** for highly protein-bound **phenytoin/valproate** in uraemia/hypoalbuminaemia.
- ▶ **Phenytoin** = classic zero-order drug → small dose change, large level change.
- ▶ **Digoxin:** target 0.5–0.9 ng/mL in HF; don’t sample <6 h after oral dose; **hypokalaemia** potentiates toxicity.
- ▶ Drugs monitored by **surrogate, not level:** warfarin (INR), heparin (aPTT), insulin (glucose/HbA1c), antihypertensives (BP), levothyroxine (TSH).
- ▶ **QT interval** at 1–2 h post-dose for sotalol/dofetilide; **vancomycin trough** for efficacy/nephrotoxicity.
- ▶ **Pre-emptive pharmacogenomics:** TPMT/NUDT15 (thiopurines), HLA-B1502 (*carbamazepine*), HLA-B5701 (abacavir), HLA-B*5801 (allopurinol), G6PD (rasburicase/primaquine), DPYD (5-FU).

SOURCE & COVERAGE

- ▶ Harrison's *Principles of Internal Medicine*, 22e — "Principles of Clinical Pharmacology" (therapeutic index/window, pharmacokinetic timing, trough vs peak, QT and vancomycin monitoring, free vs total drug, zero-order kinetics, effects of renal/hepatic disease) and "Pharmacogenomics" (variant responders).
- ▶ CMDT 2026 — Appendix e5: "Therapeutic Drug Monitoring" (Table e5-1 target concentrations, half-lives, sampling specimens/timing) and "Selected Pharmacogenetic Tests: Clinical Relevance" (Table e5-2 — TPMT/NUDT15, HLA-B*57:01/*58:01, G6PD, CYP2C19, CYP2C9/VKORC1, DPYD, UGT1A1, SLCO1B1).
- ▶ *Coverage note*: INR target ~2–3 and heparin aPTT ~1.5–2.5× are stated as universally accepted standard internal medicine; the corpus confirms these drugs are monitored by INR/aPTT but does not quote the numeric targets in the chapters used.



X-linked Disorders

Asked in: Paper I Nov 2022 — RGUHS MD General Medicine

Definition / Introduction — X-linked disorders are monogenic diseases caused by mutations in genes residing on the **X chromosome**, so their transmission and expression are governed by sex. Because males carry only a single X (they are **hemizygous**), a mutant allele is fully expressed in them regardless of whether it is dominant or recessive, whereas heterozygous females show variable expression that depends on the degree of **X-inactivation** and the function of the gene. X-linked conditions account for roughly 5% of **human monogenic disorders** (about 65% are autosomal dominant and 25% autosomal recessive). The two hallmark pedigree features are **absence of father-to-son (male-to-male) transmission** and the fact that **all daughters of an affected male are obligate carriers**.

Genetic basis and terminology

- ▶ **Sex-chromosome transmission**: A daughter *always* inherits her father's single X plus one of her mother's two X chromosomes; a son inherits the Y from his father and one **maternal X**. Hence an affected father can never pass an X-linked allele to a son.
- ▶ **Hemizygosity**: Males have one X, so a single mutant allele produces the phenotype. Females may be **heterozygous** or **homozygous**; the qualifiers *X-linked dominant* and *X-linked recessive* therefore strictly describe expression of the mutant phenotype **in women**.
- ▶ **X-inactivation (functional mosaicism, "Lyonization")**: In every somatic cell of a female, most genes on one of the two X chromosomes are silenced. Random inactivation gives a ~50:50 mix of cells expressing each X; **skewed (non-random) inactivation** can unmask disease in a carrier ("manifesting carrier").

- ▶ **Carrier expression is gene-dependent:** Most heterozygous carriers of factor VIII deficiency (haemophilia A) are asymptomatic because enough factor VIII is made; in contrast, females heterozygous for α -galactosidase A deficiency (Fabry's disease) may develop mild painful neuropathy and other features.

X-linked recessive vs X-linked dominant — characteristic features

Feature	X-linked recessive (XLR)	X-linked dominant (XLD)
Males (hemizygous)	Affected by a single mutant allele	Affected; often severe, may be lethal in utero
Heterozygous females	Usually unaffected carriers (may manifest if X-inactivation skewed)	Affected (variable, generally milder than males)
Father → son transmission	Absent	Absent
Affected father's daughters	All obligate carriers	All affected
Pedigree pattern	“Criss-cross”; chiefly males affected, skipped generations	Affected in successive generations; ~2:1 female:male excess
Examples	Haemophilia A/B, G6PD deficiency, Duchenne/Becker MD, Fabry, Fragile X	Rett syndrome (MECP2)

Pedigree and segregation patterns

- ▶ **Affected male × normal female:** all daughters are obligate carriers, all sons unaffected (no male-to-male spread).
- ▶ **Carrier female × normal male (XLR):** each son has a **50% chance of being affected**; each daughter has a **50% chance of being a carrier** (standard Mendelian extension).
- ▶ **Skipped generations** with predominantly affected males are typical of XLR — the disease appears to “jump” through unaffected carrier females (criss-cross inheritance).
- ▶ XLD pedigrees resemble autosomal dominant transmission but show **no father-to-son transmission** and an excess of affected females.

Important X-linked disorders (grounded in Harrison 22e)

Disorder	Gene / product	Pattern	Key point / management
Haemophilia A	F8 / factor VIII	XLR	Factor VIII replacement; carrier females usually asymptomatic
Haemophilia B	F9 / factor IX	XLR	Factor IX replacement

Disorder	Gene / product	Pattern	Key point / management
G6PD deficiency	G6PD	XLR	Avoidance of oxidant drugs and certain foods
Fabry's disease	α -galactosidase A (GLA)	XLR	Lipid-storage defect; heterozygous females may have mild neuropathy
Duchenne / Becker MD	DMD / dystrophin	XLR	Commonest muscular dystrophy; corticosteroids, physiotherapy, antisense-oligonucleotide exon skipping, stop-codon read-through
Nephrogenic diabetes insipidus	AVPR2 (AQP2 is AR)	XL	Vasopressin-resistant; thiazide/low-solute measures
Fragile X (FRAXA / FRAXE)	FMR1 / FMR2 protein	XLR	CGG / GCC repeat expansion; intellectual disability
Spinobulbar muscular atrophy (Kennedy)	Androgen receptor (CAG)	XLR	Trinucleotide-repeat disease, Xq12
Androgen insensitivity	Androgen receptor	XL recessive (missense)	Complete/partial; 46,XY with female phenotype
Rett syndrome	MECP2 (methyl-binding protein)	XLD	Developmental regression + stereotypic hand movements in girls

- ▶ **Duchenne muscular dystrophy** is the **commonest cause of muscular dystrophy**, reflecting the very large DMD gene (2.3 Mb, 79 exons); the phenotype is expressed in hemizygous males who have only one X. Dystrophin is part of a large complex linking the cytoskeleton to the muscle membrane. DMD mutations cause severe **Duchenne** or milder **Becker** disease depending on the severity of the protein defect (allelic heterogeneity).

X-linked dominant and X-linked trinucleotide-repeat disorders

- ▶ **X-linked dominant**: mutant allele expressed in heterozygous females and hemizygous males; many are **lethal or very severe in males** (e.g., **Rett syndrome (MECP2)**, which predominantly affects girls). *Standard additional examples*: X-linked (vitamin D-resistant) hypophosphataemic rickets and incontinentia pigmenti.

- ▶ **X-linked trinucleotide-repeat (dynamic-mutation) disorders** (Harrison Table 479-5):
 - **Fragile X (FRAXA)**: CGG repeat, Xq27.3; normal 6–50 → disease 200–300 (full mutation), FMR-1 protein.
 - **Fragile X (FRAXE)**: GCC repeat, Xq28; FMR-2 protein.
 - **Spinobulbar muscular atrophy (Kennedy)**: CAG repeat, Xq12; normal 11–34 → disease 40–62; androgen receptor.
- ▶ **Anticipation**: when repeat length increases across generations, disease becomes more severe or presents earlier — a key feature of these dynamic-mutation X-linked diseases.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- ▶ **X-linked recessive pedigree (3 generations)**: labels — *Affected male* (filled square), *Carrier female* (circle with central dot), *Unaffected male/female* (open symbols), “No male-to-male transmission”, “All daughters of affected male = obligate carriers”, “Skipped generation / criss-cross inheritance”.
- ▶ **Punnett square — carrier mother ($X^A X$) × normal father ($X Y$)**: label gametes X^A , X (mother) and X , Y (father); offspring boxes — *Unaffected daughter* (XX), *Carrier daughter* ($X^A X$), *Unaffected son* (XY), *Affected son* ($X^A Y$); annotate “50% sons affected, 50% daughters carriers.”

Clinical / Diagnostic significance

- ▶ **Carrier detection and counselling**: identifying obligate/possible carrier females (daughters of affected men, mothers of an affected son) allows **genetic counselling, prenatal diagnosis and recurrence-risk estimation**; molecular testing is now routine for monogenic disorders.
- ▶ **Manifesting carriers**: skewed X-inactivation explains why some carrier women (e.g., Fabry, occasionally DMD) show clinical features — do not assume all female carriers are asymptomatic.
- ▶ **Genotype–phenotype and management**: DMD mutation type predicts Duchenne vs Becker severity; targeted therapies include **exon-skipping antisense oligonucleotides** and **stop-codon read-through**. G6PD carriers/patients must **avoid oxidant drugs and fava beans**; haemophilia is managed with the **specific deficient factor**.
- ▶ **Sex-reversal correlate (Y-linked)**: SRY/testis-determining factor and AZF deletions are male-specific — useful contrast in disorders-of-sex-development work-up.

High-yield exam pointers

- ▶ **No male-to-male transmission** is the single most discriminating feature of X-linked inheritance.
- ▶ **All daughters of an affected male are obligate carriers**; affected sons inherit the mutant X from a carrier mother.
- ▶ Males are **hemizygous** → express both X-linked recessive and dominant alleles fully.

- ▶ *X-linked dominant / recessive* terminology applies to **expression in females**, modulated by **X-inactivation**.
- ▶ Haemophilia A (factor VIII), haemophilia B (factor IX), G6PD deficiency, Fabry, DMD/Becker, Fragile X, Kennedy disease = classic XLR; Rett syndrome (MECP2) = classic XLD.
- ▶ DMD (dystrophin, 2.3 Mb, 79 exons) is the commonest muscular dystrophy; allelic severity → Duchenne vs Becker.
- ▶ Fragile X, Kennedy disease are X-linked trinucleotide-repeat disorders showing anticipation.
- ▶ Carrier females may be symptomatic (“manifesting carriers”) through skewed X-inactivation.

SOURCE & COVERAGE

Harrison’s Principles of Internal Medicine, 22e — Ch 479 “Principles of Human Genetics” (X-linked & Y-linked inheritance, X-inactivation, genotype–phenotype correlation, Tables 479-2/479-5) and Ch 480 “The Integration of Inherited Genetics into Clinical Practice” (monogenic disorders with genetics-based interventions — haemophilia A/B, G6PD deficiency, nephrogenic DI, DMD; genetic counselling/carrier testing). **Coverage note:** The eponym “*Lyonization/Lyon hypothesis*” for X-inactivation, the gene symbol *GLA* for Fabry’s α-galactosidase A, the carrier-cross segregation ratios (50% affected sons / 50% carrier daughters), the female:male excess in XLD, and the additional XLD examples (X-linked hypophosphataemic rickets, incontinentia pigmenti) are universally accepted standard genetics added for completeness and are not stated verbatim in Ch 479/480; the X-inactivation mechanism, hemizyosity, transmission rules and all listed disorders/genes are grounded in the provided text.

