تَذكَّر:

إنَّ الطِّبَّ وسِيلةٌ.. لا غايَةٌ!



Messenger of Allah (s.a.w) said:

"The feet of the slave of Allah shall not move [on the Day of Judgement]
until he is asked about four things:
about his life and what he did with it,
about his knowledge and what he did with it,
about his wealth and how he earned it and where he spent it on,
about his body and for what did he wear it out."

Jami' at-Tirmidhi 2417

Contact & Updates:
Ehab Alroud

Endocrinology

Diabetes Mellitus (DM) 9
DKA & HHS 10
Hypoglycaemia 15
Diabetes Insipidus (DI) 16
SIADH 16
Multiple Endocrine Neoplasias (MEN) 17
Pancreatic Tumors 17
Pituitary Prolactinoma 18
Hypopituitarism 18
Acromegaly 19
Congenital Adrenal Hyperplasia (CAH) 20
Cushing Syndrome 21
Hyperaldosteronism 22
Adrenal Insufficiency (AI) 23
Pheochromocytoma 24
Hyperthyroidism & Hypothyroidism 25
Thyroid Nodules 26
Euthyroid Sick Syndrome (ESS) 30
Hyperparathyroidism & Hypoparathyroidism 31
Hypercalcemia 32
Milk Alkali Syndrome 33
Hypocalcemia 34
PCOS 35

Cardiology

A-Fib & Other Murmurs 37
Mitral Stenosis & Other Valvular Diseases 38
Angina & Myocardial Infarction (MI) 40
Acute Pericarditis 45
Constrictive Pericarditis 45
Cardiac Tamponade 46
Cardiomyopathy 47
Amyloidosis 49
Myocarditis 50
Rheumatic Fever 50
Heart Failure (HF) 51
Cor Pulmonale 54
ECG 55
Arrhythmias 56

BLS & ACLS 60
Hypertension 61
Coarctation of Aorta 65
Aortic Dissection 65
Aneurysm 66
Pulmonary Embolism (PE) 67
Syncope 68
Shock 70
Infective Endocarditis & NBTE 71
Cholesterol Emboli Syndrome 72
Peripheral Arterial Disease (PAD) 73
Peripheral Venous Disease 75

Pulmonology

Physical Examination 77
Flow-Volume Loop 78
Paradoxical Vocal Cord Motion 79
Capnogram 80
O2-Hb Dissociation Curve 81
Hypoxemia 83
Hypercapnea 84
Pulmonary Function Test (PFT) 85
Interstitial Lung Disease (ILD) 86
Idiopathic Pulmonary Fibrosis (IPF) 87
Hypersensitivity Pneumontits 87
Acute Respiratory Distress Syndrome (ARDS) 88
Asthma 91
COPD 96
Bronchiectasis 100
Chronic Cough 102
Obstructive Sleep Apnea (OSA) 103
Obesity Hypoventilation Syndrome (OHS) 103
Pulmonary Hypertension 105
Diffuse Alveolar Hemorrhage 106
Pulmonary Edema 107
Pleural Effusion 108
Pneumoconioses 110
Mesothelioma 110
Bronchogenic Carcinoma 111
Pancoast Tumor 112
Solitary Pulmonary Nodule 113
Acute Bronchitis 114

Pneumonia 115
Tuberculosis (TB) 119
Aspergillosis 120
Anaphylaxis 121
Myasthenic Crisis 122
Sarcoidosis 122
Goodpasture Syndrome 123
Acute Chest Syndrome 124

Gastroenterology

Oropharyngeal Candidiasis 126
Esophagitis 126
GERD 127
Esophageal Cancer 127
Esophageal Stricture 128
Diffuse Esophageal Spasm 128
Achalasia 129
Gastric Cancer 130
Gastritis 130
Peptic Ulcer Disease (PUD) 131
Upper GI Bleeding 132
Acute Liver Failure (ALF) 133
Cirrhosis & Ascites 134
Spontaneous Bacterial Peritonitis (SBP) 135
Autoimmune Hepatitis 136
Ischemic Hepatitis 136
Drug-induced Hepatitis 136
Viral Hepatitis 137
Alcoholic Hepatitis 138
Nonalcoholic Fatty Liver Disease (NAFLD) 138
Hereditary Hemochromatosis (HH) 139
Wilson Disease 139
Alpha-1-Antitrypsin Deficiency 140
Gilbert Syndrome 140
Acute Cholangitis 141
Primary Sclerosing Cholangitis (PSC) 141
Primary Biliary Cholangitis (PBC) 141
Acute Pancreatitis 142
Chronic Pancreatitis 143
Pancreatic Cancer 143
Celiac Disease 144
Whipple Disease 145

Lactose Intolerance 145
Giardiasis 145
Clostridium Difficile Colitis 146
Laxative-induced Diarrhea 146
Chemotherapy-related Diarrhea 146
Carcinoid 147
Angiodysplasia 147
Inflammatory Bowel Disease (IBD) 148
Colon Cancer 149
Fecal impaction 150
Gonococcal Proctitis 150
Proctalgia Fugax 151
Gastroparesis 151
Inflammatory Bowel Syndrome (IBS) 152
Anorexia Nervosa & Eating Disorders 153
Pellagra 154
Splenic Infarction 155
Chronic Mesenteric Ischemia 155

Hemato-Oncology

IDA & Other Microcytic Anemia 157
Macrocytic Anemia 159
Normocytic Anemia 161
Pancytopenia 164
Transfusions 165
1° & 2° Hemostasis 167
ITP & Other Platelet Disorders 168
TTP & HUS 169
DIC & vWF Disease 169
Hemophilia 170
Anti-Phospholipid Antibody Syndrome 170
Hereditary Thrombophilia 171
DVT & VTE 171
Anti-coagulants 172
Hodgkin Lymphoma 173
Non-Hodgkin Lymphoma (NHL) 174
ALL & Other Leukemias 175
Polycythemia Vera (PV) & Other Myeloproliferative Neoplasms 177
Multiple Myeloma (MM) 179
Chemotherapy & Radiation & Bone Marrow Graft 180
Tumor Lysis Syndrome (TLS) 182
Pain Management 182

Nephrology

Acute Kidney Injury (AKI) 184
Acute Interstitial Nephritis (AIN) 185
Renal Papillary Necrosis 185
Acute Tubular Necrosis (ATN) 186
Rhabdomyolysis 187
Chronic Kidney Disease (CKD) 188
Renal Transplant 190
Nephritic Syndrome 191
Nephrotic Syndrome 194
Hepatorenal Syndrome & Cardiorenal Syndrome 195
Acid-Base Disturbance 196
Renal Tubular Acidosis (RTA) 199
Hyponatremia & Other Electrolyte Disturbance 200
Familial Hypocalciuric Hypercalcemia (FHH) 205
Cystitis & Pyelonephritis (UTI) 206
Renal Abscess 207
ADPKD & Other Renal Cystic Diseases 208
Renal Cell Carcinoma (RCC) 210
Renal Vein Thrombosis 211

Rheumatology

Rheumatoid Arthritis (RA) 213
Osteoarthritis (OA) 215
Systemic Lupus Erythematosis (SLE) 216
Mixed Connective Tissue Disease (MCTD) 217
Raynaud Phenomenon 218
Systemic Sclerosis 219
Sjogren Syndrome 220
Ankylosing spondylitis & Other Seronegative Spondyloarthritis 221
Viral Arthritis 222
Septic Arthritis 223
Gout 224
Pseudogout (CPPD) 225
Vasculitides 226
Fibromyalgia 228
Polymyalgia Rheumatica 228
Polymyositis & Dermatomyositis 229
Osteoporosis 231
Acute & Chronic Back Pain 233



Step 2

& Relevant Clinical Step 1

Endocrinology

تَذكَّر:

إنَّ الطِّبَّ وسِيلةٌ.. لا غايَةٌ!

Contact & Updates:

Ehab Alroud

As a general rule in endocrinology…

Imaging is performed after the biochemical diagnosis of a disorder is made.

DM

Diabetes mellitus

ACUTE MANIFESTATIONS	Polydipsia, polyuria, polyphagia (3 P's), weight loss, DKA (type 1), hyperosmolar hyperglycemic state (type 2). Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).
CHRONIC COMPLICATIONS	Nonenzymatic glycation: ▪ Small vessel disease (hyaline arteriolosclerosis) → retinopathy, neuropathy, nephropathy. ▪ Large vessel disease (atherosclerosis) → CAD, cerebrovascular disease, peripheral vascular disease. MI is the most common cause of death. Osmotic damage (sorbitol accumulation in organs with aldose reductase and ↓ or absent sorbitol dehydrogenase): ▪ Neuropathy: motor, sensory (glove and stocking distribution), autonomic degeneration (eg, GERD, gastroparesis, diabetic diarrhea). ▪ Cataracts.

DIAGNOSIS

TEST	DIAGNOSTIC CUTOFF	NOTES
HbA_{1c}	≥ 6.5% normally < 5.7 %	Reflects average blood glucose over prior 3 months (influenced by RBC turnover)
Fasting plasma glucose	≥ 126 mg/dL normally < 100 mg/dl	Fasting for > 8 hours
2-hour oral glucose tolerance test	≥ 200 mg/dL normally < 140 mg/dl	2 hours after consumption of 75 g of glucose in water
Random plasma glucose	≥ 200 mg/dL	Presence of hyperglycemic symptoms is required

Type 1 vs type 2 diabetes mellitus

	Type 1	Type 2
1° DEFECT	Autoimmune T-cell–mediated destruction of β cells	↑ resistance to insulin, progressive pancreatic β-cell failure
INSULIN NECESSARY IN TREATMENT	Always	Sometimes
AGE (EXCEPTIONS COMMON)	< 30 yr	> 40 yr
ASSOCIATION WITH OBESITY	No	Yes
GENETIC PREDISPOSITION	Relatively weak (50% concordance in identical twins), polygenic	Relatively strong (90% concordance in identical twins), polygenic
ASSOCIATION WITH HLA SYSTEM	Yes, HLA-DR4 and -DR3 (4 – 3 = type 1)	No
GLUCOSE INTOLERANCE	Severe	Mild to moderate
INSULIN SENSITIVITY	High	Low
KETOACIDOSIS	Common	Rare
β-CELL NUMBERS IN THE ISLETS	↓	Variable (with amyloid deposits)
SERUM INSULIN LEVEL	↓	↑ initially, but ↓ in advanced disease
CLASSIC SYMPTOMS OF POLYURIA, POLYDIPSIA, POLYPHAGIA, WEIGHT LOSS	Common	Sometimes
HISTOLOGY	Islet leukocytic infiltrate	Islet amyloid polypeptide deposits

Even in the absence of hypertension, screening for diabetes is advised for patients age 35-70 with a BMI ≥25.

The dawn phenomenon causes early-morning (2-8 AM) fasting hyperglycemia due to the circadian increase in growth hormone and cortisol secretion; in many patients, it can be managed by increasing the basal insulin dose.

DKA & HHS

Hyperglycemic emergencies

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
PATHOGENESIS	Insulin noncompliance or ↑ requirements due to ↑ stress (eg, infection) → lipolysis and oxidation of free fatty acids → ↑ ketone bodies (β-hydroxybutyrate > acetoacetate). **Insulin deficient, ketones present.**	Profound hyperglycemia → excessive osmotic diuresis → dehydration and ↑ serum osmolality → HHS. Classically seen in older patients with type 2 DM and limited ability to drink. **Insulin present, ketones deficient.**
SIGNS/SYMPTOMS	DKA is Deadly: Delirium/psychosis, Kussmaul respirations (rapid, deep breathing), Abdominal pain/nausea/vomiting, Dehydration. Fruity breath odor due to exhaled acetone.	Thirst, polyuria, lethargy, focal neurologic deficits, seizures.
LABS	Hyperglycemia, ↑ H^+, ↓ HCO_3^- (↑ anion gap metabolic acidosis), ↑ urine and blood ketone levels, leukocytosis. Normal/↑ serum K^+, but depleted intracellular K^+ due to transcellular shift from ↓ insulin and acidosis. Osmotic diuresis → ↑ K^+ loss in urine → total body K^+ depletion.	Hyperglycemia (often > 600 mg/dL), ↑ serum osmolality (> 320 mOsm/kg), normal pH (no acidosis), no ketones. Normal/↑ serum K^+, ↓ intracellular K^+.
COMPLICATIONS	Life-threatening mucormycosis, cerebral edema, cardiac arrhythmias.	Can progress to coma and death if untreated.
TREATMENT	IV fluids, IV insulin, and K^+ (to replete intracellular stores). Glucose may be required to prevent hypoglycemia from insulin therapy.	

Diabetic ketoacidosis causes osmotic diuresis and secondary hyperaldosteronism, leading to urinary potassium loss and a total body potassium deficit. However, laboratory potassium values are often normal or elevated. This finding is due to hyperosmolarity, which draws water and potassium into the extracellular space, and insulin deficiency, which impairs cellular uptake of potassium.

In contrast to diabetic ketoacidosis (DKA), which typically develops rapidly over hours, HHS develops over a few days to weeks. In HHS, mild ketosis (ie, urine ketones) may occur due to decreased food intake (ie, starvation ketosis); however, unlike DKA, more prominent ketosis does not occur because even relatively low insulin production suppresses ketogenesis.

* HHS can be triggered in patients with type 2 diabetes mellitus by use of atypical antipsychotics, such as olanzapine; these drugs can cause hyperglycemia acutely, possibly due to decreased insulin secretion or signaling, or chronically due to weight gain and insulin resistance.

Management of diabetic ketoacidosis	
IV fluids	• Rapid infusion of 0.9% normal saline • Add dextrose 5% when serum glucose is ≤200 mg/dL
Insulin	• Start continuous IV insulin infusion; hold if K <3.3 mEq/L • Switch to SQ (basal bolus) insulin for the following: able to eat, glucose <200 mg/dL, anion gap <12 mEq/L & serum HCO3– ≥15 mEq/L • Overlap SQ & IV insulin by 1-2 hr
Potassium	• Add IV K if serum K+ <5.3 mEq/L; hold if ≥5.3 mEq/L • Nearly all patients' K+ depleted, even with hyperkalemia
Bicarbonate	• Consider for patients with pH ≤6.9
Phosphate	• Consider for serum phosphate <1.0 mg/dL, cardiac dysfunction, or respiratory depression • Monitor serum calcium frequently

Switch to half normal saline if serum Na+ ≥135 mEq/L. Normal saline is used initially regardless of sodium levels.

Patients with DKA can have pseudohyponatremia due to hyperglycemia; corrected sodium (observed sodium + ~2 mEq/L for every 100 mg/dL glucose is over 100 mg/dL). Hypertonic saline is reserved for moderate to severe (true) hyponatremia.

* The most accurate markers indicating resolution of diabetic ketoacidosis are the serum anion gap and serum beta-hydroxybutyrate levels. The anion gap estimates the unmeasured anion concentration in the blood and returns to normal with the disappearance of ketoacid anions. The anion gap, electrolytes, and venous pH are measured every 2-4 hours, and serum glucose is measured hourly. Measurement of serum and urine glucose alone is inappropriate for monitoring response to treatment because ketosis and acidemia may still be present even when glucose levels drop below 200-250 mg/dL.

Management of type 1 diabetes mellitus	
Management	◦ Insulin replacement ◦ ↓ with "honeymoon" phase, vigorous exercise ◦ ↑ with puberty/rapid growth • Urine ketone checks with illness/ persistent hyperglycemia • Avoid alcohol use to decrease hypoglycemia risk • Hemoglobin A1c levels every 3 months
Additional evaluation	◦ Initial: ◦ Lipid panel ◦ Screening for other autoimmune conditions (eg, thyroiditis, celiac disease) ◦ Depression/eating disorder screening ◦ Age ≥10 AND diabetes mellitus ≥5 years: ◦ Urine albumin/creatinine ratio annually (nephropathy) ◦ Foot inspection & vibration testing annually (polyneuropathy) ◦ Dilated eye examination every 2 years (retinopathy)

Type 2 diabetes and comorbid cardiovascular disease	
Lifestyle	• Smoking cessation, regular exercise • Reduced saturated fat, refined sugar intake
Cardioprotective antidiabetic agents	• GLP-1 receptor agonists (eg, liraglutide) • SGLT-2 inhibitors (eg, empagliflozin)
Lipid/antiplatelet therapy	• Statins • Low-dose aspirin
Blood pressure control	• Goal BP <130-140/80-90 mm Hg • ACE inhibitor/ARB preferred

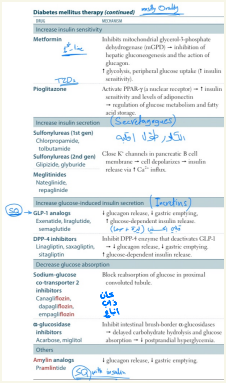
In type 2 diabetes mellitus, unrecognized hyperglycemia may be present for years before diagnosis; therefore, screening (eg, urine albumin/creatinine ratio [ACR], dilated ocular fundus examination) should be performed at diagnosis. In contrast, type 1 diabetes mellitus usually presents acutely after disease onset, so screening usually starts after 5 years, not at diagnosis.

Alcohol is associated with severe hypoglycemia because it is metabolized by the liver and leads to decreased gluconeogenesis. Alcohol also suppresses glycogenolysis and increases insulin sensitivity. Patients with diabetes mellitus should be encouraged to abstain from alcohol but, if unable, should drink it only with food, check blood glucose levels frequently, and limit intake to a single drink a day.

* In patients with diabetes mellitus, intensive blood glucose control with insulin decreases the risk of microvascular complications (eg, retinopathy, nephropathy) but has an uncertain effect on macrovascular outcomes (eg, stroke, myocardial infarction) and mortality. Very strict glycemic control (eg, goal A1c ≤6.5%) is associated with increased risk of hypoglycemia and increased cardiovascular mortality. Therefore, the recommended target hemoglobin A1c for most nonelderly patients is 7.0%

When either albuminuria or hypertension is present, ACE inhibitors (eg, lisinopril) or angiotensin II receptor blockers (ARBs) are indicated to control blood pressure and/or slow the progression of diabetic nephropathy. Sodium-glucose cotransporter-2 inhibitors (eg, dapagliflozin) also slow nephropathy progression and may be used when glycemic control is suboptimal or when cardiac comorbidities (eg, heart failure) are present.

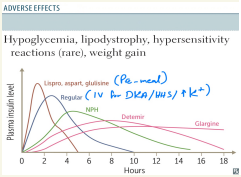
Health maintenance in diabetes mellitus	
Glycemic control	• Check A1c every 3-6 months • Goal A1c: • ≤7% (younger, otherwise healthy) • ≤8% (older, limited life expectancy, comorbidities)
Nephropathyscreening	• Annual random urine albumin/creatinine ratio* • Normal value: <30 mg/g • Periodic serum creatinine level
Retinopathyscreening	• Dilated eye examination every 1-2 years*
Neuropathyscreening	• Visual inspection at each visit • Annual comprehensive foot examination
Cardiovascularrisk reduction	• Address lifestyle factors (eg, tobacco, obesity, diet & exercise) • Annual lipid & BP screening • Aspirin and statin (depending on other risk factors)
*Begin at time of diagnosis for type 2 diabetes mellitus & 5 years after diagnosis for type 1.	

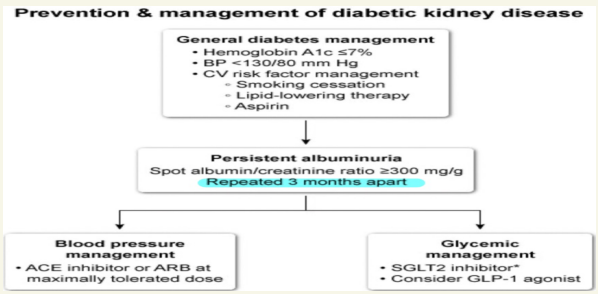


Insulin preparations

Rapid acting (no lag):
lispro, aspart, glulisine
Short acting:
regular
Intermediate acting:
NPH
Long acting:
detemir, glargine
Very long acting:
degludec

Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase • Upregulates AMP-activated protein kinase
Metabolic effects	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption • ↑ Peripheral glucose uptake/utilization • ↓ Lipogenesis
Pharmacokinetics	• Renal clearance • No significant metabolites
Adverse effects	• Diarrhea • Lactic acidosis • Vitamin B_{12} deficiency
Precautions/ contraindications	• Renal insufficiency (check serum creatinine) • Hepatic insufficiency • Decompensated heart failure

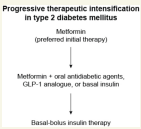




Diabetic nephropathy (DN) is characterized by persistent albuminuria (≥30 mg/g) and/or decreased glomerular filtration rate. In the absence of signs suggestive of another etiology, the diagnosis can be presumed in patients with renal dysfunction and either a prolonged history of diabetes (≥5 years for type 1 diabetes) or proliferative diabetic retinopathy, which correlates with the presence of DN.

SGLT2 Contraindications:

- Type 1 DM
- History of DKA
- Impaired renal function (eGFR <30-45 mL/min/1.73 m2)



* Patients with diabetes mellitus who have an elevated hemoglobin A1c despite normal fasting glucose levels may have postprandial hyperglycemia. A combined regimen, including a long-acting basal insulin (to control fasting glucose) and a rapid-acting premeal insulin (to control postprandial glucose), can improve glycemic control.

Clinical features of diabetic autonomic neuropathy	
Cardiovascular	• Tachycardia, impaired exercise tolerance • Postural hypotension with loss of diurnal blood pressure variation
Peripheral nerves	• Dry skin, pruritus, callus formation • Foot ulcers & poor wound healing • Charcot arthropathy (increased fracture risk with resultant secondary ulceration)
Gastrointestinal	• Gastroparesis with delayed gastric emptying • Esophageal dysmotility with possible dyspepsia • Intestinal involvement with possible diarrhea, constipation, or fecal incontinence
Genitourinary	• Erectile dysfunction & retrograde ejaculation in men, decreased libido & dyspareunia in women • Decreased ability to sense full bladder leading to incomplete emptying & decreased urination • Eventual recurrent urinary tract infections &/or overflow incontinence (eg, dribbling, poor urinary stream)

Distal sensory peripheral neuropathy in diabetes mellitus

	Large fiber neuropathy*	Small fiber neuropathy*
Sensoryfunction	• Pressure, proprioception & balance	• Pain & temperature
Majorsymptoms	• Numbness & poor balance	• Burning & stabbing pain
Examinationfindings	• Diminished/absent ankle reflexes • Reduced/absent vibration, light touch & proprioception	• Reduced pinprick sensation • Ankle reflexes possibly preserved

*Patients can have mixed large & small fiber neuropathy.







* Symmetric distal sensorimotor polyneuropathy is the most common neuropathy in DM.

Diabetes mellitus is the most common cause of peripheral neuropathy, with the risk related to the duration of the disease and glycemic status. Neuronal injury in diabetes is due to a number of factors, including microvascular injury, demyelination, oxidative stress, and deposition of glycation end products. The use of metformin, which decreases intestinal absorption of vitamin B12, can also contribute. This leads to a length-dependent axonopathy, with clinical features occurring first in the longest nerves (eg, feet).

- Small fiber injury is characterized by the predominance of positive symptoms (eg, pain, paresthesia, allodynia).
- Large fiber involvement is characterized by the predominance of negative symptoms (eg, numbness, loss of proprioception and vibration sense, diminished ankle reflexes).

The loss of position sense causing gait imbalance (worsened with eye closure due to lack of visual compensation), and the weakness & imbalance of the intrinsic muscles of the feet leading to foot deformities (eg, hammer toe, claw toe deformity).

Neuropathic ulcers most commonly occur in the feet under bony prominences, such as the metatarsal heads. They typically have a punched-out or undermined border.

Peripheral sensory neuropathy can be documented by testing for pressure sensation with a 10-g monofilament (placed on the plantar surface at a right angle with increasing pressure until filament buckles). Patients with neuropathy have a higher pressure threshold and loss of monofilament sensation, which are associated with an increased risk of foot ulcerations. Other sensory deficits may include decreased vibratory sensation (tested with a tuning fork), decreased pinprick pain, or decreased temperature sensation. Diabetic neuropathy can affect the large nerve fibers in the lower extremities, causing decreased/absent ankle reflexes. However, the knee reflex is usually not affected.

Initial treatment options for painful diabetic neuropathy include tricyclic antidepressants (e.g., Amitriptyline), SNRIs, and anticonvulsants. Pregabalin decreases pain by inhibiting the release of excitatory neurotransmitters.

Hypoglycemia (glucose <70 mg/dL)

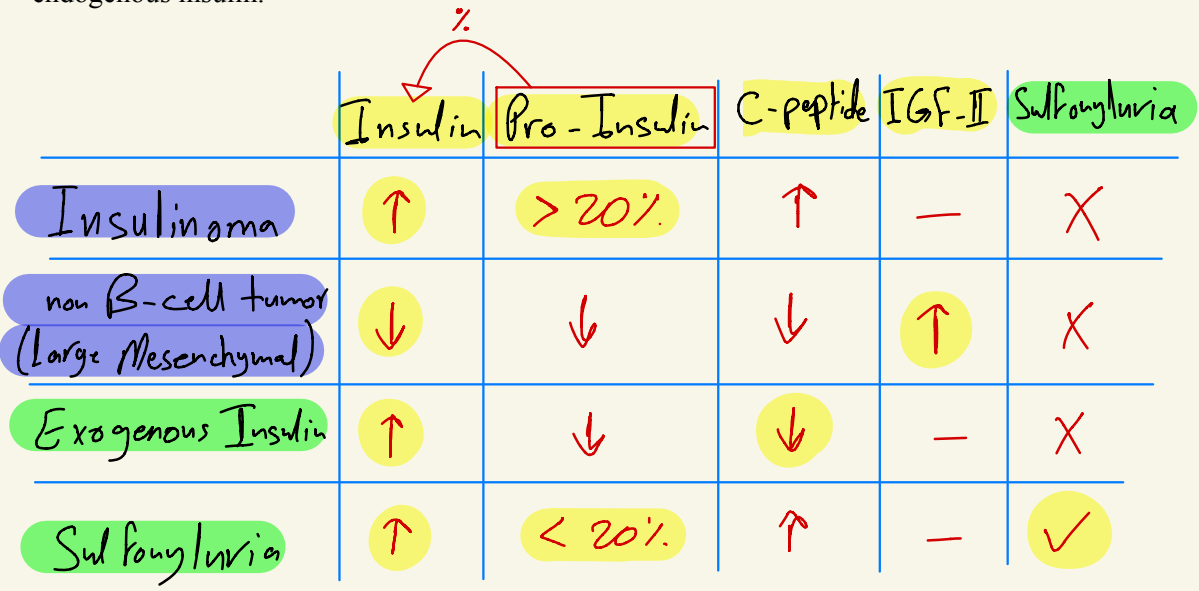
In diabetes mellitus usually occurs in patients treated with insulin or insulin secretagogues (eg, sulfonylureas, meglitinides) in the setting of high-dose treatment, inadequate food intake, and/or exercise because insulin continues to be released from the injection site despite falling glucose levels. Patients with chronic kidney disease are at increased risk due to delayed clearance of insulin by the kidneys. Chronic pancreatitis or pancreatic resection can cause loss of insulin-producing beta cells, leading to pancreatogenic diabetes; exogenous insulin is required. Patients typically also lose glucagon-secreting alpha cells and are at risk for rapid and severe hypoglycemia. Those with long-standing diabetes (ie, >5 yr) often also have alpha cell failure, which can lead to decreased glucagon secretion and exacerbate hypoglycemia

- Neurogenic (autonomic) symptoms: diaphoresis, tachycardia, tremor, anxiety, hunger. Allow perception of glucose (hypoglycemia awareness).

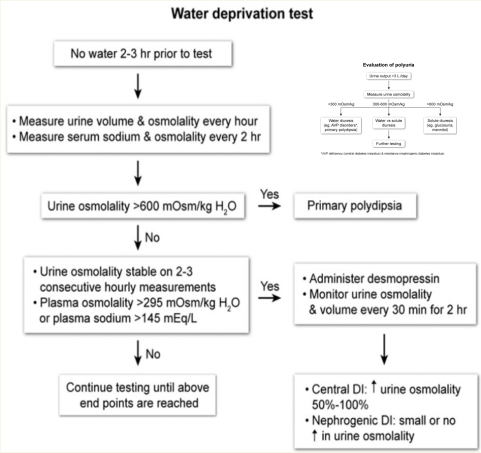
- Neuroglycopenic symptoms: altered mental status, seizures, death due to insufficient glucose in CNS. May occur in the absence of preceding neurogenic symptoms in patients with attenuated autonomic response (hypoglycemia unawareness).

Treatment: simple carbohydrates (eg, glucose tablets, fruit juice), IM glucagon, IV dextrose.

Hypoglycemia in normal person can occur in patients with critical illness due to increased use of glucose in the tissues and suppression of gluconeogenesis in the liver. The risk is higher in patients with renal insufficiency, likely due to decreased renal gluconeogenesis and reduced clearance of endogenous insulin.



Diabetes Insipidus



Characterized by the production of large amounts of dilute urine +/– thirst. Urine specific gravity < 1.006. Urine osmolality usually < 300 mOsm/kg. Central DI may be transient if damage is below hypothalamic median eminence or in the posterior pituitary (ADH in hypothalamus can still be secreted systemically via portal capillaries in median eminence).
In AVP-D, serum sodium is usually slightly elevated or high-normal, which serves to stimulate thirst and continued water intake needed to compensate for urinary water losses. Uric acid may be slightly elevated if mild dehydration is present; more severe hypernatremia can result if the thirst mechanism is impaired (eg, hypothalamic lesion).

	Primary polydipsia	Central DI	Nephrogenic DI
DEFINITION	Excessive water intake	↓ ADH release	ADH resistance
CAUSES	Psychiatric illnesses, hypothalamic lesions affecting thirst center	Idiopathic, brain injury (trauma, hypoxia, tumor, surgery, infiltrative diseases)	Hereditary (ADH receptor mutation), drugs (eg, lithium, demeclocycline), hypercalcemia, hypokalemia
SERUM OSMOLALITY	↓	↑	↑
ADH LEVEL	↓ or normal	↓	Normal or ↑
WATER RESTRICTION[a]	Significant ↑ in urine osmolality (> 700 mOsm/kg)	No change or slight ↑ in urine osmolality	No change or slight ↑ in urine osmolality
DESMOPRESSIN ADMINISTRATION[b]	—	Significant ↑ in urine osmolality (> 50%)	Minimal change in urine osmolality
TREATMENT	Water restriction	Desmopressin (DDAVP)	Manage the underlying cause; low-solute diet, HCTZ, amiloride, indomethacin

Study SIADH in Pulmonolgy, page 46

SIADH

Characterized by excessive free water retention, euvolemic hyponatremia with continued urinary Na+ excretion, urine osmolality > serum osmolality.
Body responds to water retention with decreasing aldosterone and increasing both ANP and BNP —> increasing urinary Na+ secretion —> normalization of extracellular fluid volume —> euvolemic hyponatremia.

Treatment: fluid restriction (first line), salt tablets, IV hypertonic saline, diuretics, ADH antagonists (eg, conivaptan, tolvaptan, demeclocycline).

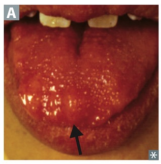
SIADH causes include (HEELD-up water):
- Head trauma/CNS disorders
- Ectopic ADH (eg, small cell lung cancer)
- Exogenous hormones (eg, vasopressin, desmopressin, oxytocin)
- Lung disease
- Drugs (eg, SSRIs, carbamazepine, cyclophosphamide)

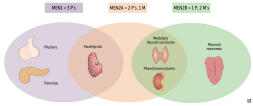
Multiple Endocrine Neoplasias

Multiple endocrine neoplasias

All MEN syndromes have autosomal dominant inheritance.
The X-MEN are dominant over villains.

SUBTYPE	CHARACTERISTICS
MEN1	Pituitary tumors (prolactin or GH) Pancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare) (Gastrinoma) Parathyroid adenomas Associated with mutation of *MEN1* (tumor suppressor, codes for menin, chromosome 11), angiofibromas, collagenomas, meningiomas
MEN2A	Parathyroid hyperplasia Medullary thyroid carcinoma—neoplasm of parafollicular C cells; secretes calcitonin; prophylactic thyroidectomy required Pheochromocytoma (secretes catecholamines) Associated with mutation in *RET* (protooncogene, codes for receptor tyrosine kinase, chromosome 10)
MEN2B	Medullary thyroid carcinoma Pheochromocytoma Mucosal neuromas A (oral/intestinal ganglioneuromatosis) Associated with marfanoid habitus; mutation in *RET* gene





Nearly 75% of VIPomas are in the pancreatic tail and 60%-80% have metastasized to the liver by the time of diagnosis. Treatment involves intravenous volume repletion, octreotide to decrease diarrhea, and possible hepatic resection in patients with metastasis to the liver.

Although most MTC is sporadic, approximately one third of MTC is inherited as a component of multiple endocrine neoplasia (MEN) types 2A and 2B that also associated with pheochromocytoma, which can be asymptomatic at the time of diagnosis but cause life-threatening hypertensive crisis during surgical procedures (eg, thyroidectomy). In light of this risk, most patients with MTC should undergo RET mutation testing and screening for pheochromocytoma with a plasma fractionated metanephrine assay. If found, pheochromocytoma should be resected prior to thyroidectomy.

Insulinoma & Glucagonoma & Somatostatinoma

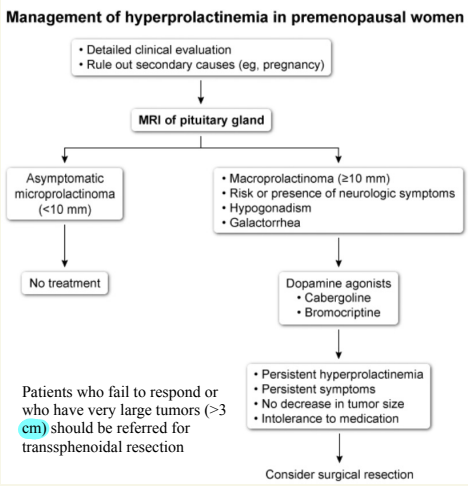
Pancreatic islet cell tumors

Insulinoma	Tumor of pancreatic β cells → overproduction of insulin → hypoglycemia. May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of plasma glucose levels. Symptomatic patients have ↓ blood glucose and ↑ C-peptide levels (vs exogenous insulin use). ~ 10% of cases associated with MEN1 syndrome. Treatment: surgical resection.
Glucagonoma	Tumor of pancreatic α cells → overproduction of glucagon. Presents with 6 D's: dermatitis (necrolytic migratory erythema), diabetes (hyperglycemia), DVT, declining weight, depression, diarrhea. Treatment: octreotide, surgical resection.
Somatostatinoma	Tumor of pancreatic δ cells → overproduction of somatostatin → ↓ secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP). May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria. Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

Glucagonoma is often diagnosed late in the disease course due to nonspecific early features; necrolytic migratory erythema (NME) is the presenting feature in ~70% of patients. NME, likely due to amino acid deficiency, is characterized by painful/pruritic papules that coalesce to form large, indurated plaques with scaling and central clearing on the face, groin, and extremities.

Laboratory evaluation typically shows normocytic, normochromic anemia, which may be due to anemia of chronic disease or a direct effect of glucagon on erythropoiesis. A markedly elevated serum glucagon level (>500 pg/mL) confirms the diagnosis, and abdominal imaging can localize the tumor and evaluate for metastases.

Pituitary Prolactinoma & Hypopituitarism



Pituitary surgery can be complicated by postoperative arginine vasopressin deficiency (formerly central diabetes insipidus) and/or syndrome of inappropriate antidiuretic hormone secretion. Serum electrolytes should be measured for several weeks after the procedure.

Male secondary hypogonadism	
Clinical features	• Fatigue, decreased libido • Testicular atrophy • Laboratory: low testosterone, low/normal LH
Common causes	• Pituitary tumors, hyperprolactinemia • Medications: opioids, glucocorticoids, exogenous androgens (withdrawal phase) • Infiltrative disease (eg, hemochromatosis) • Chronic/severe illness • Eating disorders, severe weight loss

Hypopituitarism:

Undersecretion of pituitary hormones due to:

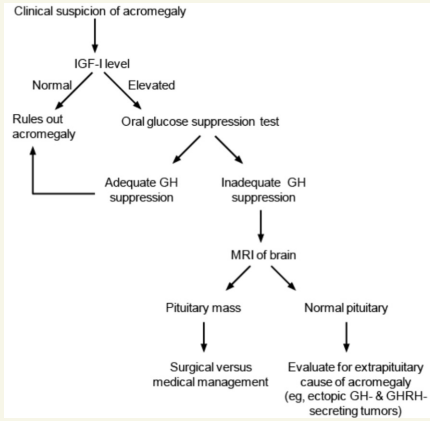
- Nonsecreting pituitary adenoma, craniopharyngioma
- Sheehan syndrome—ischemic infarct of pituitary following severe postpartum hemorrhage; pregnancy-induced pituitary growth increasing the susceptibility to hypoperfusion. Usually presents with failure to lactate, amenorrhea, cold intolerance (anterior pituitary hormones mainly affected).
- Pituitary apoplexy—sudden hemorrhage of pituitary gland, often in the presence of an existing pituitary adenoma. Usually presents with sudden onset severe headache, visual impairment (eg, bitemporal hemianopia, diplopia due to CN III palsy), and features of hypopituitarism
- Brain injury
- Radiation

Clinical presentation:

- ACTH deficiency (secondary adrenal insufficiency)
  - Postural hypotension, tachycardia, fatigue, weight loss, hypoglycemia, eosinophilia
- Hypothyroidism (central)
  - Fatigue, cold intolerance, constipation, dry skin, bradycardia, slowed deep tendon reflexes
- Gonadotropins
  - Women: Amenorrhea, infertility
  - Men: Infertility, loss of libido

Treatment: hormone replacement therapy (glucocorticoids, thyroxine, sex steroids, human growth hormone)

Acromegaly



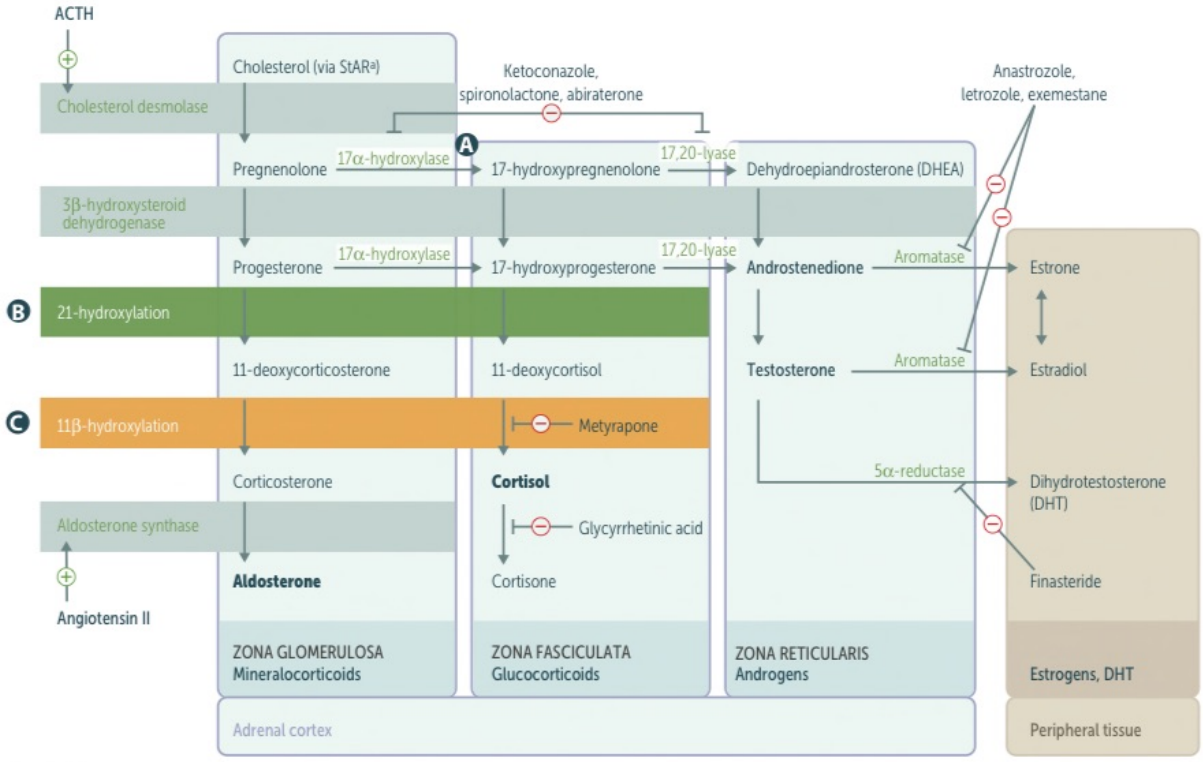


Cardiovascular disease is the leading cause of death in patients with acromegaly, but normalization of growth hormone levels following successful treatment markedly reduces cardiovascular mortality.

IGF-1 levels in patients with acromegaly are consistently elevated throughout the day and are useful as an initial test, in contrast to GH, which fluctuates widely and has low sensitivity and specificity.
Treatment can alleviate many of the physiologic effects (eg, hyperglycemia) of acromegaly, although skeletal and joint abnormalities are largely irreversible. Initial treatment for most patients includes transsphenoidal resection of the pituitary adenoma. For patients with residual or unresectable tumors, medical therapy is indicated; options include somatostatin analogues (eg, octreotide) or growth hormone receptor antagonists (eg, pegvisomant).

Clinical features of acromegaly	
Local tumor effect	Headache, visual field defects, cranial nerve defects
Musculoskeletal	Gigantism, frontal bossing, malocclusion of jaw, macrognathia, arthritis, carpal tunnel syndrome, enlargement of hands/feet
Skin	Skin thickening, hyperhidrosis (odor), skin tags
Cardiovascular	Cardiomyopathy, hypertension, heart failure
Respiratory	Sleep apnea
Gastrointestinal	Colon polyps/cancer, diverticulosis
Endocrine	Galactorrhea, hypogonadism, diabetes mellitus, hypertriglyceridemia
Additional features	Enlarged tongue, thyroid, salivary glands, liver, spleen, kidney, prostate

Congenital Adrenal Hyperplasia (CAH)



[a]Rate-limiting step.

ENZYME DEFICIENCY	MINERALOCORTICOIDS	[K⁺]	BP	CORTISOL	SEX HORMONES	LABS	PRESENTATION
A 17α-hydroxylase[a]	↑	↓	↑	↓	↓	↓ androstenedione	XY: atypical genitalia, undescended testes XX: lacks 2° sexual development
B 21-hydroxylase[a]	↓	↑	↓	↓	↑	↑ renin activity ↑ 17-hydroxy-progesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
C 11β-hydroxylase[a]	↓ aldosterone ↑ 11-deoxycorti-costerone (results in ↑ BP)	↓	↑	↓	↑	↓ renin activity	Presents in infancy (severe hypertension) or childhood (precocious puberty) XX: virilization

[a]All congenital adrenal enzyme deficiencies are autosomal recessive disorders and most are characterized by skin hyperpigmentation (due to ↑ MSH production, which is coproduced and secreted with ACTH) and bilateral adrenal gland enlargement (due to ↑ ACTH stimulation).

If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.

Cushing Syndrome

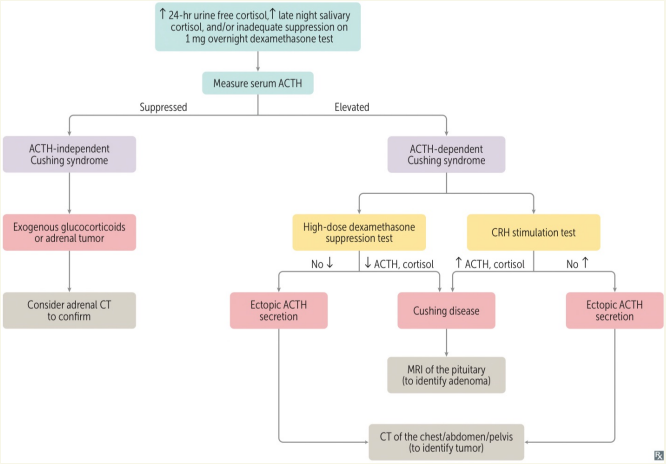




↑ cortisol due to a variety of causes:

- Exogenous glucocorticoids → ↓ ACTH → bilateral adrenal atrophy. Most common cause.
- Primary adrenal adenoma, hyperplasia, or carcinoma → ↓ ACTH → atrophy of uninvolved adrenal gland.
- ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids) → bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

MOON FACIES: **M**etabolic syndrome (hypertension, hyperglycemia, hyperlipidemia), **O**besity (truncal weight gain with wasting of extremities, round "moon" facies **A**, dorsocervical fat pad "buffalo hump"), **O**steoporosis, **N**europsychiatric (depression, anxiety, irritability), **F**acial plethora, **A**ndrogen excess (acne, hirsutism), **C**ataract, **I**mmunosuppression, **E**cchymoses (easy bruising), **S**kin changes (thinning, striae **B**, hyperpigmentation).



Myopathy in Cushing syndrome (ie, glucocorticoid-induced myopathy) is characterized by progressive, painless muscle weakness mostly involving the proximal muscles. It results from the direct catabolic effects of cortisol on skeletal muscle that lead to muscle atrophy. Creatine kinase and erythrocyte sedimentation rate (ESR) are typically normal.

Women can have features of hyperandrogenism (eg, menstrual irregularities, acne, hirsutism) due to co-secretion of adrenal androgens with cortisol.

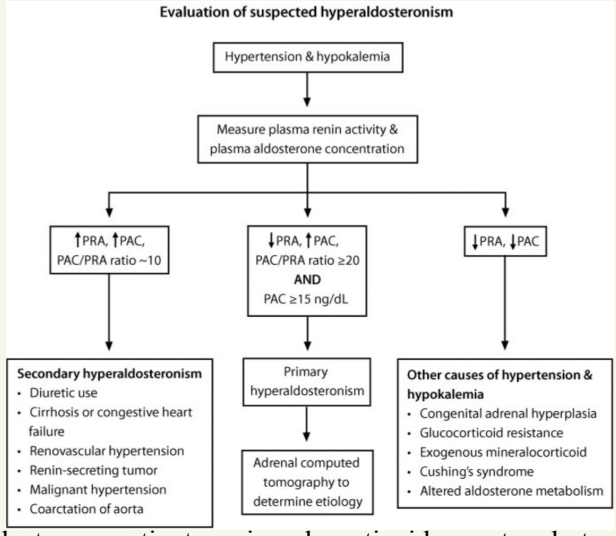
Hyperglycemia is common (due to peripheral insulin resistance and hypercortisolism-induced gluconeogenesis). Hypokalemia and alkalosis may be present (due to the partial mineralocorticoid effects of cortisol) if cortisol levels are very high.

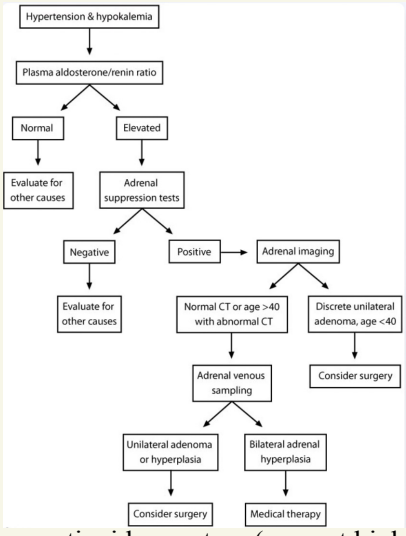
Hyperaldosteronism

Increased secretion of aldosterone from adrenal gland. Clinical features include hypertension, low or normal K+, metabolic alkalosis. 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema.

Primary: Seen in patients with bilateral adrenal hyperplasia or adrenal adenoma (Conn syndrome). increased aldosterone, decreased renin. Leads to treatment-resistant hypertension. —> high plasma aldosterone concentration (PAC) (>15 ng/dL) accompanied by low plasma renin activity (PRA), which results in a high PAC/PRA ratio (>20). However, drugs that significantly alter the PAC/PRA ratio (eg, spironolactone, eplerenone, amiloride, triamterene) should be withdrawn for 4 weeks before testing.

Secondary: Seen in patients with renovascular hypertension, juxtaglomerular cell tumors (renin-producing), and edema (eg, cirrhosis, heart failure, nephrotic syndrome). increased aldosterone, increased renin.

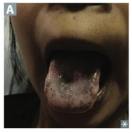


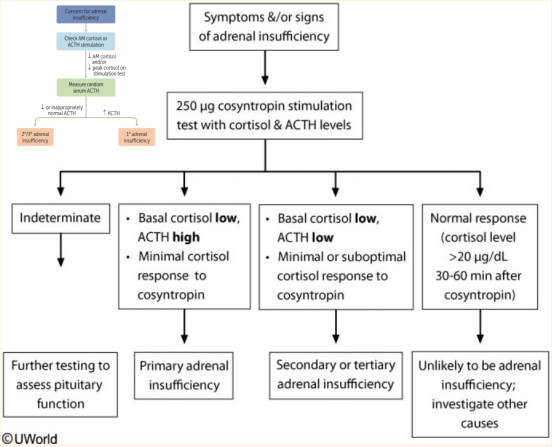


Aldosterone activates mineralocorticoid receptors but not glucocorticoid receptors (even at high levels). Therefore, primary hyperaldosteronism (ie, Conn syndrome) would cause hypertension and hypokalemia (mineralocorticoid activity), but features of hypercortisolism (eg, hyperglycemia, restlessness, significant weight gain) would not be expected.
Aldosterone causes wasting of potassium, leading to hypokalemia, which can cause muscle weakness and decreased exercise tolerance. Patients with mild primary hyperaldosteronism may not have spontaneous hypokalemia, but they are prone to developing diuretic-induced hypokalemia.

Rapidly progressive hirsutism with virilization suggests very high androgen levels due to an androgen-producing neoplasm. Elevated dehydroepiandrosterone sulfate levels are seen in androgen-producing adrenal tumors. AS, DHEA, and T are produced by both the gonads and the adrenals. In contrast, DHEAS is produced predominantly in the adrenal glands.

Adrenal Insufficiency

Adrenal insufficiency	Inability of adrenal glands to generate enough glucocorticoids +/– mineralocorticoids for the body's needs. Can be acute or chronic. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings. Treatment: glucocorticoid +/– mineralocorticoid replacement.
Primary adrenal insufficiency 	↓ gland function → ↓ cortisol, ↓ aldosterone → hypotension (hyponatremic volume contraction), hyperkalemia, metabolic acidosis, skin/mucosal hyperpigmentation A (↑ melanin synthesis due to ↑ MSH, a byproduct of POMC cleavage). Primary pigments the skin/mucosa. Addison disease—chronic 1° adrenal insufficiency; caused by adrenal atrophy or destruction. Most commonly due to autoimmune adrenalitis (high-income countries) or TB (low-income countries).
Secondary and tertiary adrenal insufficiency	↓ pituitary ACTH secretion (secondary) or ↓ hypothalamic CRH secretion (tertiary). No hyperkalemia (aldosterone synthesis preserved due to functioning adrenal gland, intact RAAS), no hyperpigmentation. 2° adrenal insufficiency is due to pituitary pathologies, 3° adrenal insufficiency is most commonly due to abrupt cessation of chronic glucocorticoid therapy (HPA suppression). Tertiary from treatment.
Acute adrenal insufficiency	Also called adrenal (addisonian) crisis; often precipitated by acute stressors that ↑ glucocorticoid requirements (eg, infection) in patients with pre-existing adrenal insufficiency or on glucocorticoid therapy. May present with acute abdominal pain, nausea, vomiting, altered mental status, shock. Waterhouse-Friderichsen syndrome—bilateral adrenal hemorrhage in the setting of sepsis (eg, meningococcemia) → acute 1° adrenal insufficiency.



Because cortisol acts as an inhibitor of antidiuretic hormone, AI often leads to the syndrome of inappropriate antidiuretic hormone release (SIADH) with hyponatremia.

A peripheral eosinophilia is common, likely due to reduced migration of eosinophils from the bloodstream into the tissues in the setting of low cortisol. Reduced production of adrenal androgens (eg, dehydroepiandrosterone) can lead to decreased libido and secondary sexual characteristics (eg, pubic hair); these effects are typically only seen in women because testicular androgen production continues in men.

Some patients with manifestations strongly suggestive of PAI may have low-normal cortisol levels (5-15 µg/dL) that fall within the normal range. Because of this, and because the ACTH assay can take several days, an ACTH stimulation test (cosyntropin test) is usually performed concurrently to rapidly confirm the diagnosis. Cosyntropin is a synthetic ACTH analog.

- Infusion of a 250-µg bolus of cosyntropin normally triggers a rapid increase in serum cortisol.
- In contrast, patients with PAI will not have a significant rise.
- In addition, most patients with central adrenal insufficiency have a blunted (minimal or suboptimal) response due to adrenal atrophy from chronically low ACTH.
- If results are indeterminate, further pituitary function testing can be considered.

Pheochromocytoma

Pheochromocytoma	
Indications for testing	• Classic triad: episodic headache, sweating & tachycardia • Resistant HTN or HTN accompanied by unexplained ↑ glucose • Family history or familial syndrome (eg, MEN2, NF1, VHL)
Diagnostic approach	• Urine or plasma metanephrine levels • Confirmatory abdominal imaging for ↑ metanephrines
Notable features	• 10% bilateral, 10% extraadrenal, 10% malignant
Management	• Preoperative alpha blockade prior to beta blockade • Laparoscopic or open surgical resection

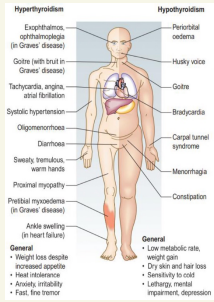
Pheochromocytoma is the most common tumor of the adrenal medulla in adults. Derived from chromaffin cells (arise from neural crest). Rare.

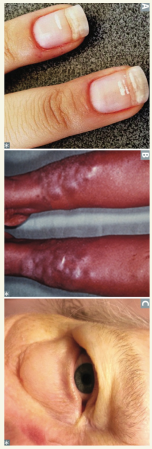
The classic symptomatic triad, consisting of episodic headache, sweating, and tachycardia, is present in less than half of patients. Paroxysmal hypertension (eg, highly variable blood pressure readings) is present in about half of patients.

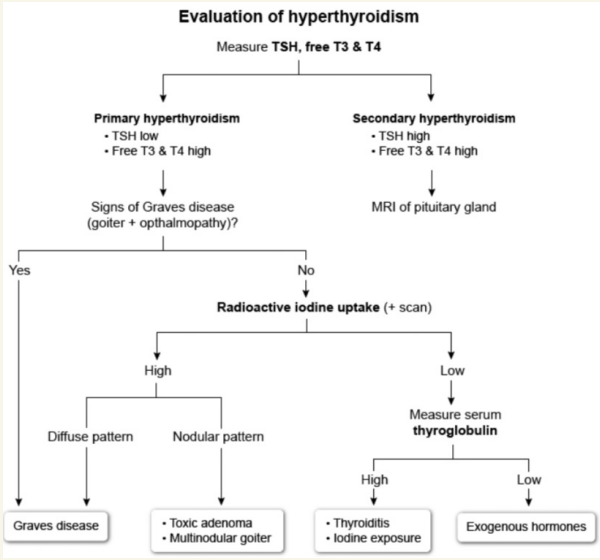
Elevated metanephrine levels have high sensitivity for pheochromocytoma; therefore, normal levels usually rule out the disease. The specificity of elevated metanephrine levels is poor. Therefore, elevated levels warrant additional testing in the form of abdominal CT scan or MRI and/or positron emission tomography (PET) to confirm the presence and location of a pheochromocytoma.

Hyperthyrodism & Hypothyroidism

	Hypothyroidism	Hyperthyroidism
METABOLIC	Cold intolerance, ↓ sweating, weight gain (↓ basal metabolic rate → ↓ calorigenesis), hyponatremia (↓ free water clearance)	Heat intolerance, ↑ sweating, weight loss (↑ synthesis of Na^+/K^+-ATPase → ↑ basal metabolic rate → ↑ calorigenesis)
SKIN/HAIR	Dry, cool skin (due to ↓ blood flow); coarse, brittle hair; diffuse alopecia; brittle nails; puffy facies and generalized nonpitting edema (myxedema) due to ↑ GAGs in interstitial spaces → ↑ osmotic pressure → water retention	Warm, moist skin (due to vasodilation); fine hair; onycholysis (A); pretibial myxedema in Graves disease B
OCULAR	Periorbital edema C	Ophthalmopathy in Graves disease (including periorbital edema, exophthalmos), lid lag/ retraction (↑ sympathetic stimulation of superior tarsal muscle)
GASTROINTESTINAL	Constipation (↓ GI motility), ↓ appetite	Hyperdefecation/diarrhea (↑ GI motility), ↑ appetite
MUSCULOSKELETAL	Hypothyroid myopathy (proximal weakness, ↑ CK), carpal tunnel syndrome, myoedema (small lump rising on the surface of a muscle when struck with a hammer)	Thyrotoxic myopathy (proximal weakness, normal CK), osteoporosis/↑ fracture rate (T_3 directly stimulates bone resorption)
REPRODUCTIVE	Abnormal uterine bleeding, ↓ libido, infertility	Abnormal uterine bleeding, gynecomastia, ↓ libido, infertility
NEUROPSYCHIATRIC	Hypoactivity, lethargy, fatigue, weakness, depressed mood, ↓ reflexes (delayed/slow relaxing)	Hyperactivity, restlessness, anxiety, insomnia, fine tremors (due to ↑ β-adrenergic activity), ↑ reflexes (brisk)
CARDIOVASCULAR	Bradycardia, dyspnea on exertion (↓ cardiac output)	Tachycardia, palpitations, dyspnea, arrhythmias (eg, atrial fibrillation), chest pain and systolic HTN due to ↑ number and sensitivity of β-adrenergic receptors, ↑ expression of cardiac sarcolemmal ATPase and ↓ expression of phospholamban
LABS	↑ TSH (if 1°)	↓ TSH (if 1°)





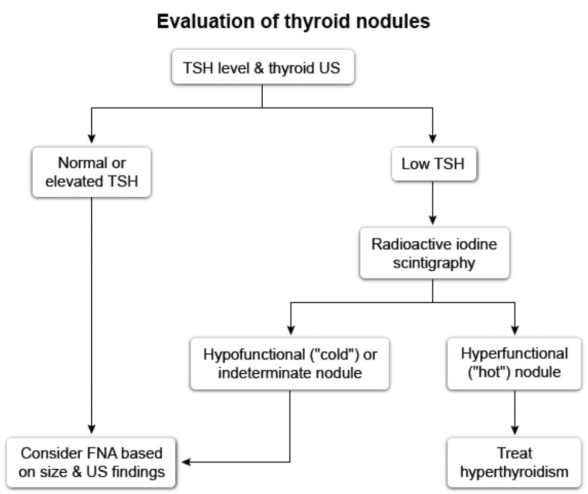


Thyroid Storm:

Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/ untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery, or in acute iodine load (eg, iodine contrast) which is called contrast-induced thyroiditis (Jod-Basedow phenomenon)

Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May increase LFTs. Treat with the 4 P's: β-blockers (eg, propranolol), propylthiouracil, glucocorticoids (eg, prednisolone), potassium iodide (Lugol iodine). Iodide load decreases T4 synthesis by Wolff-Chaikoff effect.

Thyroid Nodules



Once a thyroid nodule is found, cancer risk factors (family history, radiation exposure) should be assessed by history. Physical examination should evaluate the size, mobility, and firmness of the thyroid nodule and whether enlarged cervical lymph nodes are present.

Serum TSH levels should be obtained, along with a thyroid ultrasound to determine nodule size and sonographic features. Certain sonographic features (microcalcifications, irregular margins, internal vascularity) carry a much higher risk of malignancy than others (cystic or spongiform lesions). Thyroid nodules >1 cm with these high-risk sonographic features—and all noncystic thyroid nodules >2 cm—should undergo fine-needle aspiration (FNA) biopsy.

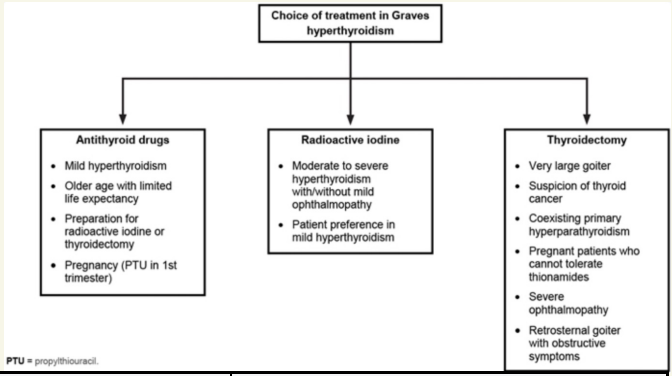
Thyroiditis		
	Clinical features	Diagnostic testing
Chronic autoimmune thyroiditis(Hashimoto thyroiditis)	• Predominant hypothyroid features • Diffuse goiter	• Positive TPO antibody • Variable radioiodine uptake
Painless thyroiditis(silent thyroiditis)	• Variant of chronic autoimmune thyroiditis • Mild, brief hyperthyroid phase • Small, nontender goiter • Spontaneous recovery	• Positive TPO antibody • Low radioiodine uptake
Subacute (granulomatous) thyroiditis(de Quervain thyroiditis)	• Likely postviral inflammatory process • Prominent fever & hyperthyroid symptoms • Painful/tender goiter	• Elevated ESR & CRP • Low radioiodine uptake

Painful thyroiditis Pain & tenderness Systemic symptoms	**Painless thyroiditis** Autoimmune/+TPO antibody Destruction of follicles Release of preformed hormone & thyroglobulin	**Graves** +TSI/TRAb ↑ Thyroid hormone synthesis	**Fibrotic** Replacement of follicles with fibrotic tissue
Subacute (granulomatous, DeQuervain) • Tender goiter • Transient hyperthyroid phase • Postviral syndrome	**Chronic lymphocytic** (Hashimoto) • Common • Usually hypothyroid at diagnosis	**Graves disease** • Overt hyperthyroidism • ↑ RAIU • Ophthalmopathy	**Riedel thyroiditis** • Hard/fixed goiter • Compression of esophagus & trachea
Acute (suppurative) • Fever • Asymmetry • Fluctuance	**Postpartum** • ≤12 months after parturition • Transient hyperthyroid phase		

Painless thyroiditis does not require specific antithyroid therapy; however, patients with signs of adrenergic overstimulation (eg, palpitations, tachycardia, tremulousness) should be treated with a beta blocker (eg, propranolol) rather than only observation and monitoring.

Struma ovarii is a very rare cause of thyrotoxicosis and is due to production of thyroid hormone by an ovarian teratoma. It typically presents in women over age 40 with a pelvic mass, ascites, or abdominal pain. The thyroid gland is not enlarged with this condition.

Antithyroid peroxidase (anti-TPO) antibodies are present in >90% of patients with Hashimoto thyroiditis, and high titers of anti-TPO are associated with an increased risk of progression to overt hypothyroidism. High titers of anti-TPO are also associated with increased risk of miscarriage in both euthyroid and hypothyroid women. Antibodies against TSH receptors can block the interaction of TSH with its receptors on thyroid follicular cells and are a less common cause of hypothyroidism. Hypothyroid individuals with TSH-blocking antibodies would have thyroid atrophy rather than enlargement. Anti-TPO antibodies are more likely associated with miscarriage. Subclinical hypothyroidism happens when you have elevated thyroid-stimulating hormone (TSH) levels with normal levels of thyroxine (T4).



Treatment	Adverse effects
Antithyroid drugs(thionamides)	• Agranulocytosis • Methimazole: 1st-trimester teratogen, cholestasis • Propylthiouracil: hepatic failure, ANCA-associated vasculitis
Radioiodineablation	• Permanent hypothyroidism • Worsening of ophthalmopathy • Possible radiation adverse effects
Surgery	• Permanent hypothyroidism • Risk for recurrent laryngeal nerve damage • Risk for hypoparathyroidism

Fever and sore throat in any patient taking antithyroid drugs suggests agranulocytosis. Antithyroid drugs should be stopped and WBC count checked. Routine WBC count measurement in patients taking antithyroid drugs is not cost effective. Agranulocytosis is the most feared side effect, and is seen in approximately 0.3% of patients treated with antithyroid drugs. It is caused by immune destruction of granulocytes, and most cases occur within 90 days of treatment. A total WBC count less than 1,000/cubic mm warrants permanent discontinuation of the drug. If the total WBC count is more than 1,500 per cubic mm, antithyroid drug toxicity is unlikely to be the cause of the sore throat and fever.

Prednisone or nonsteroidal anti-inflammatory drugs are used for treatment of subacute (de Quervain/ granulomatous) thyroiditis, a postviral syndrome.

In patients who have significant symptoms and thyroid hormone levels >2-3 times normal, an ATD with a beta blocker is initially recommended to stabilize the patient before definitive treatment with RAI or thyroidectomy. Pretreatment with ATDs is also recommended for patients at increased risk (eg, elderly, significant comorbidities) for complications due to the transient worsening of hyperthyroidism following RAI treatment.

RAI (131I) is taken up by the thyroid follicular cells in a manner similar to that of natural iodine, and the subsequent beta emission induces slow necrosis of the thyroid follicular cells. This leads to clinical and biochemical resolution of hyperthyroidism over the subsequent 6-18 weeks (not rapidly). The goal of RAI in Graves disease is to administer a sufficient dose of radiation to prevent recurrence of hyperthyroidism. However, the diffuse uptake of radioiodine eventually leads to permanent hypothyroidism within months in >90% of patients. In contrast, when RAI is used to treat toxic nodular goiter and toxic adenoma, the radioisotope is taken up only by the autonomous thyroid tissue, and the function of the remaining normal tissue is usually adequate to prevent permanent hypothyroidism. RAI can acutely worsen Graves ophthalmopathy due to increased titers of thyroid-stimulating immunoglobulins (TSI autoantibodies). Thyroidectomy is preferred in those with significant ocular manifestations. Pharmacologic doses of iodine (eg, in potassium iodide solutions) are occasionally used to transiently reduce the synthesis and release of thyroid hormones in patients with Graves disease. In contrast, the dose of iodine used in RAI, although sufficient to induce radiation necrosis, is much lower than that required to biochemically inhibit thyroid hormone synthesis.

Major drug interactions of levothyroxine	
↓ Levothyroxineabsorption	• Bile acid–binding agents (eg, cholestyramine) • Iron, calcium, aluminum hydroxide • Proton pump inhibitors, sucralfate
↑ TBGconcentration	• Estrogen replacement, oral contraceptives • Tamoxifen
↓ TBGconcentration	• Androgens, glucocorticoids • Anabolic steroids
↑ Thyroid hormonemetabolism	• Rifampin • Phenytoin • Carbamazepine

Drugs that inhibit deiodination of T4 to T3 include glucocorticoids, beta blockers, and propylthiouracil

High levels of estrogen (eg, pregnancy, oral contraceptive pills, hormone replacement therapy) increase the level of TBG by decreasing its catabolism and increasing its synthesis in the liver. As the additional TBG binds more thyroid hormone, thyroid hormone production increases to maintain a euthyroid state; this most likely explains the slight elevation in total T4 level (free T4 level would be expected to be normal).

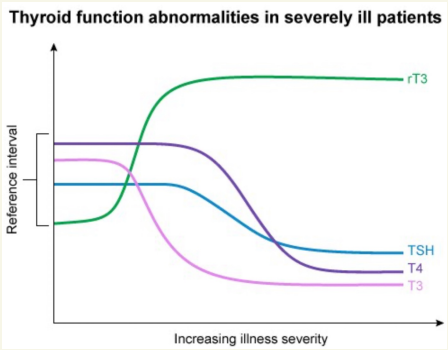
In patients with normal hypothalamic-pituitary feedback, displacement of T4 from its binding proteins leads to decreased thyroid hormone production and lower total T4 levels with normal free hormone levels. Medications with this effect include salicylates, furosemide, and heparin.

The liver produces serum binding proteins for thyroid hormones (eg, thyroxine-binding globulin, transthyretin, albumin, lipoproteins). Cirrhosis leads to decreased synthesis of these proteins, which lowers the total triiodothyronine (T3) and thyroxine (T4) in circulation; however, free T3 and T4 levels are unchanged, and TSH will be normal, reflecting a euthyroid status.

Thyroid hormones undergo significant enterohepatic circulation, with reabsorption in the jejunum and upper ileum. Excessive fecal loss of thyroid hormone can occur in small intestinal disease (eg, Crohn disease, celiac disease).

ESS

Euthyroid sick syndrome		
	Early/mild	Prolonged/severe
T3	↓	↓
T4	Normal	↓
TSH	Normal	↓
Reverse T3	↑	↑



ESS may represent a mild, transient central hypothyroid state that functions to minimize catabolism in severe illness.

Thyroid function tests often are abnormal in patients with severe, acute illness. Euthyroid sick syndrome (ESS) is a common pattern of thyroid function markers often seen in hospitalized patients. A characteristic feature of ESS is decreased peripheral conversion of T4 to T3 by 5'-monodeiodinase.

In general, thyroid testing should be avoided in hospitalized patients unless a clear indication is present, as in patient with acute atrial fibrillation (possibly precipitated by pneumonia). Treatment of ESS with exogenous thyroid hormone (ie, levothyroxine) does not improve clinical outcomes and is not indicated. During recovery, patients may experience a modest, transient increase in TSH levels, which may be misinterpreted as subclinical hypothyroidism. Therefore, follow-up testing should be delayed until the patient has returned to baseline health.

Pituitary (or hypothalamic) injury can cause central hypothyroidism (ie, low T4, low TSH, low T3, and low rT3) that in some cases may be difficult to differentiate from ESS due to overlapping laboratory features. In such cases, serum cortisol should be obtained; a normal level makes overt central hypopituitarism unlikely.

Hyperparathyrodism

Primary hyperparathyroidism



Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal stones), polyuria (thrones), hypophosphatemia, ↑ PTH, ↑ ALP, ↑ urinary cAMP. Most often asymptomatic. May present with bone pain, weakness, constipation ("groans"), abdominal/flank pain (kidney stones, acute pancreatitis), neuropsychiatric disturbances ("psychiatric overtones").

Osteitis fibrosa cystica—cystic bone spaces filled with brown fibrous tissue A ("brown tumor" consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain). Due to ↑ PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism.

"Stones, thrones, bones, groans, and psychiatric overtones."

Secondary hyperparathyroidism

2° hyperplasia due to ↓ Ca^{2+} absorption and/or ↑ PO_4^{3-}, most often in chronic kidney disease (causes hypovitaminosis D and hyperphosphatemia → ↓ Ca^{2+}). **Hypocalcemia**, hyperphosphatemia in chronic kidney disease (vs hypophosphatemia with most other causes), ↑ ALP, ↑ PTH.

Renal osteodystrophy—renal disease → 2° and 3° hyperparathyroidism → bone lesions.

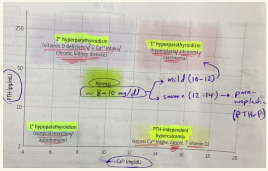
Tertiary hyperparathyroidism

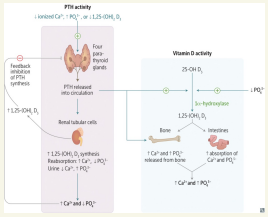
Refractory (autonomous) hyperparathyroidism resulting from end-stage renal disease. ↑↑ PTH, ↑ Ca^{2+}.

Familial hypocalciuric hypercalcemia

Autosomal dominant. Defective G-coupled Ca^{2+}-sensing receptors in multiple tissues (eg, parathyroids, kidneys). Higher than normal Ca^{2+} levels required to suppress PTH. Excessive renal Ca^{2+} reabsorption → mild hypercalcemia and hypocalciuria with normal to ↑ PTH levels.

Primary hyperparathyroidism causes gradual-onset, mild-to-moderate hypercalcemia (usually <14 mg/dL).





Hypoparathyrodism

Hypoparathyroidism



Due to injury to parathyroid glands or their blood supply (usually during thyroid surgery), autoimmune destruction, or DiGeorge syndrome. Findings: tetany, hypocalcemia, hyperphosphatemia.

Chvostek sign—tapping of facial nerve (tap the Cheek) → contraction of facial muscles.

Trousseau sign—occlusion of brachial artery with BP cuff (cuff the Triceps) → carpal spasm.

Pseudohypoparathyroidism type 1A—autosomal dominant, maternally transmitted mutations (imprinted *GNAS* gene). GNAS1-inactivating mutation (coupled to PTH receptor) that encodes the G_s protein α subunit → inactivation of adenylate cyclase when PTH binds to its receptor → end-organ resistance (kidney and bone) to PTH.

Physical findings: Albright hereditary osteodystrophy (shortened 4th/5th digits A, short stature, round face, subcutaneous calcifications, developmental delay).

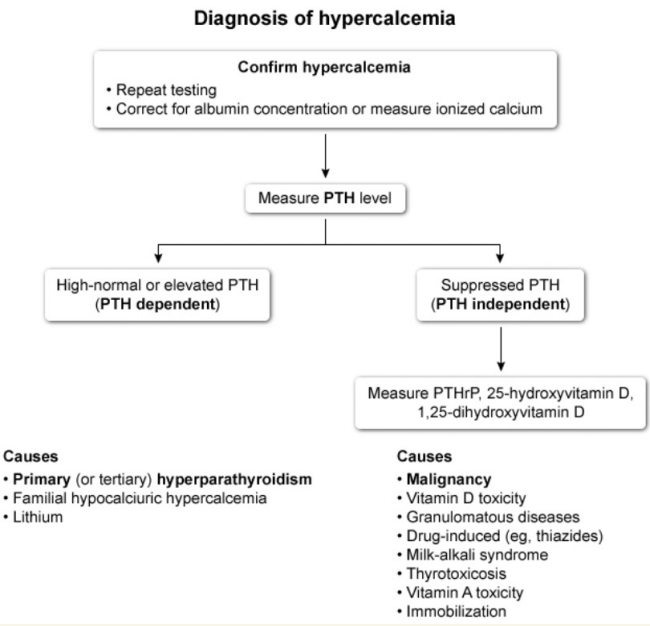
Labs: ↑ PTH, ↓ Ca^{2+}, ↑ PO_4^{3-}.

Pseudopseudohypoparathyroidism—autosomal dominant, paternally transmitted mutations (imprinted *GNAS* gene) but without end-organ resistance to PTH due to normal maternal allele maintaining renal responsiveness to PTH.

Physical findings: same as Albright hereditary osteodystrophy.

Labs: normal PTH, Ca^{2+}, PO_4^{3-}.

Hypercalcemia



Granulomatous diseases (eg, sarcoidosis) and lymphoma can cause hypercalcemia due to extrarenal production of 1,25-dihydroxyvitamin D. However, hypercalcemia due to excess 1,25-dihydroxyvitamin D would be associated with hyperphosphatemia rather than hypophosphatemia. Also, sarcoidosis is more common at age <40.

Hydrochlorothiazide increases urinary calcium reabsorption, which can mildly increase serum calcium levels (usually <12 mg/dL). Severe hypercalcemia does not occur.

Rapid bony destruction due to skeletal metastasis may cause hypercalcemia, but the gradual bone loss seen in osteoporosis does not affect serum calcium levels.

HHM is the most common cause of PTH-independent hypercalcemia and frequently presents with very high (eg, >14 mg/dL), symptomatic (eg, polyuria, constipation, nausea) and rapid-onset hypercalcemia. The diagnosis is often suspected on clinical grounds and can be confirmed by an elevated PTHrP level and suppressed PTH level. HHM is usually seen in advanced malignancy and confers a poor prognosis.

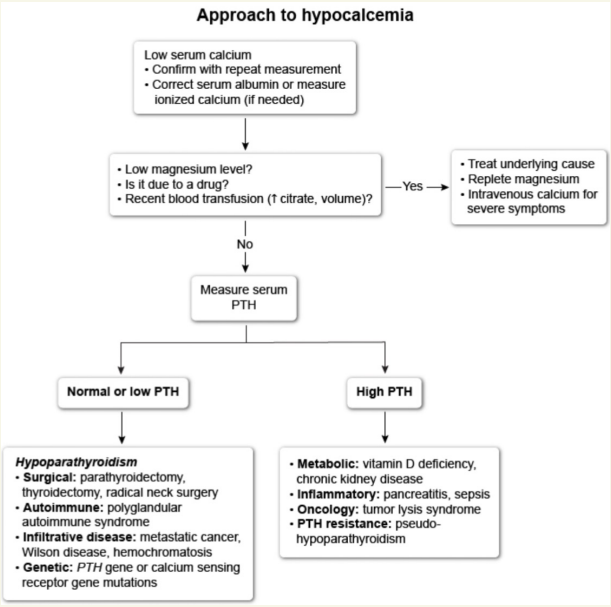
HHM is due to secretion of PTH-related protein (PTHrP) by malignant cells and is associated with squamous cell (eg, lung, head and neck), renal, bladder, breast, or ovarian carcinomas. PTHrP causes increased bone resorption and increased reabsorption of calcium in the distal renal tubule. However, PTHrP does not induce the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D to the same extent as PTH does, and so 1,25-dihydroxyvitamin D levels will be low or low-normal.

Other causes of PTH-independent hypercalcemia in malignancy include bony destruction by osteolytic metastasis (eg, breast, non-small cell lung cancer, non-Hodgkin lymphoma, multiple myeloma), increased production of 1,25-dihydroxyvitamin D (eg, lymphoma), and increased interleukin-6 levels (eg, multiple myeloma).

Milk Alkali Syndrome

Milk-alkali syndrome	
Pathophysiology	• Excessive intake of calcium & absorbable alkali • Renal vasoconstriction & decreased GFR • Renal loss of sodium & water, reabsorption of bicarbonate
Symptoms	• Nausea, vomiting, constipation • Polyuria, polydipsia • Neuropsychiatric symptoms
Laboratoryfindings	• Hypercalcemia • Metabolic alkalosis • Acute kidney injury • Suppressed PTH
Treatment	• Discontinuation of causative agent • Isotonic saline followed by furosemide

Hypocalcemia



Hypocalcemia due to hypomagnesemia is typically refractory to treatment with calcium unless magnesium is replaced as well. Although PTH levels increase rapidly after magnesium replacement, hypocalcemia takes longer to improve because PTH resistance persists despite improvement in magnesium levels. Despite PTH deficiency, phosphorus levels are normal or low in magnesium deficiency; this is possibly due to intracellular phosphorus depletion.

Patients with adequate dietary and dermal sources of vitamin D can develop deficiency due to increased catabolism of vitamin D. Commonly used anticonvulsants (eg, carbamazepine, phenytoin), Rifampin, Isoniazid can induce CYP24A1, which catabolizes vitamin D to inactive forms, leading to vitamin D deficiency.

Chronic vitamin D deficiency leads to Osteomalacia which lead to secondary hyperparathyrodism; the net effect is increased PTH, very low serum phosphorus, and mildly low or low-normal serum calcium.

The first step in evaluating hypocalcemia is to measure the serum albumin level because hypoalbuminemia lowers total circulating calcium (The serum calcium concentration decreases by 0.8 mg/dL for every 1 g/dL decrease in serum albumin) without affecting the metabolically active ionized calcium concentration (pseudohypocalcemia). If albumin is low, a corrected calcium level can be calculated (corrected calcium = [measured calcium] + 0.8 × [4.0 g/dL − serum albumin in g/dL]).

Once true hypocalcemia is confirmed, the next step is to exclude causes such as massive blood transfusion, whereby citrate in transfused products binds to ionized calcium; and hypomagnesemia, which causes resistance to PTH secretion & action, the hormone that regulates minute-to-minute calcium concentrations.

once hypoparathyroidism has been excluded, the next step is to measure a serum 25-hydroxyvitamin D level to rule out vitamin D deficiency. Common causes of vitamin D deficiency include inadequate dietary intake, inadequate sunlight exposure (which converts 7-dehydrocholesterol to vitamin D3 in the skin), and malabsorptive disorders. Levels of 1,25-dihydroxyvitamin D correlate with PTH activity rather than total body vitamin D stores and are not usually measured.

Fibroblast growth factor 23 (FGF23) lowers phosphate levels by decreasing intestinal absorption and increasing urinary excretion of phosphate. Elevated plasma FGF23 levels are seen in patients with phosphate retention and secondary hyperparathyroidism due to chronic kidney disease.

PCOS

Polycystic ovary syndrome	
Clinical features	• Androgen excess (eg, acne, male pattern baldness, hirsutism) • Oligoovulation or anovulation (eg, menstrual irregularities) • Obesity • Polycystic ovaries on ultrasound
Pathophysiology	• ↑ Testosterone levels • ↑ Estrogen levels • LH/FSH imbalance
Comorbidities	• Metabolic syndrome (eg, diabetes, hypertension) • Obstructive sleep apnea • Nonalcoholic steatohepatitis • Endometrial hyperplasia/ cancer
Treatment options	• Weight loss (first-line) • Oral contraceptives for menstrual regulation • Letrozole for ovulation induction

The first-line therapy for menstrual regulation is a combination of weight loss and combined estrogen/progestin oral contraceptives. Combined oral contraceptives contain progesterone to stimulate endometrial differentiation (ie, limit continued proliferation) and estrogen to stabilize the uterine lining, which restores normal cycles. In addition, combined oral contraceptives reduce hirsutism by blocking adrenal androgen secretion and increasing production of sex hormone-binding globulin, which binds and decreases free testosterone.



Step 2

& Relevant Clinical Step 1

Cardiology

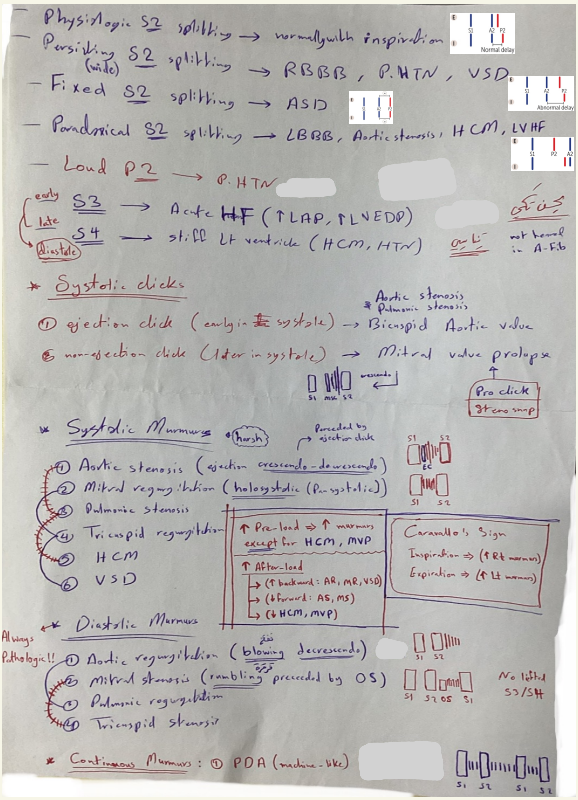
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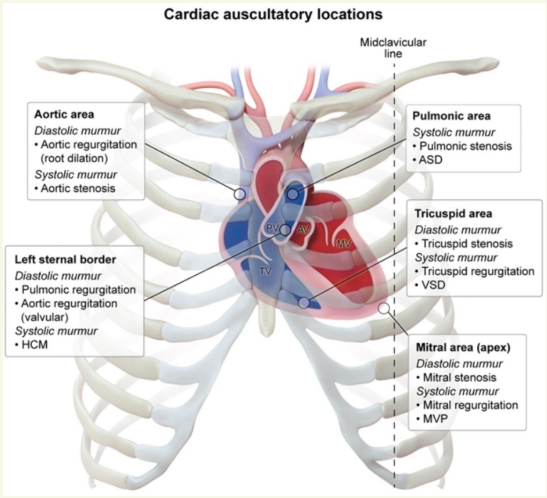
إنَّ الطِّبَّ وسِيلةٌ.. لا غايَةٌ!

Contact & Updates:

Ehab Alroud

Murmurs





MANEUVER	CARDIOVASCULAR CHANGES	MURMURS THAT INCREASE WITH MANEUVER	MURMURS THAT DECREASE WITH MANEUVER
Standing, Valsalva (strain phase)	↓ preload (↓ LV volume)	MVP (↓ LV volume) with earlier midsystolic click HCM (↓ LV volume)	Most murmurs (↓ flow through stenotic or regurgitant valve)
Passive leg raise	↑ preload (↑ LV volume)	Most murmurs (↑ flow through stenotic or regurgitant valve)	MVP (↑ LV volume) with later midsystolic click HCM (↑ LV volume)
Squatting	↑ preload, ↑ afterload (↑ LV volume)		
Hand grip	↑↑ afterload → ↑ reverse flow across aortic valve (↑ LV volume)	Most other left-sided murmurs (AR, MR, VSD)	AS (↓ transaortic valve pressure gradient) HCM (↑ LV volume)
Inspiration	↑ venous return to right heart, ↓ venous return to left heart	Most right-sided murmurs	Most left-sided murmurs

Midsystolic murmurs in otherwise young, asymptomatic adults are usually benign and do not require further evaluation.

A soft S4 can also be a normal finding in the elderly (eg, age >70) due to a physiologic, age-related loss of ventricular compliance.

Extra (gallop) heart sounds		
	Features	**Associated pathology***
S3	• Heard just after S2 • Caused by reverberant sound as blood fills an enlarged LV cavity during passive diastolic filling	• Heart failure with reduced EF • High-output states (eg, thyrotoxicosis) • Mitral or aortic regurgitation
S4	• Heard just before S1 • Caused by blood striking a stiff LV wall during atrial contraction	• Concentric LV hypertrophy • Restrictive cardiomyopathy • Acute myocardial infarction
*S3 can be normal in children, young adults & during pregnancy. S4 can be normal in the elderly (eg, age >70).		

Both an S3 and S4 are best heard at the cardiac apex with the bell of the stethoscope. In ACS, myocardial ischemia leads to a depletion of adenosine triphosphate (ATP). Because myocardial relaxation (ie, diastole) is an ATP-dependent process, myocardial ischemia causes the left ventricular (LV) walls to become stiff and unable to relax. Therefore, during atrial contraction, blood strikes against the stiffened LV wall and creates a fourth heart sound (ie, S4) in most patients with acute myocardial ischemia (eg, ischemia-induced myocardial dysfunction).

Valvular Diseases

- ## Mitral Regurgitation

Acute mitral regurgitation	
Etiology	• Ruptured mitral chordae tendineae from: ◦ Mitral valve prolapse ◦ Infective endocarditis ◦ Rheumatic heart disease ◦ Trauma • Papillary muscle displacement or rupture due to MI
Clinical features	• Rapid onset of pulmonary edema • Acute LV failure (also causing acute RV failure) • Hypotension, cardiogenic shock
Physical examination	• Jugular venous distension, pulmonary crackles • Hyperdynamic cardiac impulse • Apical systolic murmur (often absent) • Diaphoresis, cool extremities (if shock is present)
Management	• Bedside echocardiography • Emergency surgical intervention

Acute mitral regurgitation (MR) can occur due to papillary muscle displacement in patients with acute myocardial infarction. It leads to an abrupt elevation in left atrial and ventricular filling pressures with consequent acute pulmonary edema and heart failure. MR is classically associated with an apical holosystolic murmur, but acute MR may manifest with only a soft, early systolic murmur (or no murmur at all) because the abrupt valve failure may be so severe that there is little pressure gradient between the LV and LA. Unlike chronic MR, acute MR does not involve any significant change in left atrial or ventricular size or compliance. The posteromedial mitral papillary muscle is more commonly affected due to singular blood supply from the right coronary artery along the inferior wall.

Patients with severe mitral regurgitation develop left ventricular volume overload and LV dilation, with an audible S3 gallop typically present.

Mitral valve prolapse (MVP)

is the most common cause of chronic MR in developed countries. MVP occurs due to myxomatous degeneration of the mitral valve leaflets and chordae and causes a mid-systolic click followed by a mid-to-late systolic murmur. As the severity of leaflet dysfunction and MR worsens, the murmur becomes holosystolic and the click may not be audible.

- ## Mitral Stenosis

Mitral stenosis in adults	
Etiology	• Rheumatic heart disease (vast majority of cases) • Age-related calcification, radiation induced
Clinical presentation	• Exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, hemoptysis • Pulmonary edema ± right-sided heart failure (eg, lower extremity edema) • Atrial fibrillation, ↑ risk for systemic embolization
Diagnosis	• Opening snap with middiastolic rumble at the apex • Echocardiography: ↑ transmitral flow velocity
Treatment	• Percutaneous valvotomy or surgical repair/replacement

Atrial fibrillation in the setting of MS also carries an even higher thrombogenic risk than nonvalvular atrial fibrillation, and routine anticoagulation with warfarin is indicated regardless of CHA2DS2-Vasc score.

- # Aortic Regurgitation

Chronic aortic regurgitation	
Common etiologies	• Congenital bicuspid aortic valve • Postinflammatory (eg, rheumatic heart disease, endocarditis) • Aortic root dilation (eg, Marfan syndrome, syphilis)
Pathophysiology	• Backflow from aorta into LV → ↑ LV end-diastolic volume • LV initially compensates with eccentric hypertrophy → ↑ SV & CO • Eventual LV dysfunction → ↓ SV & CO → heart failure
Clinical findings	• Decrescendo diastolic murmur • Widened pulse pressure (↑SBP & ↓DBP) • Rapid rise-rapid fall ("water-hammer") pulsation • Abrupt carotid distension & collapse, "pistol-shot" femoral pulses

The most common cause of AR in developing countries is rheumatic heart disease; in developed countries it is often due to aortic root dilation or congenital bicuspid valve.

A diastolic murmur best heard when the patient is sitting up is typical of aortic regurgitation. Unlike chronic AR, in acute AR the diastolic pressure gradient between the aorta and left ventricle is small, so the murmur is short (early diastolic) and soft or may not be audible. Uvular pulsation (Müller's sign) may be appreciated with the high-amplitude systolic pulsation and rapid diastolic collapse that occurs with severe aortic regurgitation. The increase in LV size brings the ventricular apex close to the chest wall, causing a pounding sensation and an uncomfortable awareness of the heartbeat, especially in the left lateral decubitus position.

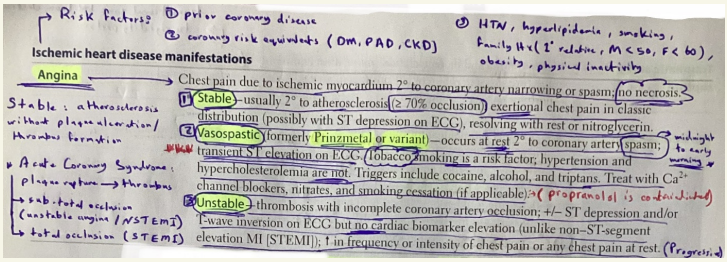
- # Aortic Stenosis

Aortic stenosis	
Causes	• Calcific disease (most common, age >70) • Congenital bicuspid valve (younger patients) • Rheumatic heart disease (common worldwide but rare in developed countries)
Clinicalmanifestations*	• Dyspnea on exertion, decreased exercise tolerance • Angina pectoris • Syncope • Heart failure
Physicalexamination	• Crescendo-decrescendo systolic murmur best heard at RUSB with radiation to carotids & axillae • Slow-rising (delayed) & weak carotid pulse (pulsus parvus et tardus)
Management	• Aortic valve replacement for severe AS causing symptoms or LV systolic dysfunction

The 3 most common causes of aortic stenosis in the general population are senile calcific aortic stenosis, bicuspid aortic valve, and rheumatic heart disease. A bicuspid aortic valve is the cause of aortic stenosis in the majority of patients age <70.

Aortic stenosis (valve area <3 cm) is a common cause of exertional dyspnea, angina, syncope, and heart failure; however, such symptoms are rare until the AS becomes severe (usually indicated by valve area <1 cm) which increases the pressure load on the left ventricle and can lead to concentric left ventricular hypertrophy (LVH) and restricts stroke volume and typically leads to low pulse pressure. In patients with mild to moderate AS, anginal symptoms are likely due to another cause, most commonly obstructive coronary artery disease.

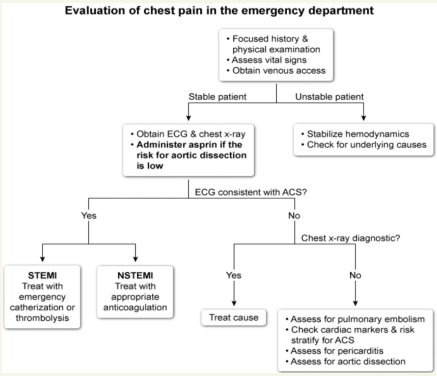
Angina & MI

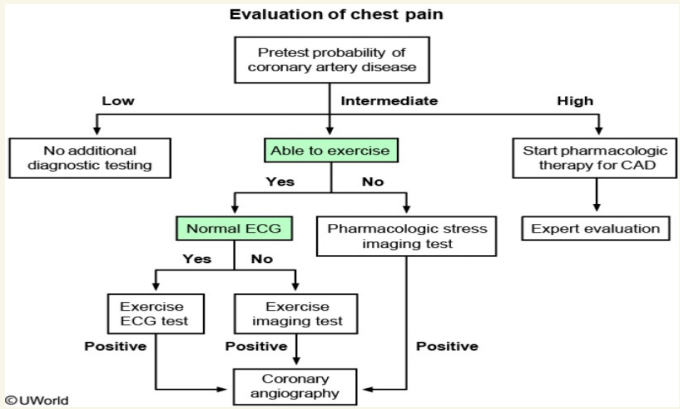


	Stable angina	Unstable angina	NSTEMI	STEMI
PAIN	On exertion	Mild exertion or at rest	At rest	At rest
TROPONIN LEVEL	No elevation	No elevation	Elevated	Elevated
INFARCTION	None	None	 Subendocardial	 Transmural
ECG CHANGES	Possible ST depression and/or T-wave inversion	Possible ST depression and/or T-wave inversion	ST depression and/or T-wave inversion	ST elevation, pathologic Q waves

Vasospastic angina	
Pathogenesis	• Hyperreactivity of coronary smooth muscle
Clinicalpresentation	• Young patients (age <50) • Smoking (minimal other CAD risk factors) • Recurrent chest discomfort ◦ Occurs at rest or during sleep ◦ Spontaneous resolution ≤15 min
Diagnosis	• Ambulatory ECG: ST-segment elevation • Coronary angiography: no CAD
Treatment	• Calcium channel blocker (preventive) • Sublingual nitroglycerin (abortive)

Diltiazem, a weak systemic arterial dilator but potent coronary arterial dilator, is commonly used; the dihydropyridines (eg, amlodipine, felodipine) are also effective.



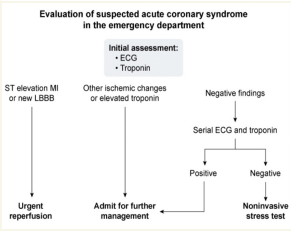


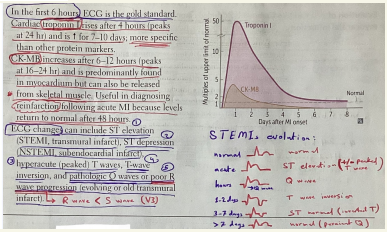
Patients presenting to the emergency department with chest pain and suspected acute coronary syndrome (ACS) should be administered aspirin as soon as possible.

If serial ECGs and cardiac biomarkers are normal and suspicion for ACS remains, bedside echocardiography can be considered to look for wall motion abnormalities.

Pretest probability of coronary artery disease	
Low (<10%)	Asymptomatic people of all ages Atypical chest pain in women age <50
Intermediate (20%-80%)	Atypical angina in men of all ages Atypical angina in women age ≥50 Typical angina in women age 30-50
High (>90%)	Typical angina in men age ≥40 Typical angina in women age ≥60

Classification of angina	
Classic	Typical location (eg, substernal), quality & duration Provoked by exercise or emotional stress Relieved by rest or nitroglycerin
Atypical	2 of the 3 characteristics of classic angina
Nonanginal	<2 of the 3 characteristics of classic angina





Differential diagnosis & features of chest pain	
Coronary arterydisease	• Substernal • Precipitated by exertion • Relieved by rest or nitroglycerin
Pulmonary/pleuritic(pleurisy, pneumonia,pericarditis, PE)	• Sharp/stabbing pain • Worse with inspiration • Pericarditis: worse when lying flat
Aortic(dissection,intramural hematoma)	• Abrupt (maximal at onset), severe "tearing" pain • May radiate to back • Hypertension and/or inherited aortopathy
Esophageal	• Substernal, may refer to neck • Associated with regurgitation • Provoked by recumbent position • Nonexertional, relieved by antacids
Chest wall/musculoskeletal	• Persistent pain • Worse with movement or change in position • Often follows repetitive activity

Esophageal chest pain (eg, from gastroesophageal reflux disease) is the most common mimicker of angina and is the second most common cause of chest pain in the primary care population (after musculoskeletal pain).

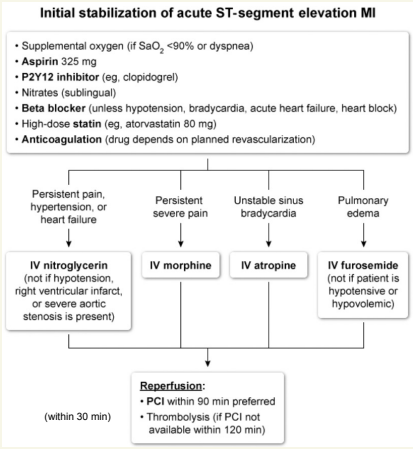
Costochondritis presents with tenderness of >1 costochondral or sternochondral joints and is the most common cause of musculoskeletal chest pain. Patients typically have sharp, localized chest pain that is reproducible with palpation. The course is typically benign and self-limiting with resolution in a matter of weeks; however, in some cases the discomfort may persist for up to a year. Initial management involves reassurance along with topical or systemic analgesics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs).

Distinguishing acid reflux from angina		
	GERD	**Angina**
Symptoms	• Substernal burning or dull pain; may radiate to arms, neck, jaw • Frequently accompanied by cough or reflux	• Substernal pressure; may radiate to arms, neck, jaw • Frequently accompanied by dyspnea
Symptom duration	• Prolonged, constant (eg, >1 hr)	• Short, intermittent (eg, 2-5 min for chronic angina; >15 min suggests ACS)
Precipitating factors	• Recumbency • Trigger foods (eg, alcohol, coffee)	• Physical exertion • Stress
Alleviating factors	• Antacids	• Rest • Nitroglycerin

	Left ventricular MI	**Right ventricular MI**
Clinical features	Pulmonary edema S3 & S4	Clear lungs & JVD Marked hypotension
ECG findings	Ischemic changes in anterior, lateral, or inferior leads	Inferior ischemic changes ST-segment elevation in V_4R Bradyarrhythmias
Hemodynamic findings	↑ LV & RV preload ↑ SVR	↑ RV preload, ↓ LV preload ↑ SVR
Management	Fluid restriction Preload & afterload reduction Reperfusion therapy	Fluid resuscitation Avoid preload reduction Reperfusion therapy

Management of RVMI differs from left ventricular MI in that the failing right ventricle is highly sensitive to inadequate preload. Nitrates (eg, sublingual nitroglycerin) should be avoided because they reduce RV preload and can profoundly worsen hypotension.

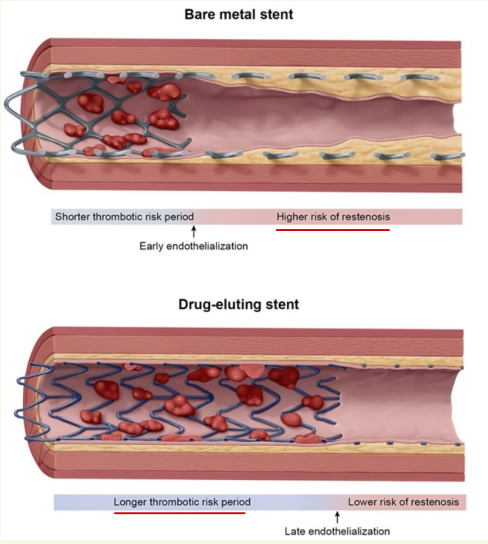
The right ventricle is involved in up to half of inferior wall MIs, which are recognized by ischemic changes in ECG leads II, III, and aVF and commonly present with atypical epigastric pain rather than classic substernal chest pain. Nausea is also common, but when MI primarily affects the right ventricle, shortness of breath is rarely present (due to absence of pulmonary edema). Because inferior wall MI usually results from obstruction of the right coronary artery, which usually supplies blood to the sinoatrial and atrioventricular nodes, bradyarrhythmias (eg, sinus bradycardia, atrioventricular block) are frequently present. So, B-blockers are contraindicated.



Acute management of acute coronary syndrome (STEMI, NSTEMI, or unstable angina)	
Nitrates	• Rapid chest pain relief • Caution with hypotension (eg, RV infarction)
Beta blocker	• Cardioselective (eg, metoprolol, atenolol) • Decreases myocardial O2 demand to limit infarct size • Contraindicated in cardiogenic shock & bradycardia
Antiplatelet therapy	• Aspirin + P2Y12 inhibitor (eg, prasugrel, clopidogrel)* • Reduces platelet activity
Anticoagulation	• Unfractionated heparin, bivalirudin, or enoxaparin • Limits thrombus expansion
Statin therapy	• High potency (eg, atorvastatin, rosuvastatin) • Stabilizes atherosclerotic plaque
Coronary reperfusion	STEMI • PCI <90 min from 1st medical contact • Fibrinolytics (eg, alteplase) if PCI is unavailable NSTEMI or unstable angina • Coronary angiography often within 24 hr

*In patients with NSTEMI or unstable angina, P2Y12 inhibitor therapy is often held until after coronary angiography in case the atherosclerotic coronary anatomy indicates the need for coronary artery bypass grafting.

Optimal medical management following myocardial infarction	
Medication	**Indication**
Dual antiplatelet therapy(low-dose aspirin + $P2Y_{12}$ inhibitor)	• All patients (regardless of stent placement) • Low-dose aspirin continued indefinitely • $P2Y_{12}$ inhibitor continued for 12 months
Beta blocker(eg, metoprolol, carvedilol)	• All patients, continued indefinitely • Reduces myocardial oxygen demand, decreases arrhythmia risk & inhibits remodeling
ACE inhibitor or angiotensin II receptor blocker	• All patients, continued indefinitely for reduced LVEF • Inhibits post-MI remodeling
High-intensity statin(ie, atorvastatin, rosuvastatin)	• All patients, continued indefinitely • Stabilizes atherosclerotic plaque & reduces recurrent MI
Mineralocorticoid antagonist(eg, spironolactone)	• Reduced LVEF with symptoms or comorbid DM • Inhibits post-MI remodeling



Current guidelines recommend primary PCI for patients with acute STEMI as follows:

- Within 12 hours of symptom onset

AND

- Within 90 minutes from first medical contact to device time at a PCI-capable facility

OR

- Within 120 minutes from first medical contact to device time at a non–PCI-capable facility (to allow time for transport to a PCI-capable facility)

The most common cause of stent thrombosis is poor adherence to, or inability to take, the recommended DAPT(Dual-Anti-Platelet-Therapy), a concern for patients with limited access to medical care (eg, those who are uninsured).

Approximately 50% of bypass grafts (CABG) fail within 10 years of surgery, sometimes leading to ischemic heart failure.

The cornerstone of NSTEMI medical management is dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor blocker (eg, clopidogrel, prasugrel), which should be given to all patients with no contraindications (eg, allergy, bleeding). Compared to aspirin therapy alone, long-term DAPT reduces the risk of recurrent MI and cardiovascular death in NSTEMI. Patients with NSTEMI should also receive anticoagulants (eg, heparin) to inhibit clot formation (typically for 48 hr). In addition to DAPT, other medications that reduce morbidity and mortality rates in coronary artery disease include:

- Beta blockers (reduce myocardial oxygen demand)
- Statins (anti-inflammatory effects)
- ACE inhibitors or angiotensin II receptor blockers (facilitate cardiac remodeling)
- Aldosterone antagonists (in select patients)

Loop diuretics (eg, furosemide) are indicated for the management of acute myocardial infarction (MI) complicated by decompensated heart failure and pulmonary edema.

Beta blockers improve mortality in acute MI but should be avoided in the setting of decompensated heart failure.

Mineralocorticoid antagonists (eg, spironolactone) inhibit post-MI remodeling and are indicated following MI in patients with a symptomatic reduction of left ventricular ejection fraction. However, these drugs are not indicated in the acute setting; they have only a weak diuretic effect and do not significantly improve acute pulmonary edema.

Anticoagulation (eg, with a heparin product, parenteral direct thrombin inhibitor, or parenteral factor Xa inhibitor) is part of the initial acute management of NSTEMI, but long-term anticoagulation therapy is not typically given following MI in the absence of another indication (eg, atrial fibrillation).

Long-acting nitrates (eg, isosorbide mononitrate) are used in patients with persistent stable angina, but they are not indicated in asymptomatic patients following MI.

In many patients, any systolic dysfunction following MI will normalize or significantly improve with medical therapy, lowering the risk of SCD. However, in patients with persistent LV ejection fraction ≤30% despite ≥3 months of optimal medical therapy, the risk of SCD remains high and primary prevention with placement of an implantable cardioverter-defibrillator (ICD) is indicated.

Myocardial infarction complications

COMPLICATION	TIMEFRAME	FINDINGS	NOTES
Cardiac arrhythmia	First few days to several weeks	Can be supraventricular arrhythmias, ventricular arrhythmias, or conduction blocks.	Due to myocardial death and scarring. Important cause of death before reaching the hospital and within the first 48 hours post-MI.
Peri-infarction pericarditis (Post-MI (Fibrinous Pericarditis))	1–3 days	Pleuritic chest pain, pericardial friction rub, ECG changes, and/or small pericardial effusion.	Usually self-limited.
Papillary muscle rupture	2–7 days	Can result in acute mitral regurgitation → cardiogenic shock, severe pulmonary edema. • holosystolic murmur	Posteromedial >> anterolateral papillary muscle rupture A, as the posteromedial has single artery blood supply (PDA) whereas anterolateral has dual (LAD, LCX).
Interventricular septal rupture (VSD)	3–5 days	Symptoms can range from mild to severe with cardiogenic shock and pulmonary edema. → (↑ JVP) (loud • holosystolic murmur + thrill)	Macrophage-mediated degradation → VSD → ↑ O_2 saturation and ↑ pressure in RV.
Ventricular pseudoaneurysm • < 2 weeks • inferior wall	3–14 days	May be asymptomatic. Symptoms may include chest pain, murmur, arrhythmia, syncope, HF, embolus from mural thrombus. Rupture → cardiac tamponade.	Free wall rupture contained by adherent pericardium or scar tissue B—does not contain endocardium or myocardium. More likely to rupture than true aneurysm.
Ventricular free wall rupture	5–14 days	Free wall rupture C → cardiac tamponade; acute form usually leads to sudden death.	LV hypertrophy and previous MI protect against free wall rupture.
True ventricular aneurysm • > 2 weeks • anterior wall	2 weeks to several months	Similar to pseudoaneurysm: symptoms may include chest pain, murmur, arrhythmia, syncope, HF, embolus from mural thrombus. Rupture → cardiac tamponade.	Outward bulge with contraction ("dyskinesia"). Associated with fibrosis. → that replaces infarcted tissue (commonly anterior wall)
Postcardiac injury syndrome ("Dressler's Syndrome")	Weeks to several months	Fibrinous pericarditis due to autoimmune reaction. • chest pain (pleuritic) • friction rub • treatment: NSAIDs / steroids	Also called Dressler syndrome. Cardiac antigens released after injury → deposition of immune complexes in pericardium → inflammation.

Post-Cardiac Injury Syndrome (PCIS) treatment: nonsteroidal anti-inflammatory drug (NSAID) in the form of high-dose aspirin (eg, 975 mg 3 times a day) or a nonaspirin NSAID (eg, ibuprofen 800 mg 3 times a day); aspirin usually is preferred because post-MI patients are already taking it in low doses for the antiplatelet effect.

In contrast to PCIS, peri-infarction pericarditis (PIP) results from local myopericardial inflammation and usually develops within 4 days of MI. Treatment with NSAIDs is usually avoided due to a possible increased risk of myocardial rupture in the early post-MI period.

Acute Pericarditis

Etiology	• Viral or idiopathic • Autoimmune disease (eg, SLE) • Uremia (acute or chronic kidney failure) • Post myocardial infarction ◦ Early: peri-infarction pericarditis ◦ Late: Dressler syndrome
Clinical features & diagnosis	• Pleuritic chest pain (↓ when sitting) ± fever • Pericardial friction rub (highly specific) • ECG: diffuse ST-segment elevation & PR-segment depression • Echocardiography: pericardial effusion
Treatment	• NSAIDs & colchicine for viral or idiopathic etiology • Variable for other etiologies

Pericardial effusion commonly occurs as a complication of acute pericarditis, which may be recognized by a triphasic pericardial friction rub best heard at the left lower sternal border with the patient leaning forward.
Initial ECG typically shows subtle (diffuse) PR depression and diffuse ST elevation that eventually evolves to diffuse T wave inversion.

All patients suspected of having Peri-Infarction Pericarditis (PIP) should undergo echocardiography, which allows for characterization of any associated pericardial effusion and helps rule out other post-MI complications (eg, free wall rupture). Patients should be monitored for a pericardial effusion large enough to cause cardiac tamponade, even though it is rare with PIP.

Treatment is usually supportive. Acetaminophen may be taken for pain control, but anti-inflammatory agents (eg, nonsteroidal anti-inflammatory drugs) are typically avoided for at least 7 days due to a possible increased risk of free wall rupture.

Viral pleurisy is an inflammation of the lung pleura that typically presents with fever and pleuritic chest pain. A pleural friction rub may be present and is differentiated from a pericardial friction rub by disappearance during breath holding

Constrictive Pericarditis

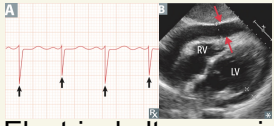
Etiology	• Recurrent idiopathic or viral pericarditis • Cardiac surgery or radiation therapy • Tuberculous pericarditis (where endemic)
Clinical presentation	• Fatigue, dyspnea on exertion • Peripheral edema, ascites, hepatic congestion • Pericardial knock in early diastole • JVD with positive Kussmaul sign* & prominent *y* descent
Diagnostic findings	• ECG: low-voltage QRS complexes • Chest x-ray/CT: pericardial calcification • Echocardiogram: biatrial enlargement, normal ventricular wall thickness & cavity size
*Increase in JVD with inspiration. (Kussmaul sign)	

A high-pitched sound in early diastole (ie, pericardial knock), reflecting abrupt arrest of ventricular filling, is a helpful clue.

Treatment involves surgical removal of the stiff and fibrotic pericardium (ie, pericardiectomy) to restore ventricular diastolic function.

Cardiac Tamponade

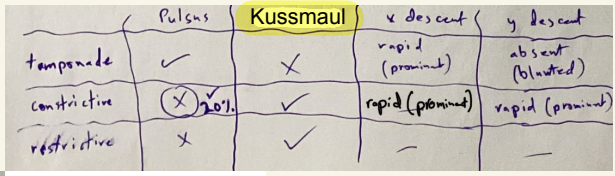
Etiology	• Blood in pericardial space (eg, LV rupture, cardiac surgery) • Pericardial effusion (eg, malignancy, infection, uremia)
Clinicalsigns	• Beck triad: hypotension, JVD, ↓ heart sounds • Pulsus paradoxus: SBP ↓ >10 mm Hg during inspiration
Diagnosis	• ECG: low-voltage QRS complex, electrical alternans • Chest x-ray: enlarged cardiac silhouette,* clear lungs • Echocardiography: right atrial & ventricular collapse, IVC plethora
Treatment	• Intravenous fluids to increase right-sided preload • Drainage via pericardiocentesis or pericardial window
*Subacute but not acute tamponade.	

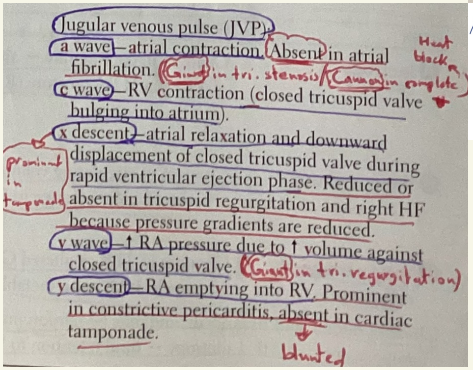


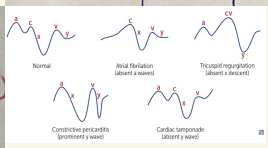
Electrical alternans is a specific but poorly sensitive finding for pericardial effusion with cardiac tamponade; it results from the heart changing position within the fluid-filled pericardial sac with each heartbeat.

Pulsus paradoxus— decrease in amplitude of systolic BP by > 10 mm Hg during inspiration. Increase venous return during inspiration —> increase RV filling —> interventricular septum bows toward LV (due to pericardial compliance) —> decrease LV ejection volume —> decrease systolic BP. Seen in constrictive pericarditis, obstructive pulmonary disease (eg, Croup, OSA, Asthma, COPD), and cardiac tamponade.

Normally, there is a small variation in intrathoracic pressure with respiration, which drops 2-5 mm Hg below atmospheric pressure during inspiration. In patients with severe asthma or COPD, the drop in intrathoracic pressure is greatly exaggerated (up to 40 mm Hg). This negative pressure causes pooling of blood in the pulmonary vasculature decreasing left ventricular preload. Marked expansion of the lungs in asthma and COPD can also impinge upon the outward expansion of the heart. Together, these factors lead to an excessive drop in blood pressure that is detected as pulsus paradoxus.







cannon A waves are commonly seen in complete atrioventricular block and frequent premature ventricular contractions. Patients may sometimes report symptoms associated with cannon A waves, including headache, jaw pain, and sensation of neck pulsation.

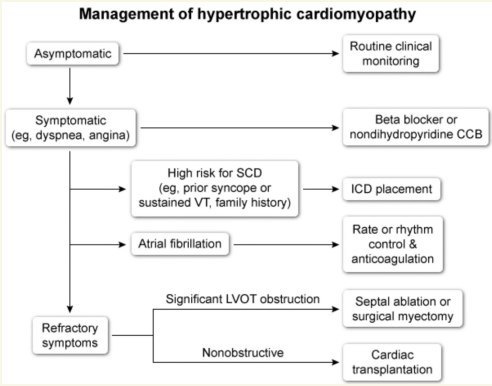
Cardiomyopathy

Dilated cardiomyopathy 	Most common cardiomyopathy (90% of cases). Often idiopathic or familial (eg, due to mutation of *TTN* gene encoding the sarcomeric protein titin). Other etiologies include drugs (eg, alcohol, cocaine, doxorubicin), infection (eg, coxsackie B virus, Chagas disease), ischemia (eg, CAD), systemic conditions (eg, hemochromatosis, sarcoidosis, thyrotoxicosis, wet beriberi), peripartum cardiomyopathy, tachycardia-mediated (A-Fib). Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR. Treatment: Na^+ restriction, ACE inhibitors/ARBs, β-blockers, sacubitril, diuretics, mineralocorticoid receptor blockers (eg, spironolactone), ICD, heart transplant.	Leads to systolic dysfunction. Displays eccentric hypertrophy A (sarcomeres added in series). Compare to athlete's heart, where LV and RV enlargement facilitates ↑ SV and ↑ CO. Stress cardiomyopathy (also called takotsubo cardiomyopathy, broken heart syndrome)—ventricular apical ballooning likely due to ↑ sympathetic stimulation (eg, stressful situations).
Hypertrophic cardiomyopathy 	60–70% of cases are familial, autosomal dominant (most commonly due to mutations in genes encoding sarcomeric proteins, such as myosin binding protein C and β-myosin heavy chain). Causes syncope during exercise and may lead to sudden death (eg, in young athletes) due to ventricular arrhythmia. Findings: S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure. Treatment: cessation of high-intensity athletics, use of β-blocker or nondihydropyridine Ca^{2+} channel blockers (eg, verapamil). ICD if high risk. Avoid drugs that decrease preload (eg, diuretics, vasodilators).	Diastolic dysfunction ensues. Displays ventricular concentric hypertrophy (sarcomeres added in parallel) B, often septal predominance. Myofibrillar disarray and fibrosis. Classified as hypertrophic obstructive cardiomyopathy when LV outflow tract is obstructed. Asymmetric septal hypertrophy and systolic anterior motion of mitral valve → outflow obstruction → dyspnea, possible syncope. Other causes of concentric LV hypertrophy: chronic HTN, Friedreich ataxia. Fabry disease, Severe aortic Stenosis
Restrictive/infiltrative cardiomyopathy	Postradiation fibrosis, Löffler endocarditis, Endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Amyloidosis, Sarcoidosis, Hemochromatosis (PLEASe Help!).	Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially in amyloidosis). Löffler endocarditis—associated with hypereosinophilic syndrome; histology shows eosinophilic infiltrates in myocardium.

An elevation in ventricular contraction rate (eg, >100/min) that is sustained for weeks or more can cause left ventricular dilation and cardiomyocyte dysfunction known as **tachycardia-induced cardiomyopathy**. The cardiomyopathy is usually reversible with slowing of the ventricular contraction rate; in atrial fibrillation this is accomplished via improved rate control or reestablishment of sinus rhythm (ie, rhythm control).

Hypertrophic Cardiomyopathy (HCM)

Pathophysiology	• Genetic mutations affecting cardiac sarcomere proteins • Autosomal dominant inheritance • Variable phenotypic penetrance
Clinical features	• Many patients are asymptomatic • Exertional dyspnea, fatigue, angina, light-headedness, syncope • Systolic ejection murmur accentuated by ↓ LV blood volume • Diastolic dysfunction with audible S4 • ↑ Risk for atrial fibrillation & ventricular tachycardia
Diagnosis	• ECG: left axis deviation, abnormalities of depolarization (eg, Q waves) or repolarization (eg, inverted T waves) • Echocardiography: septal LV hypertrophy, dynamic LVOT obstruction, LA dilation
Management	• Beta blocker or nondihydropyridine CCB (facilitate ↑ LV blood volume) • Avoidance of dehydration & vasodilators (avoid ↓ LV blood volume) • ICD placement for increased risk for SCD • Septal ablation, cardiac transplantation



Affected patients often have a recognizable family history of HCM but not always because sporadic mutations can occur, not all mutations responsible for the HCM phenotype have been identified, and the phenotypic penetrance of known mutations is not complete (ie, not all patients with an identifiable gene mutation demonstrate the HCM phenotype).

Symptomatic patients should be treated with a beta blocker (eg, metoprolol) as the negative chronotropy and inotropy increase left ventricular volume to reduce left ventricular outflow tract obstruction and improve symptoms.

Peripartum Cardiomyopathy

Risk factors	• Maternal age >30 • Multiple gestation • Eclampsia or preeclampsia
Clinical features	• Left ventricular ejection fraction <45% • Onset at ≥36 weeks gestation or ≤5 months postdelivery • No other causes of heart failure
Management	• Urgent delivery if hemodynamic instability present • Standard management of heart failure with reduced ejection fraction (eg, beta blocker, diuretics)

Patients with suspected PPCM should be evaluated using echocardiography. PPCM often causes secondary mitral regurgitation which can be recognized by a holosystolic murmur best heard at the apex.

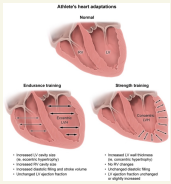
Chagas disease is a chronic disease that can cause megaesophagus, megacolon, and/or cardiac dysfunction (dilated cardiomyopathy). The protozoan Trypanosoma cruzi, endemic to South America, is responsible.

Fabry disease is a rare, X-linked inherited disorder involving deficiency of lysosomal hydrolase alpha-galactosidase A that leads to lysosomal accumulation of glycosphingolipids (specifically globotriaosylceramide [Gb3]). Affected patients typically develop neurologic manifestations (eg, paresthesias) during adolescence with cardiac manifestations including concentric LV hypertrophy, myocardial fibrosis, and heart failure developing at age >30.

	Hypertrophic cardiomyopathy	Athlete's Heart
Family history	Common	Usually unremarkable
ECG findings	LVH criteria + depolarization &/or repolarization abnormalities*	LVH criteria without other abnormalities
Left atrial size	Enlarged	Normal
LV cavity size	Usually decreased	Slightly enlarged
LV wall thickness	≥15 mm	<15 mm
Focal septalhypertrophy	Yes	No
LV diastolicfunction	Impaired	Normal

*Common depolarization abnormalities include prominent Q waves; common repolarization abnormalities include T-wave inversions.

Isolated T-wave inversion in V1 is relatively common in the general population, including in athletes.



Takotsubo Cardiomyopathy

Risk factors	• Postmenopausal woman • Recent physical or emotional stressor
Clinical features	• Chest pain mimicking myocardial infarction • Decompensated heart failure • Moderate troponin elevation • ECG: ischemic changes in precordial leads
Diagnosis	• Catheterization: no obstructive CAD • Echo: LV apical hypokinesis, basilar hyperkinesis
Treatment	• Resolves in several weeks with supportive care

CAD = coronary artery disease; **LV** = left ventricular.

Amyloidosis

Etiology	• Extracellular deposition of insoluble protein fibrils ◦ AL: produced by clonal plasma cells ◦ AA: secondary to chronic inflammation ◦ ATTR: age-related or hereditary ◦ AB2-m: dialysis-related
Clinical presentation*	• Nephrotic syndrome (AL & AA) • Hepatomegaly with/without splenomegaly (AL & AA) • Restrictive cardiomyopathy (AL & ATTR) • CTS, scapulohumeral periarthritis (AB2-m) • Peripheral/autonomic neuropathy • Periorbital purpura, waxy skin, macroglossia
∗Clinical presentation varies depending on the type of amyloid present. **AA** = amyloid A; **AB2-m** = amyloid beta2-microglobulin; **AL** = amyloid light chain; **ATTR** = amyloid transthyretin; **CTS** = carpal tunnel syndrome.	

Clinical manifestations of amyloidosis (primary & secondary)	
Renal	• Heavy proteinuria with nephrotic syndrome • Peripheral edema
Cardiac	• Restrictive cardiomyopathy • Conduction defects, low voltage
CNS	• Peripheral &/or autonomic neuropathy • Stroke
GI	• Hepatomegaly • Dysmotility, malabsorption • GI bleeding due to vascular fragility
Pulmonary	• Pulmonary nodules, tracheobronchial infiltration, pleural effusions
Musculoskeletal	• Enlarged tongue, shoulder pad enlargement
Skin	• Thickening of skin, subcutaneous nodules/plaques • Ecchymoses, periorbital purpura
Heme	• Anemia, thrombocytopenia

Primary amyloid (amyloid light chain [AL]) results from overproduction of protein fibrils by a clonal line of plasma cells, but amyloid proteins may also accumulate related to age (amyloid transthyretin [ATTR]) or secondary to chronic disease (eg, rheumatoid arthritis) (amyloid A [AA]).

Cardiac involvement is common, typically manifesting as restrictive cardiomyopathy that may later progress to dilated cardiomyopathy. Amyloid cardiomyopathy should be suspected in patients with unexplained congestive heart failure, proteinuria, and left ventricular hypertrophy in the absence of a history of hypertension.

Sarcoidosis

Study sarcoidosis in Pulmonolgy, page 46 **&** Nephrology, page 21

Cardiac sarcoidosis should be suspected in any young patient (age <55) with unexplained second- or third-degree heart block or when ECG changes occur in a patient with known or suspected systemic sarcoidosis (eg, dyspnea with midfield lung opacities, uveitis). Definitive diagnosis can be challenging due to poor sensitivity of endomyocardial biopsy, but a combination of imaging findings, ECG findings, and history often strongly suggests the diagnosis.

Autopsy studies have suggested evidence of cardiac noncaseating granulomas in at least 25% of patients with sarcoidosis. However, only 5% of patients demonstrate signs or symptoms of cardiac involvement, suggesting that cardiac sarcoidosis is underdiagnosed or often remains subclinical. Infiltration of noncaseating granulomas leads to surrounding inflammation and can result in conduction defects (complete AV block is most common), restrictive cardiomyopathy (early manifestation), dilated cardiomyopathy (late manifestation), valvular dysfunction, and heart failure. Sudden cardiac death can occur due to complete AV block or ventricular arrhythmia.

Myocarditis

- ↑ Troponin
- ↑ CK-MB
- CXR (enlarged heart)
- ECG (sinus tachy)

Inflammation of myocardium. Major cause of SCD in adults < 40 years old.
Presentation highly variable, can include dyspnea, chest pain, fever, arrhythmias (persistent tachycardia out of proportion to fever is characteristic).

Multiple causes:

- Viral (eg, adenovirus, coxsackie B, parvovirus B19, HIV, HHV-6, COVID-19); lymphocytic infiltrate with focal necrosis highly indicative of viral myocarditis
- Parasitic (eg, Trypanosoma cruzi, Toxoplasma gondii)
- Bacterial (eg, Borrelia burgdorferi, Mycoplasma pneumoniae, Corynebacterium diphtheriae)
- Toxins (eg, carbon monoxide, black widow venom)
- Rheumatic fever
- Drugs (eg, doxorubicin, cocaine)
- Autoimmune (eg, Kawasaki disease, sarcoidosis, SLE, polymyositis dermatomyositis)

Cardiomyopathy due to viral myocarditis	
Clinical presentation	• Commonly asymptomatic & resolves without detection • Heart failure that may progress to DCM* • Chest pain, ventricular arrhythmia with risk of SCD • Relatively young adults usually affected (eg, age <55) • ± Viral prodrome (eg, fever, malaise, myalgia)
Diagnosis	• ECG: nonspecific findings • Laboratory: mild to moderate serum troponin elevation • Echocardiography: 4-chamber dilation with diffuse hypokinesis • Cardiac MRI: epicardial or midwall enhancement • Biopsy: lymphocytic infiltration, viral DNA or RNA**
Treatment	• HFrEF medications (eg, diuretic, ACE inhibitor, beta blocker) • Temporary ventricular assist device, if needed • Heart transplant if no recovery

*Most common symptomatic presentation.

**Endomyocardial biopsy is rarely required for diagnosis.

Complications include sudden death, arrhythmias, heart block, dilated cardiomyopathy, HF, mural thrombus with systemic emboli.

Rheumatic Fever

A consequence of pharyngeal infection with group A β-hemolytic streptococci. Late sequelae include rheumatic heart disease, which affects heart valves—mitral > aortic >> tricuspid (high-pressure valves affected most). Early valvular regurgitation, late valvular stenosis.

Associated with Aschoff bodies (granuloma with giant cells, Anitschkow cells (enlarged macrophages with ovoid, wavy, rodlike nucleus), ↑ anti-streptolysin O (ASO) and ↑ anti-DNase B titers.

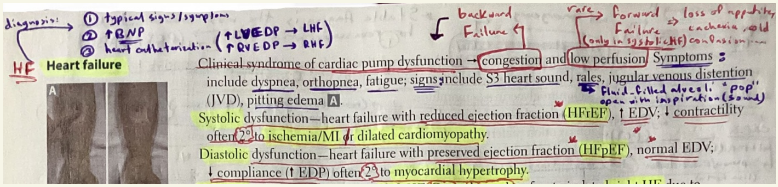
Immune mediated (type II hypersensitivity); not a direct effect of bacteria. Antibodies to M protein cross-react with self antigens, often myosin (molecular mimicry).

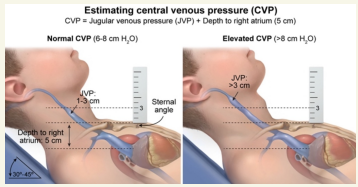
Treatment/prophylaxis: penicillin.

JONES (major criteria):

- Joint (migratory polyarthritis)
- ♥ (carditis)
- Nodules in skin (subcutaneous)
- Erythema marginatum (evanescent rash with ring margin)
- Sydenham chorea (involuntary irregular movements of limbs and face)

Heart Failure (HF)





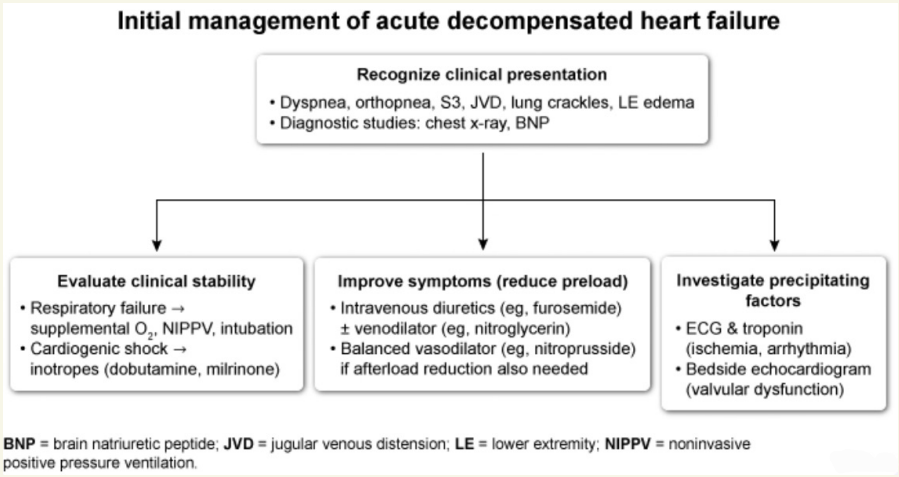
Heart failure with preserved ejection fraction (HFpEF) results from impaired diastolic relaxation (ie, diastolic dysfunction) in the setting of a normal left ventricular (LV) ejection fraction (ie, >50%). Concentric LV hypertrophy due to chronic hypertension is usually the primary contributor. HFpEF is the result of progressive cardiac remodeling that is induced by both systemic and local factors affecting cardiac myocytes and the surrounding interstitium. Chronic hypertension results in elevated systemic vascular resistance, which exerts a hydraulic stress on the left ventricle (LV) by increasing afterload. This stress on the LV initiates concentric hypertrophy of cardiac sarcomeres, which is perpetuated by systemic inflammation commonly seen in individuals who are sedentary and/or obese (eg, cytokines released from adipocytes). Systemic inflammation predisposes patients to microvascular ischemia, which leads to further sarcomeric hypertrophy and collagen deposition in the interstitial space. The result of these changes is stiffening of the LV, impaired diastolic filling (decreased compliance), and heart failure (reduced cardiac output).

Atrial fibrillation is a common precipitant of an acute exacerbation of HFpEF. Due to impaired diastolic filling at baseline, patients with HFpEF are highly sensitive to the loss of atrial kick that occurs with atrial fibrillation.

Clinical findings for heart failure		
	Sensitivity	**Specificity**
Dyspnea	High	Low
Serum BNP >100 pg/mL	High	Moderate
Lower extremity edema	Moderate	Moderate
Jugular venous distension	Moderate	Moderate
Pulmonary crackles	Moderate	Moderate
Orthopnea	Moderate	High
Audible S3	Low	High

Elevated serum brain natriuretic peptide (BNP) >100 pg/mL is highly sensitive for heart failure in patients without obesity. Therefore, a low serum BNP is highly useful in ruling out heart failure in patients with shortness of breath but without obesity (because BNP undergoes increased clearance by fat cells).

Hepatojugular reflux is useful for differentiating between cardiac disease– and liver disease–related causes of ascites, splenomegaly, and lower extremity edema. Positive hepatojugular reflux (ie, sustained >3-cm rise in jugular venous pressure elicited by compression of the upper abdomen) is highly specific for right ventricular failure. Hepatojugular reflux is not expected with liver cirrhosis.



BNP = brain natriuretic peptide; **JVD** = jugular venous distension; **LE** = lower extremity; **NIPPV** = noninvasive positive pressure ventilation.

Agent	Mortality benefit
Angiotensin receptor-neprilysin inhibitor (eg, sacubitril-valsartan) = Entresto OR **ACE inhibitor** (eg, lisinopril) OR **Angiotensin II receptor blocker** (eg, losartan)	Yes
Beta blocker (eg, metoprolol, carvedilol)	Yes
Mineralocorticoid receptor antagonist (eg, spironolactone, eplerenone)	Yes
Sodium-glucose cotransporter-2 inhibitor (eg, dapagliflozin, empagliflozin)	Yes
Diuretic (eg, furosemide, metolazone) (Lasix)	No*
Digoxin	No**

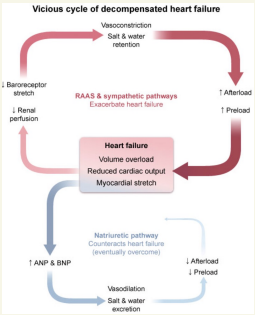
*Improves symptoms & reduces hospitalization.

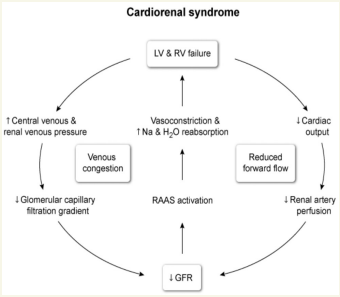
**Reduces hospitalization.

Typically, patients with HFrEF initially are given an angiotensin system inhibitor, a beta blocker, and a loop diuretic (eg, furosemide). A mineralocorticoid receptor antagonist is added for patients with LV ejection fraction ≤35% and persistent heart failure symptoms. Certain beta blockers (eg, metoprolol succinate) reduce long-term mortality in patients with chronic HFrEF. However, they can acutely worsen heart failure symptoms and should not be initiated during an episode of ADHF. Only after adequate diuresis should beta blockers be initiated.

Heart failure with preserved ejection fraction	
Etiology	• LV diastolic dysfunction due to impaired relaxation
Risk factors	• Chronic hypertension (concentric LV hypertrophy) • Obesity & sedentary lifestyle (myocardial interstitial fibrosis) • CAD & related risk factors (eg, diabetes mellitus)
Management	• Specific therapies to reduce hospitalization & possibly mortality: ◦ MRAs (eg, spironolactone) ◦ SGLT2 inhibitors (eg, dapagliflozin) • Loop diuretics as needed to treat volume overload • Additional antihypertensives PRN to reduce afterload • Treatment of exacerbating conditions (eg, CAD, OSA, A-fib) • Exercise training/cardiac rehabilitation

Chronic hyponatremia is common in patients with HFrEF; it parallels disease severity and is an independent predictor of mortality. Patients with HFrEF and serum sodium <130 mEq/L have an estimated 1-year survival as low as 15%. It likely results primarily from ongoing and profound nonosmotic stimulation for antidiuretic hormone secretion in the setting of reduced renal perfusion. Initial treatment is fluid restriction, but when hyponatremia becomes severe and symptomatic, specific antagonists of the vasopressin V2 receptor (eg, tolvaptan) can be used to oppose the effects of ADH and raise serum sodium concentration. These drugs can reduce symptoms but do not improve mortality.





Cardiorenal syndrome involves a reduction in glomerular filtration rate (GFR) that results from elevated renal venous pressure and reduced cardiac output in the setting of an acute exacerbation of heart failure. Intravenous diuretics reduce renal venous pressure and improve cardiac output to help restore the glomerular capillary filtration gradient and increase GFR.

High-Output Heart Failure

Pathophysiology	• ↓ SVR leads to ↑ cardiac output & ↑ venous return	
Causes	**Increased quantity of peripheral vessels**	Morbid obesity Paget disease
	Bypass of systemic arteriolar resistance	Acquired AV fistula (eg, trauma, HD) Congenital AV malformation
	Vasodilation due to unmet metabolic demand in tissues	Hyperthyroidism Severe anemia Thiamine deficiency (wet beriberi)
	AV = arteriovenous; **HD** = hemodialysis.	
Clinical presentation	• Hyperdynamic circulation (↑ PP, warm extremities) • Peripheral & pulmonary edema • Laterally displaced PMI, systolic flow murmur	
Echocardiographic findings	• Dilated LV, RV & inferior vena cava • Elevated resting cardiac index	

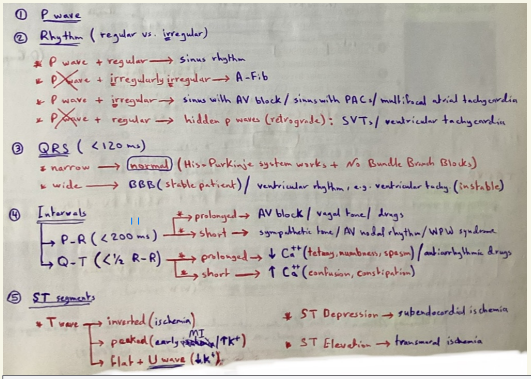
The reduced SVR and increased CO also lead to increased venous return to the heart (increased cardiac preload). Despite high output, the left ventricle is unable to keep up with the increased venous return and venous hydrostatic pressure increases, causing peripheral swelling and pulmonary edema. Eccentric left ventricular hypertrophy may develop (eg, laterally displaced point of maximal impulse), and the high blood flow can create a systolic flow murmur.

Cor Pulmonale

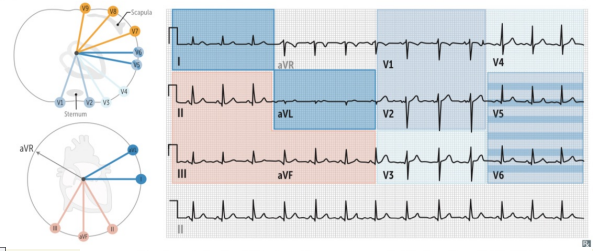
Pathophysiology	• Right-sided heart failure due to primary pulmonary disorder • Absence of left-sided heart disease
Commonetiologies	◦ Parenchymal disease/chronic hypoxia ◦ COPD (most common) ◦ Cystic fibrosis ◦ Interstitial lung disease ◦ Obstructive sleep apnea • Pulmonary vascular disease: pulmonary embolism
Symptoms	• Dyspnea & fatigue on exertion • Exertional angina (due to ↑ cardiac demand) • Exertional syncope (due to ↓ cardiac output)
Examination	• Jugular venous distension • Peripheral edema • Palpable RV heave, loud P2, tricuspid regurgitation murmur • Hepatomegaly with pulsatile liver
Diagnosticevaluation	◦ Electrocardiography ◦ Incomplete/complete right bundle branch block ◦ Right axis deviation, RV hypertrophy, RA enlargement ◦ Echocardiography ◦ Pulmonary hypertension, RV dilation/dysfunction, tricuspid regurgitation ◦ Catheterization (gold standard) ◦ Elevated filling pressures, decreased cardiac output, pulmonary hypertension

Right heart catheterization will show pulmonary systolic pressure >25 mm Hg.

ECG



INFARCT LOCATION	LEADS WITH ST-SEGMENT ELEVATIONS OR Q WAVES
Anteroseptal (LAD)	V_1–V_2
Anteroapical (distal LAD)	V_3–V_4
Anterolateral (LAD or LCX)	V_5–V_6
Lateral (LCX)	I, aVL
Inferior (RCA)	II, III, aVF
Posterior (PDA)	V_7–V_9. ST depression in V_1–V_3 with tall R waves



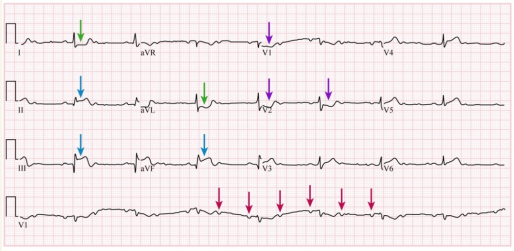
Localization of ST-segment elevation myocardial infarction

Involved myocardium	ST-segment elevation leads	Occluded vessel
Septal	V_1, V_2	LAD
Anterior	V_3, V_4	LAD
Lateral*	V_5, V_6, I, aVL; V_7 through V_9 (posterior leads)	LAD or LCx
Posterior	V_1 through V_3 (reciprocal ST-segment depression); V_7 through V_9 (ST-segment elevation)	RCA or LCx
Inferior	II, III, aVF	RCA or LCx
Right ventricle**	II, III, aVF, V_4R through V_6R	RCA

*Most lateral/posterolateral STEMIs are electrically silent due to poor coverage, usually corresponding to LCx territory.

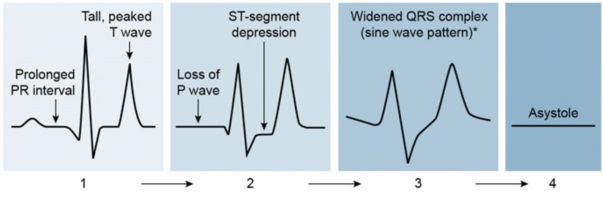
**Involved in ~50% of inferior STEMIs; confirmed by ST-segment elevations in leads V_4R through V_6R placed on right precordial area.

Posteroinferior ST-elevation myocardial infarction (STEMI)



Pathophysiology	Key features
• Most commonly due to RCA occlusion • Less commonly due to LCx occlusion	• ST elevation in II, III, & aVF (inferior wall STEMI) • ST depression in V1 & V2 (posterior wall STEMI) • Reciprocal ST depression • 2:1 AV block (every other P wave not conducted)

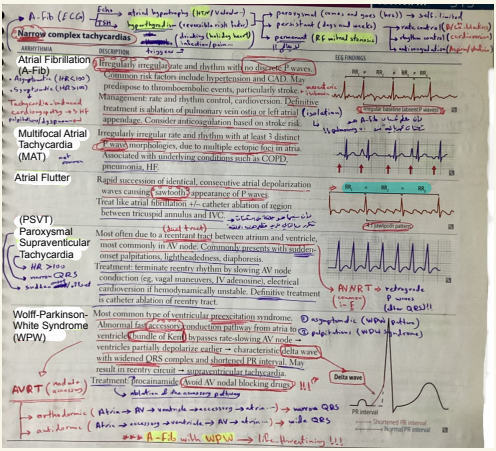
Hyperkalemia & progression of ECG changes

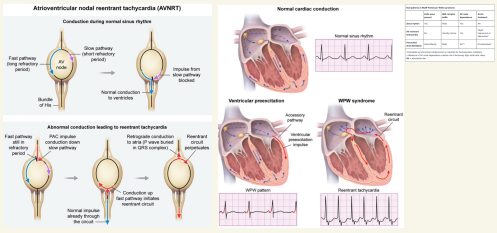


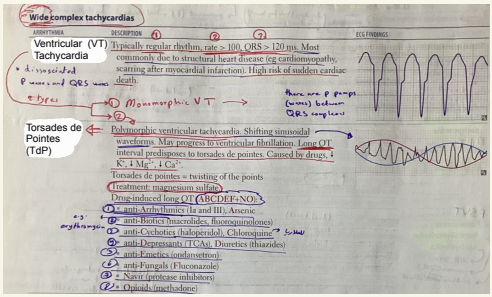
*Atrioventricular node & bundle-branch blocks can also develop.

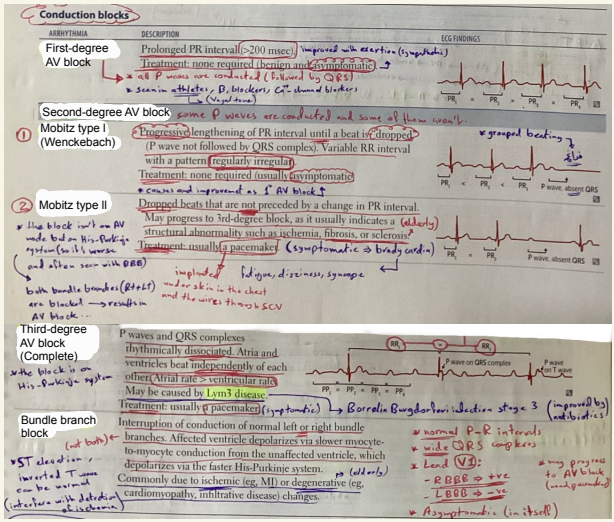
Hyperkalemic emergency usually arises when serum potassium is >6.5 mEq/L; it is marked by altered repolarization of skeletal and cardiac muscle, which leads to lethargy, muscle weakness, cardiac arrhythmias, and/or progressive changes on ECG (eg, peaked T waves → loss of P waves → widened QRS → sine wave pattern → asystole). Patients with hyperkalemia-induced ECG changes require urgent treatment with calcium gluconate to stabilize the cardiac membranes and insulin plus glucose to drive potassium into cells. This temporarily counters the cardiac abnormalities, which provides time for removal of potassium from the body via stool (eg, patiromer), urine (eg, furosemide), and/or blood (eg, hemodialysis).

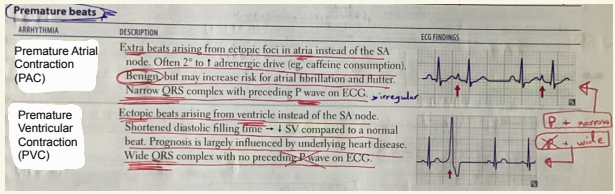
Arrhythmias

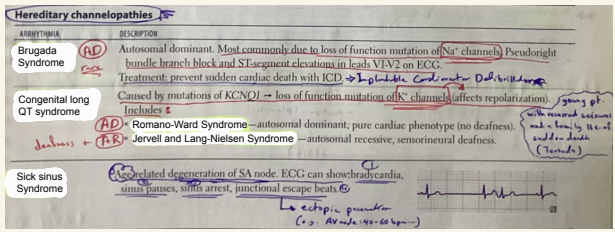








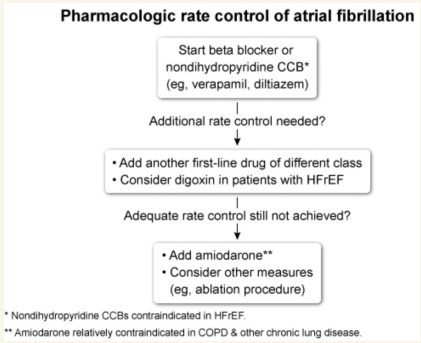




Tobacco and alcohol are reversible risk factors for premature atrial contractions. Beta blockers are often helpful in symptomatic patients.

Patients with TdP who are hemodynamically unstable should undergo immediate electrical cardioversion. Those who are hemodynamically stable should receive intravenous magnesium as first-line therapy; it is effective even in patients with normal serum magnesium concentrations. Magnesium is thought to serve as a calcium channel blocker (eg, during repolarization), which delays further depolarizations thereby preventing TdP. In addition to magnesium administration, precipitants of TdP should also be investigated and addressed (eg, stop fluconazole and moxifloxacin in the patient).

Comorbidities that encourage atrial fibrillation	
Precipitants of atrial dilation &/or conduction remodeling	• Advanced age • Systemic hypertension • Mitral valve dysfunction • Left ventricular failure • Coronary artery disease & related factors (eg, DM, smoking) • Obesity & obstructive sleep apnea • Chronic hypoxic lung disease (eg, COPD)
Triggers of increased automaticity	• Hyperthyroidism • Excessive alcohol use • Increased sympathetic tone ◦ Acute illness (eg, sepsis, PE, MI) ◦ Cardiac surgery • Sympathomimetic drugs (eg, cocaine)



A beta blocker (eg, metoprolol) or nondihydropyridine calcium channel blocker (eg, verapamil, diltiazem) is given initially in the acute setting to achieve a goal rate <110/min. For long-term rate control (eg, typical goal rate <80/min at rest, or lower if coronary artery disease is present) a second agent can be added if needed (eg, metoprolol added to diltiazem). Digoxin is not typically used in the acute setting or as monotherapy, but it is particularly useful as a second agent in patients with left ventricular systolic dysfunction (due to a positive inotropic effect). Amiodarone has rate-control properties (due to inhibition of calcium channels in the AV node) and is sometimes used as a third-line agent for rate control. AV nodal blocking agents such as adenosine, beta blockers, calcium channel blockers (especially verapamil), and digoxin should not be used for AF in patients with WPW as they may promote conduction across the accessory pathway and lead to degeneration of AF into VF.

Chronic hypertension is the most common comorbidity associated with atrial fibrillation and is likely one of the strongest contributors to the predisposing atrial remodeling. Aging is also a strong contributor. Chronic obstructive pulmonary disease (COPD) can also contribute to atrial fibrillation in several ways. Severe COPD associated with significant hypoxemia can cause right atrial dilation due to hypoxic pulmonary vasoconstriction and resulting pulmonary hypertension. In addition, COPD exacerbation can increase sympathetic tone and act as a trigger for atrial fibrillation. Beta-2 agonists (eg, albuterol, salmeterol) used for the treatment of COPD may also be occasional triggers of atrial fibrillation. In some cases, AF may be the only apparent clinical manifestation of hyperthyroidism.

Despite the common belief that caffeine consumption is considered a trigger for atrial fibrillation and other arrhythmias (due to increased sympathetic tone), studies have not shown any significant association.

CHA_2DS_2-VASc score for thromboembolic riskin nonvalvular atrial fibrillation		
Risk criteria		**Points**
C	Congestive heart failure	1
H	Hypertension	1
A_2	Age ≥75*	2
D	Diabetes mellitus	1
S_2	Stroke or TIA	2
V	Vascular disease (eg, PAD, prior MI)	1
A	Age 65-74*	1
Sc	Sex category female	1
	Maximum score	9

Total score		Generalized stroke risk	Antithrombotic therapy
Male	**Female****		
0	0	Low	None
1	2	Moderate	None or oral anticoagulant
≥2	≥3	High	Oral anticoagulant

*Patients are assigned to 1 of the 2 age categories.

**Different cutoffs are used for males & females. Female sex is considered a risk modifier that adds to the CHA_2DS_2-VASc score only if other nonsex risk factors are present (female patients cannot have a total score of 1).

CHA2DS2-VASc SCORE

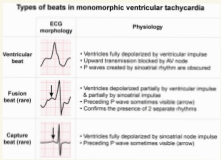
SVT refers to any tachycardia originating above the His-bundle and includes sinus tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, atrioventricular (AV) nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT), and junctional tachycardia. Patients usually present with palpitations, although some may have dizziness, lightheadedness, shortness of breath, diaphoresis, chest pain, presyncope, or syncope. Adenosine or vagal maneuvers (eg, carotid sinus massage, cold-water immersion or diving reflex, Valsalva maneuver, eyeball pressure) temporarily slow conduction via the AV node and can aid in diagnosis by unmasking "hidden" P waves in patients with atrial flutter or atrial tachycardia. They can also cause a transient AV nodal block and terminate AV node-dependent arrhythmias, including AVNRT and orthodromic AVRT.

In VT, there is usually atrioventricular dissociation, with a separate rhythm in the atria (usually a normal rhythm originating in the sinus node) that does not communicate with the abnormal rhythm originating in the ventricles (a wide-complex tachycardia). In rare circumstances, the impulse from the atrial rhythm passes through the atrioventricular node to create characteristic beats:

- If the ventricles are depolarized partially by this atrial rhythm and partially by the ventricular rhythm, a fusion beat (with a QRS complex of intermediate width) is created and confirms the presence of 2 separate rhythms.
- If the ventricles are depolarized fully by the atrial rhythm, a normal appearing beat (with a narrow complex QRS) called a capture beat is created.

Seeing fusion and capture beats within a monomorphic wide-complex tachycardia is highly suggestive of monomorphic VT.

Although NSVT (non-sustained VT) can occur in the setting of a structurally normal heart, more commonly there is an underlying predisposing condition such as cardiomyopathy or ischemic heart disease with prior myocardial infarction. Frequently, such patients at underlying risk develop NSVT in the setting of a reversible precipitating factor that increases cardiac automaticity and encourages the development of both NSVT and more serious ventricular arrhythmias (ie, sustained ventricular tachycardia, ventricular fibrillation). Therefore, rapidly identifying and treating reversible precipitants of NSVT is critical to curtail the risk that a more serious arrhythmia will develop. In patients with no known predisposing condition for ventricular arrhythmia, NSVT should prompt an investigation (eg, echocardiography) for underlying predisposing disease.

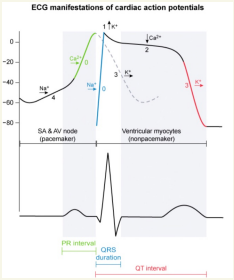


Sick Sinus Syndrome: age-related degeneration of the cardiac conduction system with fibrosis of the sinus node is the most common cause. Ischemia and infiltrative cardiac disease (eg, sarcoidosis, amyloidosis) are other potential causes. Fibrosis may also affect the atria, leading to paroxysmal atrial arrhythmias such as atrial fibrillation (palpitations) or bradycardia-tachycardia syndrome (bradycardia alternating with supraventricular tachycardia). Once a pacemaker is placed, rate-control medications (eg, beta blockers) can be administered in patients with persistent paroxysmal tachyarrhythmias.

Monomorphic nonsustained ventricular tachycardia	
Identification	• ≥3 consecutive ventricular beats (wide QRS complex) • Rate >100/min & duration <30 sec
Predisposing conditions	• Heart failure with reduced ejection fraction • Ischemic heart disease • Other cardiomyopathy (eg, HCM)
Precipitating factors	• Serum electrolyte abnormalities (eg, ↓ K, ↓ Mg) • Hypoxemia or acute myocardial ischemia • Elevated sympathetic tone (eg, sepsis)
Management	• Address precipitating factors (eg, replace electrolytes) • Consider adding (or increasing dose of) beta blockade

Anti-arrhythmics	PR interval (prolonged via Ca^{2+} channel inhibition orsympathetic blockade)	QRS duration (prolonged via Na^{+} channel inhibition)	QT interval (prolonged via K^{+} channel inhibition)
Class IA (eg, Quinidine, procainamide, disopyramide.	–	↑	↑
Class IB Lidocaine, mexiletine.	–	–	–
Class IC Flecainide, propafenone.	–	↑	
Class II (eg, metoprolol)	↑	–	–
Amiodarone	↑	↑	↑
Sotalol	↑	–	↑
Ibutilide, Dofetilide	–	–	↑
Class IV (eg, verapamil) diltiazim	↑	–	–

(class III)



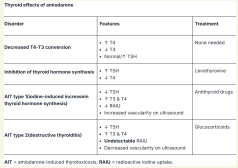
Symptoms of digoxin toxicity	
Cardiac	• **Life-threatening arrhythmias**
Gastrointestinal	• Anorexia • Nausea & vomiting • Abdominal pain
Neurologic	• Fatigue • Confusion • Weakness • **Color vision alterations**

Because digoxin is renally cleared, elderly patients who are susceptible to dehydration and acute kidney injury are particularly prone to toxicity.
Digoxin toxicity can cause a wide range of cardiac arrhythmias, typically resulting from increased automaticity of myocardial conduction and/or increased vagal tone. Atrial tachycardia with atrioventricular block involves both of these mechanisms and is the most specific arrhythmia for digoxin toxicity. The AV block can be first, second, or third degree. Mobitz type II second-degree AV block is almost never seen with digoxin toxicity, so when second degree AV block is present it is typically Mobitz type I. Chronic digoxin toxicity presents with less pronounced gastrointestinal symptoms but more significant neurologic and visual symptoms (eg, changes in color vision, scotomas, blindness). Amiodarone (or verapamil, quinidine, and propafenone) increases the serum levels of digoxin (by interfering with digoxin metabolism) and can lead to toxicity in a patient who has previously been on a stable digoxin regimen. It is recommended that the digoxin dose be decreased by 25%-50% when initiating amiodarone therapy, with close monitoring of digoxin levels once weekly for the next several weeks.

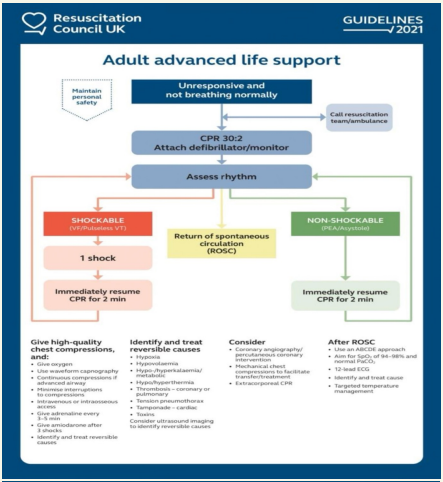
Under normal circumstances, flecainide does not cause any significant prolongation of the QRS duration or QT interval; however, in patients with rapid heart rates, the drug has less time to dissociate from sodium channels, leading to a higher number of blocked channels, which results in a progressive decrease in impulse conduction and widening of the QRS complex. This phenomenon is termed use dependence and is seen most frequently with class IC antiarrhythmic agents (less commonly with class IA drugs and rarely with class IB drugs). It is the primary mechanism behind their efficacy against supraventricular arrhythmias.

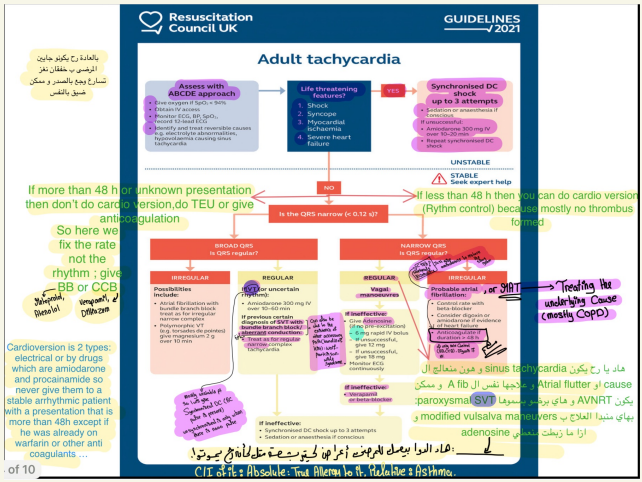
Major side effects of amiodarone	
Cardiac	• Sinus bradycardia, heart block • Risk of proarrhythmias: QT prolongation & risk of torsade de pointes
Pulmonary	• Chronic interstitial pneumonitis (cough, fever, dyspnea, pulmonary infiltrates) most common
Endocrine	• Hypothyroidism • Hyperthyroidism
Gastrointestinal/hepatic	• Elevated transaminases, hepatitis
Ocular	• Corneal microdeposits • Optic neuropathy
Dermatologic	• Blue-gray skin discoloration
Neurologic	• Peripheral neuropathy

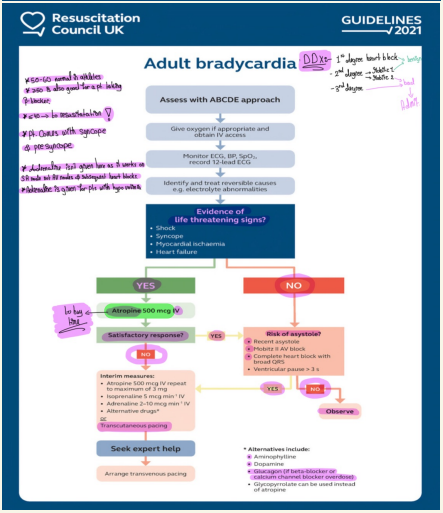
Pulmonary toxicity is a serious adverse effect of long-term amiodarone use and can occur months to several years after the initiation of therapy. Interstitial pneumonitis due to amiodarone presents with progressive dyspnea, nonproductive cough, and new reticular or ground-glass opacities on chest radiograph.



BLS & ACLS





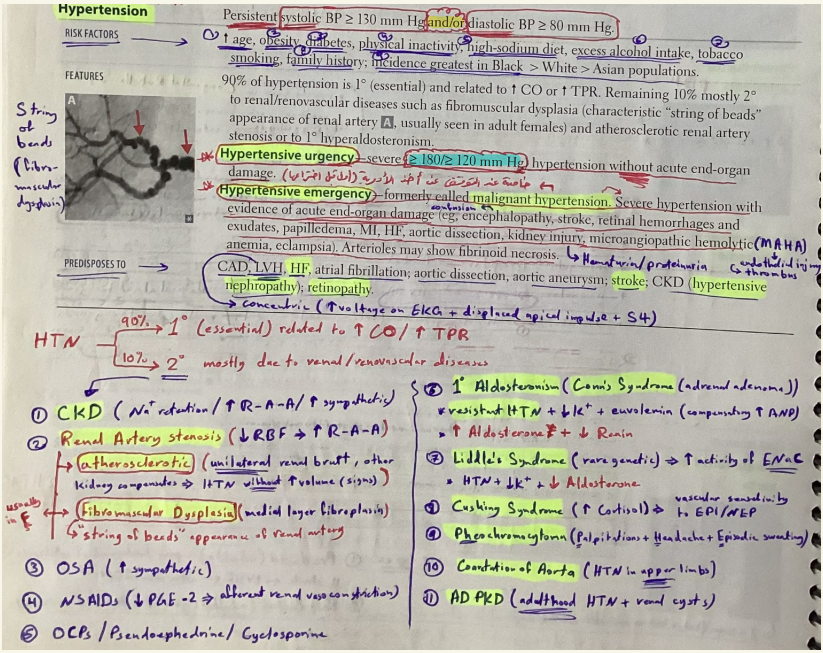


Reversible causes of asystole/pulseless electrical activity	
5 Hs	5 Ts
Hypovolemia	Tension pneumothorax
Hypoxia	Tamponade, cardiac
Hydrogen ions (acidosis)	Toxins (narcotics, benzodiazepines)
Hypokalemia or hyperkalemia	Thrombosis (pulmonary or coronary)
Hypothermia	Trauma

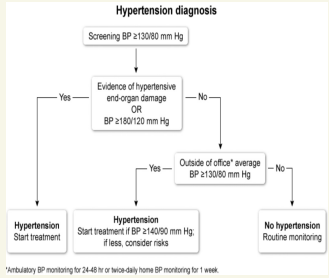
With cardioversion, energy delivery is synchronized to the QRS complex to minimize the likelihood of the shock occurring during repolarization, which can precipitate ventricular fibrillation. By contrast, immediate defibrillation (as opposed to cardioversion) provides a high-energy shock at a random point in the cardiac cycle (unsynchronized shock) and is indicated in patients with ventricular fibrillation or pulseless ventricular tachycardia.

Pulseless electrical activity (PEA) refers to a cardiac rhythm that is usually perfusing (eg, sinus tachycardia, sinus bradycardia) but cannot generate sufficient cardiac output to create a measurable blood pressure or palpable pulse. An underlying mechanical issue (eg, severe hypovolemia, massive pulmonary embolism, markedly impaired left ventricular contractility) or other potentially reversible causes is typically responsible. PEA often degenerates into asystole, which involves the complete absence of cardiac electrical activity. Acute MI (especially a massive MI) may occasionally produce PEA, but ventricular fibrillation is far more common.

Hypertension (HTN)



Laboratory evaluation of hypertension	
Renal function tests	• Serum electrolytes (Na, K, Ca) • Serum creatinine • Urinalysis • Urine albumin/creatinine ratio (optional)
Endocrine tests	• Fasting glucose or hemoglobin A1c • Lipid profile • TSH
Cardiac tests	• ECG • Echocardiography (optional)
Other tests	• Complete blood count • Uric acid (optional)



Office-based BP measurements are a poor predictor of high BP outside of the office because of the relatively common occurrence of white coat hypertension (eg, BP 5-10 mm Hg higher in the office than at home). Therefore, in the absence of end-organ damage, the diagnosis of hypertension must be confirmed by one of the following:

- Ambulatory BP readings as measured by an automatic device worn continuously by the patient for 24-48 hours. The device monitors BP at regular intervals (eg, 15-60 min).
- If continuous ambulatory BP monitoring is not available, an acceptable alternative is home BP monitoring done twice a day (morning and evening) for a week.
- If home BP monitoring is not possible, 3 office readings (preferably by an automated machine while the patient is alone) at least a week apart are needed.

In contrast, if end-organ damage (eg, left ventricular hypertrophy, retinopathy, nephropathy) is present or if the patient has a systolic BP ≥180 mm Hg or diastolic BP ≥120 mm Hg, then the diagnosis of hypertension can be established in the office without additional confirmation, and therapy should be started quickly.

In hypertensive emergencies, mean arterial pressure should be lowered by 10%-20% in the first hour and by another 5%-15% over the next 23 hours. An excessive drop in blood pressure can lead to cerebral ischemia, with altered mental status and/or generalized seizures.

Renal parenchymal disease	• Elevated creatinine level • Abnormal urinalysis (proteinuria, red blood cell casts)
Renovascular disease	• Recurrent flash pulmonary edema • Elevated creatinine level (particularly with ACE inhibitor use) • Abdominal bruit
Primary hyperaldosteronism	• Hypokalemia (spontaneous or thiazide induced) • Metabolic alkalosis
Obstructive sleep apnea	• Daytime somnolence • Increased neck circumference
Pheochromocytoma	• Paroxysmal hypertension & tachycardia • Headaches, palpitations, diaphoresis
Cushing syndrome	• Cushingoid body habitus & proximal muscle atrophy • Hyperglycemia
Thyroid disease	• Hyperthyroidism: anxiety, heat intolerance, weight loss, tachycardia • Hypothyroidism: fatigue, cold intolerance, weight gain, bradycardia
Primary hyperparathyroidism	• Mild hypercalcemia ± symptoms (eg, constipation) • Kidney stones
Coarctation of the aorta	• Upper extremity hypertension with brachial-femoral pulse delay (common) • Lateralizing hypertension (less common)

Unusual age of onset (eg, age <30 or >55) or resistant hypertension (persistent blood pressure (BP) elevation despite an appropriate regimen of ≥3 antihypertensive agents of different classes, 1 of which is a diuretic) should be evaluated for secondary causes.

In addition to hypertension, features suggesting intranasal cocaine use include epistaxis and tremor. A urine drug screen should be considered in a young patient with unexplained hypertension. A small number of patients with cocaine-associated chest pain can also have aortic dissection, so dministering a thrombolytic agent in that setting could be catastrophic and is absolutely contraindicated.

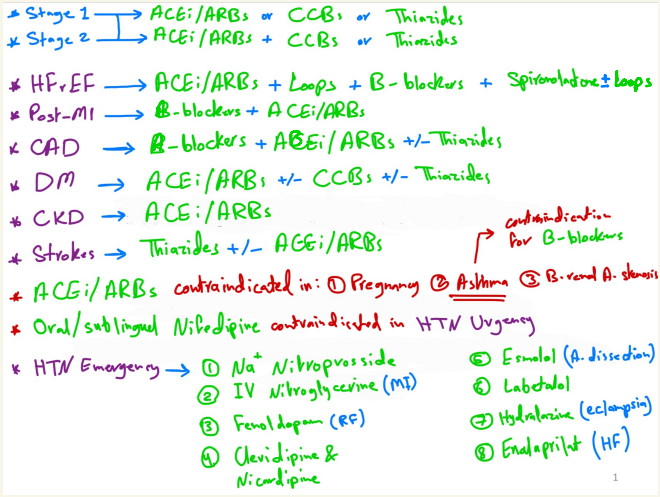
Clues to surreptitious cocaine use	
Behavioralfeatures	• Personality & mood changes • Changes in sleep patterns • Unexplained weight loss • Financial difficulties
Reportedsymptoms	• Chest pain • Epistaxis, rhinitis (intranasal use) • Headaches
Examinationsigns	• Hypertension, tachycardia • Dilated pupils • Psychomotor agitation
Emergentcomplications	• Seizures • Acute myocardial ischemia • Aortic dissection • Intracranial hemorrhage

Clinical clues to renovascular disease	
HTN-related symptoms	• Resistant HTN (uncontrolled despite 3-drug regimen) • Malignant HTN (with end-organ damage) • Onset of severe HTN (>180/120 mm Hg) after age 55 • Severe HTN with diffuse atherosclerosis • Recurrent flash pulmonary edema with severe HTN
Supportive evidence	**Physical examination** • Asymmetric renal size (>1.5 cm) • Abdominal bruit **Laboratory results** • Unexplained rise in serum creatinine (>30%) after starting ACE inhibitors or ARBs **Imaging results** • Unexplained atrophic kidney

STOP-Bang survey for obstructive sleep apnea	
1 point for each characteristic present	**S**noring Excessive daytime **t**iredness **O**bserved apneas or choking/gasping High blood **p**ressure **B**MI >35 kg/m^2 **A**ge >50 **N**eck size: men >17 in (43.2 cm), women >16 in (40.6 cm) Male **g**ender
Scoring: 0-2 points: low risk; 3-4 points: intermediate risk; ≥5 points: high risk.	

Fibromascular Dysplasia (FMD)	
Patients to screen	Women age <50 with 1 of the following: • Severe or resistant hypertension • Onset of hypertension before age 35 • Sudden increase in blood pressure from baseline • Increase in creatinine (≥0.5-1 mg/dL) after starting *angiotensin-converting enzyme inhibitor* or angiotensin receptor blocker & without significant effect on blood pressure • Systolic-diastolic epigastric bruit
Clinical presentation	• Resistant hypertension from renal artery involvement • Cerebrovascular FMD with symptoms of brain ischemia (eg, amaurosis fugax, Horner's syndrome, transient ischemic attack, stroke) • Nonspecific symptoms (eg, headache, pulsatile tinnitus, dizziness) from carotid or vertebral artery involvement • Can also involve iliac, subclavian & visceral arteries
Diagnosis & follow-up	• Noninvasive testing preferred (eg, computed tomography angiography, duplex ultrasound) • Catheter-based digital subtraction arteriography for patients with inconclusive noninvasive testing • Medically treated patients need follow-up blood pressure & creatinine every 3-4 months & renal ultrasound every 6-12 months

Polysomnography is used to diagnose obstructive sleep apnea. In OSA, upper airway obstruction (due to pharyngeal muscle relaxation during sleep) causes progressive hypoxia and hypercapnia until chemoreceptors in the carotid body and brainstem trigger arousal (by the production of catecholamines), which restores pharyngeal tone.



Cardiovascular risk factor management in type 2 diabetes mellitus	
General measures	• Healthy weight • Exercise • Smoking cessation
Blood pressure	• Medication + lifestyle changes to target of 125-130/<80 mm Hg • ACE inhibitor or ARB recommended if diabetic kidney disease is present
Cholesterol	• High-intensity statin:* established CVD or 10-year CVD risk ≥20% • Moderate-intensity statin:** all other patients with diabetes mellitus age ≥40
Glycemic control	• Lifestyle measures • SGLT2 inhibitor • GLP-1 agonist

*Atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily.

**Atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin XL 80 mg, or pitavastatin 2-4 mg daily.

Choice of antihypertensive drugfor comorbid conditions	
Coronaryatherosclerosis	• Angina pectoris: β-blocker, CCB • Post–myocardial infarction: ACE inhibitor or ARB, β-blocker
Heart failurewith reducedejection fraction	• ACE inhibitor or ARB, β-blocker, diuretic, aldosterone antagonist
Atrial fibrillationor flutter	• β-Blocker, nondihydropyridine CCB
Chronic kidneydisease	• ACE inhibitor or ARB
Gout	• Losartan, other ARB, CCB (avoid diuretics)
Osteoporosis	• Thiazide diuretic
Migraine	• β-Blocker, CCB

Lifestyle interventions for hypertension		
Modification	**Recommended plan**	**Approximate ↓ systolic BP (mm Hg)**
DASH diet	Diet high in fruits & vegetables & low in saturated & total fats	11
Weight loss	Reduction of BMI to <25 kg/m^2	6 per 10-kg loss
Aerobic exercise	30 minutes/day for 5+ days/week	7
Dietary sodium	<1.5-2.3 g/day (response varies)	5-8
Alcohol limitation	≤2 drinks/day in men, ≤1 drink/day in women	5

DASH = **D**ietary **A**pproaches to **S**top **H**ypertension.

Obesity is the single greatest contributing lifestyle risk factor for hypertension; weight loss and the Dietary Approaches to Stop Hypertension (DASH) diet are the most effective nonpharmacologic interventions for lowering blood pressure.

In general, an initial goal of <130-140/80-90 mm Hg is appropriate for a lower-risk individual with uncomplicated hypertension; lower targets may be recommended for those with certain comorbidities (eg, diabetes mellitus, heart failure, chronic kidney disease), and higher targets may be appropriate for frail elderly patients.

Thiazide diuretics can raise uric acid levels and increase the risk of gout attack. In contrast, the ARB losartan has a mild uricosuric effect, which decreases the risk of gout attack. In addition, ARBs provide the greatest reduction in LVH of all first-line antihypertensive agents.

Conventional beta blockers (eg, metoprolol, atenolol, propranolol) are associated with impaired glucose control and increased weight gain, likely via effects on skeletal muscle that lead to reduced insulin sensitivity. Therefore, these drugs are an unfavorable option for hypertension management in patients with, or at high risk for, type 2 diabetes mellitus. Normally, alpha-1 receptor stimulation causes vasoconstriction, which reduces glucose uptake into skeletal muscles (due to reduced skeletal muscle blood flow); beta-2 receptor stimulation opposes this effect. In the presence of beta blockade, alpha-1–mediated effects are unopposed, leading to further reduction in glucose uptake, higher levels of circulating glucose, and resultant increased insulin secretion from the pancreas. Insulin resistance is effectively increased (ie, insulin sensitivity is reduced). As a result, patients experience weight gain. A reduction in lipolysis in adipocytes (which is largely beta-1 receptor–mediated) likely also contributes to weight gain. In contrast, beta blockers with combined vasodilatory alpha-1 receptor–blocking properties (eg, carvedilol, labetalol) are not associated with reduced insulin sensitivity, which provides further evidence of the importance of the hemodynamic effects on skeletal muscles.

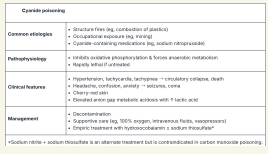
Peripheral edema is a common side effect of calcium channel blocker (CCB) therapy, with a reported incidence of approximately 25% after 6 months of therapy. The edema is likely related to preferential dilation of precapillary vessels (arteriolar dilation), which leads to increased capillary hydrostatic pressure and fluid extravasation into the interstitium.
Renin-angiotensin system antagonists (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) cause post-capillary venodilation and can normalize the increased capillary hydrostatic pressure. In clinical studies, the combination of CCB and ACE inhibitors was associated with a significantly lower risk of CCB-associated peripheral edema compared with CCB monotherapy.

ACE inhibitors can cause angioedema in approximately 0.1%-0.7% of patients. Patients typically present with nonpitting swelling of the subcutaneous or submucosal tissue, most commonly the lips, tongue, face, and upper airway. ACE inhibitors do not cause peripheral or dependent edema. Some patients may develop angioedema shortly after starting the medication, but episodes may occur at any time. Angioedema can progress rapidly and cause airway obstruction; therefore, patients should be sent directly to the emergency department and instructed to discontinue the medication.
Angiotensin-converting enzyme (ACE) inhibitors also increase the risk of angioedema by inhibiting the breakdown of bradykinin via ACE. In contrast, angiotensin II receptor blockers do not increase bradykinin levels and, when used without neprilysin inhibition, are not associated with increased risk of angioedema.

Side effects associated with beta blocker use include worsening of congestive heart failure, bradyarrhythmias, increased airway resistance in patients with asthma, generalized fatigue, and sexual dysfunction.
Beta blocker overdose presents with bradycardia, hypotension, wheezing, hypoglycemia, delirium, seizures, and cardiogenic shock. Intravenous fluids and atropine are the first-line treatment options. Intravenous glucagon should be administered in patients with profound or refractory hypotension. Glucagon increases the intracellular levels of cyclic AMP and has been effective in treating both beta blocker and calcium channel blocker toxicity.

The most common side effects of hydrochlorothiazide are electrolyte imbalances (eg, hyponatremia, hypokalemia, hypercalcemia), renal failure, hyperuricemia (which may precipitate acute gout), and elevated glucose and cholesterol levels.

Acute cyanide toxicity can occur in patients treated with nitroprusside, particularly if renal insufficiency is present. Clinical findings consistent with cyanide toxicity include metabolic acidosis, neurologic changes (eg, agitation, seizures), and cardiorespiratory stimulation (in early toxicity).



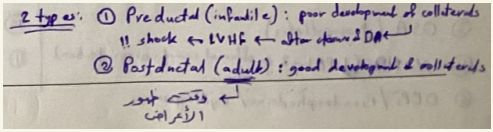
Cyanide poisoning	
Common etiologies	• Structure fires (eg, combustion of plastics) • Occupational exposure (eg, mining) • Cyanide-containing medications (eg, sodium nitroprusside)
Pathophysiology	• Inhibits oxidative phosphorylation & forces anaerobic metabolism • Rapidly lethal if untreated
Clinical features	• Hypertension, tachycardia, tachypnea → circulatory collapse, death • Headache, confusion, anxiety → seizures, coma • Cherry-red skin • Elevated anion gap metabolic acidosis with ↑ lactic acid
Management	• Decontamination • Supportive care (eg, 100% oxygen, intravenous fluids, vasopressors) • Empiric treatment with hydroxocobalamin ± sodium thiosulfate*

*Sodium nitrite + sodium thiosulfate is an alternate treatment but is contraindicated in carbon monoxide poisoning.

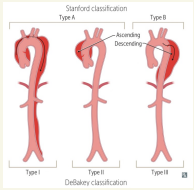
Coarctation of Aorta

Etiology	• Congenital • Acquired (rare) (eg, Takayasu arteritis)
Clinical features	• Upper body ◦ Well developed ◦ Hypertension (headaches, epistaxis) • Lower extremities ◦ Underdeveloped ◦ Claudication • Brachial-femoral pulse delay • Upper & lower extremity blood pressure differential • Left interscapular systolic or continuous murmur
Diagnostic studies	• ECG: Left ventricular hypertrophy • Chest x-ray ◦ Inferior notching of the 3rd to 8th ribs ◦ "3" sign due to aortic indentation • Echocardiography: diagnostic confirmation
Treatment	• Balloon angioplasty ± stent placement • Surgery

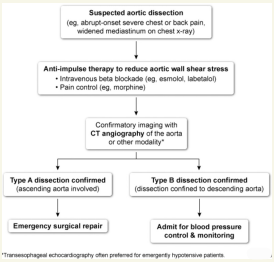
A continuous murmur can be heard at the left interscapular area due to turbulent flow across the coarctation or through large collateral vessels.



Aortic Dissection



Acute aortic dissection	
Risk factors	• Chronic hypertension (strongest overall risk factor) • Underlying aortopathy (eg, Marfan syndrome) • Cocaine use
Clinical presentation	• Severe, tearing chest or back pain, maximal at onset • ± Variation in SBP between arms >20 mm Hg • Hypertension usually present*
Diagnosis	• ECG: normal or nonspecific ST-segment & T-wave changes • Chest x-ray: mediastinal widening • CT angiography or TEE for definitive diagnosis
Treatment	• Pain control (eg, morphine) • Intravenous beta blockers (eg, esmolol) • ± Sodium nitroprusside (if SBP >120 mm Hg despite beta blockers) • Emergency surgical repair for ascending dissection
*Hypotension on presentation suggests aortic rupture or other complication (eg, cardiac tamponade, acute aortic regurgitation).	



Complications due to extension of acute aortic dissection	
Complication (involved structure)	• Stroke (carotid artery) • Horner syndrome (carotid sympathetic plexus) • Acute aortic regurgitation (aortic root/valve) • Myocardial ischemia/infarction (coronary artery ostia) • Pericardial effusion/tamponade (pericardium) • Hemothorax (pleural cavity) • Renal infarction (renal arteries) • Intestinal ischemia (mesenteric arteries) • Lower extremity paralysis (spinal arteries)

Aortic dissection involving the ascending aorta (type A) is a surgical emergency, with mortality rates of 1-2% per hour following symptom onset; therefore, rapid diagnosis and treatment are critical. An early decrescendo diastolic murmur at the left upper sternal border combined with a nondisplaced point of maximal impulse (ie, nondilated left ventricle) is consistent with acute aortic regurgitation (AR), which can result from extension into the aortic annulus and lead to cardiogenic shock.

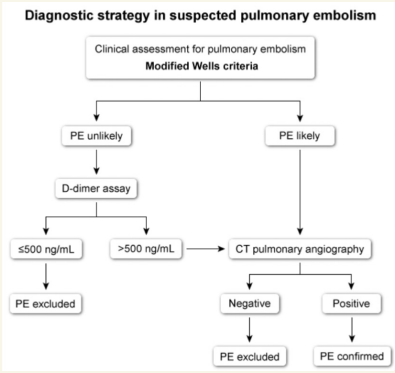
Aneurysm

Screening: abdominal aortic aneurysm	
Patientpopulation	• **Men** • Age **65-75**
Risk factorindication	• Any **smoking** history
Test	• One-time abdominal duplex ultrasonography

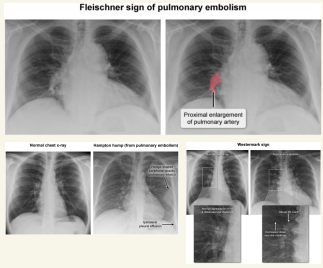
Abdominal aortic aneurysm (AAA) can be detected in approximately 10% of patients with PAD. The risk of AAA rupture is increased in patients with large aneurysm diameter (>5.5 cm), aortic expansion rate >0.5 cm/year, male sex, and current ongoing smoking.

Patients with a popliteal artery aneurysm should undergo screening (typically with ultrasonography) for aneurysms in the contralateral leg and abdominal aorta because there is a high incidence of coexistent aneurysms in these locations.

Pulmonary Embolism (PE)



Modified Wells criteria for pretest probability of pulmonary embolism	
+3 points	Clinical signs of DVT Alternate diagnosis less likely than PE
+1.5 points	Previous PE or DVT Heart rate >100 Recent surgery or immobilization
+1 point	Hemoptysis Cancer
Total score	≤4 = PE unlikely >4 = PE likely



Acute pulmonary embolism (PE) typically presents with dyspnea, pleuritic chest pain, tachypnea, and tachycardia. Chest x-ray is commonly normal or shows nonspecific findings, but it can help rule out other competing diagnoses (eg, pneumonia, pneumothorax) and occasionally shows findings highly suggestive of PE:

- Westermark sign: peripheral hyperlucency of the pulmonary arterial tree resulting from blood flow being cut off by the PE.
- Hampton hump: peripheral, wedge-shaped lung opacity representing pulmonary infarction. An ipsilateral pleural effusion is also commonly present with this sign (pulmonary infarction is the typical cause of PE-associated pleural effusion).
- Fleischner sign: Enlargement of the pulmonary artery resulting from increased pressure proximal to the PE.

Regardless of chest x-ray findings, chest CT angiography is the gold standard in confirming and ruling out acute PE.

D-dimer testing is useful in excluding PE in patients with low pretest probability, but it has no utility in the setting of high pretest probability due to an unacceptable rate of false-negative results in such patients.

Ventilation-perfusion scan is a less accurate alternative for patients with significant renal impairment, morbid obesity, or contrast allergy.

Syncope

Clues to etiology of syncope		
Reflex syncope	**Vasovagal**	• Trigger (eg, emotional stress, prolonged standing) • Prodrome (eg, nausea, sweating, warmth)
	Situational	• Occurs with micturition, defecation, swallowing, or coughing
	Carotid hypersensitivity	• Tactile stimulation of carotid sinus while standing • Advanced age, carotid atherosclerosis
Orthostatic syncope	**Medications**	• Vasodilators (eg, alpha-1 blockers, antihypertensives) • Inotropic/chronotropic blockade (eg, beta blockers)
	Hypovolemia	• History consistent with volume loss
	Autonomic dysfunction	• Advanced age • Predisposing disease (eg, DM, Parkinson)
Cardiac syncope	**LV outflow obstruction**	• Syncope with exertion • Systolic ejection murmur
	Ventricular tachycardia	• No warning symptoms • Cardiomyopathy or ischemic HD (monomorphic) • QT-interval prolongation (polymorphic)
	Conduction impairment*	• Preceding fatigue or light-headedness • ECG abnormalities (eg, sinus pauses, dropped QRS complexes)
*Sick sinus syndrome or advanced atrioventricular block.		

Cardiac syncope	
Etiology	**Clues to diagnosis**
Aortic stenosis or HCM	• Exertional syncope • Systolic murmur on examination
Ventricular tachycardia	• No preceding symptoms • Cardiomyopathy or previous MI
Sick sinus syndrome	• Preceding fatigue or dizziness • Sinus pauses on ECG
Advanced AV block	• Bifascicular block or ↑ PR interval on ECG • Dropped QRS complexes on ECG
Torsades de pointes	• No preceding symptoms • Medications that prolong QT interval • Hypokalemia or hypomagnesemia

	Seizure	**Syncope**
Preceding symptoms	Aura (eg, smell, visual disturbance) or none	Prodrome (eg, nausea, diaphoresis) or none
Patient position	Any position	Often standing (vasovagal), but can occur in any position (cardiac)
Tongue biting	Common, often lateral	Rare, frontal if present
Convulsive movements	Common, typically start before or simultaneous with LOC	Less common but can occur after LOC*
Urinary incontinence	Common	Less common but can occur after LOC*
Post-episode recovery	Variable (minutes to hours or days), residual confusion is common	Rapid (1-2 min), no residual deficit
*Due to transient cerebral hypoperfusion & hypoxia.		

Orthostatic syncope	
Etiologies	• Medications (eg, vasodilators, inotropic/chronotropic blockade, diuretics) • Autonomic dysfunction (eg, advanced age, neurodegenerative disease) • Hypovolemia (eg, fluid restriction, GI losses, fever)
Clinical features	• Typically occurs with standing from seated/supine position • Premonitory symptoms (eg, light-headedness, visual blurring) common
Diagnosis	• **Within 2-5 min of standing from a supine position**: ≥20 mm Hg ↓ in systolic blood pressure OR ≥10 mm Hg ↓ in diastolic blood pressure
Treatment	• Modify postural transitions (eg, rise slowly when standing) • Discontinue or ↓ dose of exacerbating medications • Increase fluid & salt intake

Vasovagal & situational syncope	
Triggers	• Pain,* anxiety,* emotional stress, heat, prolonged standing • Situational: cough,* micturition,* defecation, eating, hair-combing*
Clinicalpresentation	• Prodrome (eg, warmth, pallor, nausea, diaphoresis) • Rapid recovery of consciousness (eg, <1-2 min)
Diagnosis	• Mainly based on clinical history of event • Upright tilt table testing sometimes indicated in uncertain cases
Treatment	• Reassurance & avoidance of triggers • Counterpressure techniques for recurrent episodes
*Particularly common triggers in the pediatric population.	

Evidence of tongue biting is the most reliable finding to differentiate epileptic seizure and syncope. It has low sensitivity (33%) but high specificity (96%) for epileptic seizure (ie, very few false positives), making it highly useful in confirming the diagnosis when present.

Muscle jerks can occur in all types of syncope because sudden cerebral hypoperfusion often causes brief myoclonus.

Vasovagal syncope is the most common type of syncope.

Cardiac monitoring immediately preceding the reflex syncope typically shows sinus bradycardia and asystole due to sinus arrest.

For patients with recurrent vasovagal syncope, management consists of advice to avoid triggers and to assume a supine position with leg raising at the onset of symptoms. Physical counterpressure maneuvers (eg, leg crossing with tensing of muscles, handgrip and tensing of arm muscles with clenched fists) during the prodromal phase can improve venous return and cardiac output, sometimes aborting syncopal episodes. Some patients in high-risk settings associated with a potential risk of physical injury (eg, airline pilots, commercial drivers) require temporary activity restriction until these maneuvers are proven effective.

Stimulation of carotid baroreceptors while standing can cause syncope in patients with carotid hypersensitivity; those affected are usually older (eg, age >60) with carotid atherosclerotic disease.

Orthostatic hypotension occurs when blood pressure is significantly reduced on standing, typically due to hypovolemia or an impaired baroreceptor-mediated response (eg, autonomic dysfunction). In athletes, the most likely cause is hypovolemia due to fluid restriction and diuretic use, a method used by some athletes in combat sports (eg, wrestling, boxing) to achieve rapid weight loss and compete in a lighter weight category.

Holter monitoring is indicated in patients with clinical or electrocardiographic features suggesting the presence of an underlying arrhythmia. This is usually suspected in patients with underlying heart disease who have syncopal episodes (often without specific triggers or prodromal symptoms).

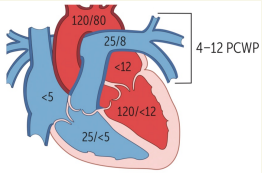
Transthoracic echocardiography should be performed in patients with syncope when structural or valvular heart disease is suspected due to history or physical examination (eg, syncope during exertion, abnormal murmurs).

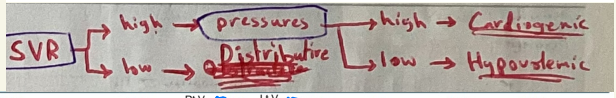
Shock

$$SvO2 = \frac{DO2 - VO2}{DO2}$$

Where:

- **DO2 (Oxygen Delivery)** is the amount of oxygen delivered to the tissues, and it depends on:
  - Cardiac Output (CO): the amount of blood pumped by the heart per minute.
  - Hemoglobin concentration (Hb): the amount of oxygen-carrying hemoglobin in the blood.
  - Arterial Oxygen Content (CaO2): the amount of oxygen carried in the arterial blood, which depends on the partial pressure of oxygen (PaO2) and the hemoglobin saturation (SaO2).





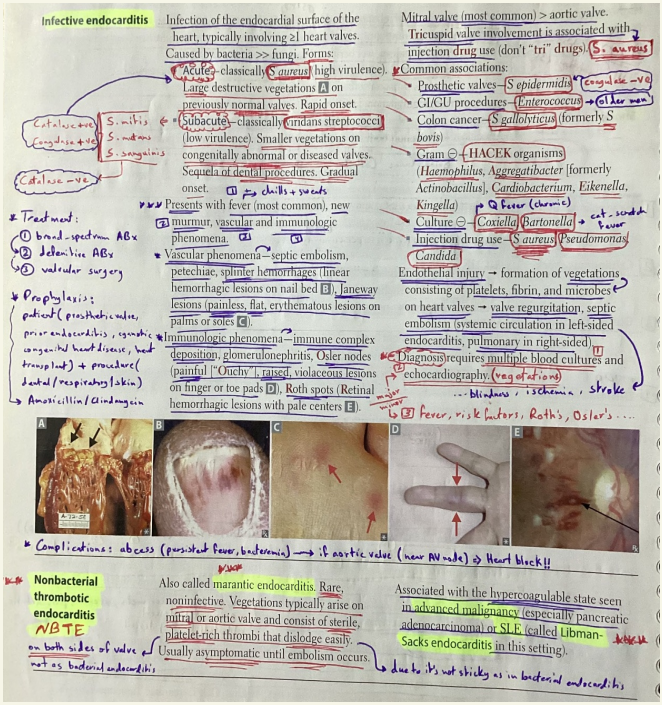
TYPE	CAUSED BY	MECHANISM	SKIN	Rt V. Preload CVP	Lt V. Preload PCWP	CI CO	Afterload SVR	SVO_2
Hypovolemic shock	Hemorrhage, dehydration, burns	Volume depletion	Cold, clammy	↓	↓	↓	↑	↓
Cardiogenic shock	MI, HF, valvular dysfunction, arrhythmia	Left heart dysfunction		↑	↑	↓	↑	↓
Obstructive shock	PE, tension pneumothorax	Impeded cardiopulmonary blood flow		↑	↓	↓	↑	↓
	Cardiac tamponade			↑	↑	↓	↑	↓
Distributive shock	Sepsis (early), anaphylaxis	Systemic vasodilation	Warm, dry	↓	↓	↑	↓	↑
	CNS injury			↓	↓	↓	↓	normal/↑

In tamponade, left-sided preload is decreased, but measured PCWP is paradoxically increased due to external compression by pericardial fluid.

Cardiac index (CI) & SvO2 are usually decreased in neurogenic shock due to impaired sympathetic reflexes.

In Septic shock, CI is initially increased due to the decrease in SVR. There is reflexively increased cardiac output in an attempt to maintain peripheral tissue perfusion, accompanied with increased pulse pressure, which results in bounding peripheral pulses. The hyperdynamic circulation leads to elevated mixed venous oxygen saturation (SvO2) as the tissues are unable to adequately extract oxygen as blood rapidly flows through the capillaries (lactic acidosis may develop from tissue hypoperfusion). In late septic shock, myocardial contractile dysfunction often develops and cardiac output decreases.
Norepinephrine, a first-line vasopressor for treatment of septic shock, acts on both alpha-1 and beta-1 adrenergic receptors, and its alpha-1 agonist properties produce potent vasoconstriction. This vasoconstriction increases MAP to provide circulation to critical organs (eg, brain); however, it also decreases perfusion to peripheral structures such as the distal digits. The resulting digital ischemia, which is typically bilateral and symmetric, can lead to tissue necrosis (eg, dry gangrene) if prolonged. It also can negatively impact the intestines (causing mesenteric ischemia) and/or kidneys (causing renal failure).

Infective Endocarditis (IE) & Non-Bacterial Thrombotic Endocarditis (NBTE)

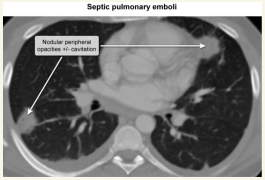


Aortic valve infective endocarditis causes perivalvular abscess in 30%-40% of cases (especially if bicuspid). This complication should be suspected in patients with persistent bacteremia or cardiac conduction abnormalities (eg, heart block). Transesophageal echocardiography (TEE) is likely the best next step in this case because it is more sensitive for perivalvular abscess compared to transthoracic echocardiography (TTE) ; surgery will likely be necessary.

NBTE primarily seen with malignancy (80%) or systemic lupus erythematosus (SLE), which is associated with the antiphospholipid antibody syndrome (APLS). Patients with SLE who develop NBTE often do so in the absence of an SLE flare.

Infective endocarditis with intravenous drug use	
Pathogenesis	• Injected particles cause microdamage to right-sidedvalves before being filtered out by the lungs • Microdamage facilitates bacterial attachment • Increased risk with HIV
Clinical features	• Tricuspid valve most commonly affected • *Staphylococcus aureus* is the most common organism • Septic pulmonary emboli present in up to 75% of cases • Audible murmur may be absent in 50% of cases • Few peripheral manifestations(eg, splinter hemorrhages, Janeway lesions) • Heart failure uncommon

Common complications of infective endocarditis	
Local (cardiac)	• Heart failure • Perivalvular abscess • Pericarditis • Intracardiac fistula
Distant (embolic)	• Septic embolism • Metastatic abscess • Mycotic aneurysm • Organ infarction

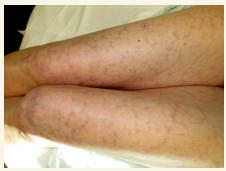


Septic pulmonary emboli typically cause cough, chest pain, and hemoptysis and on chest imaging appear as multiple round, nodular opacities with or without cavitation.

Risk of IE is greatest immediately following valve replacement because the valve is not covered with endothelium. However, because the risk of IE persists, there is no specific time cutoff following prosthetic valve placement to discontinue prophylaxis; therefore, antibiotic prophylaxis is required for procedures associated with increased risk of transient bacteremia (eg, dental cleaning). Prophylactic antibiotics administered 30-60 minutes prior to these procedures reduce the quantity and duration of transient bacteremia; therefore, antibiotics should be administered to those with a high risk of IE. Oral amoxicillin (one 2 g dose) is used prior to dental and respiratory procedures to reduce Streptococcus viridans bacteremia; it can also be used prior to GU/GI procedures in patients with active GU/GI infection to reduce Enterococcus bacteremia. Patients undergoing procedures in areas of skin and soft tissue infection usually receive intravenous vancomycin to reduce Staphylococcus bacteremia.

Cholesterol Emboli Syndrome

Cholesterol crystal embolism (atheroembolism)	
Risk factors	• Comorbid conditions (hypercholesterolemia, hypertension, type 2 diabetes mellitus) • Cardiac catheterization or vascular procedure
Clinical features	• Dermatologic (livedo reticularis, ulcers, gangrene, blue toe syndrome) • Renal (acute or subacute kidney injury) • CNS (stroke, amaurosis fugax) • Ocular involvement (Hollenhorst plaques) • Gastrointestinal (intestinal ischemia, pancreatitis)
Diagnosis	**Laboratory findings** • Elevated serum creatinine, eosinophilia, hypocomplementemia • Urinalysis, typically benign with few cells or casts, may have eosinophiluria **Skin or renal biopsy** • Biconvex, needle-shaped clefts within occluded vessels • Perivascular inflammation with eosinophils



Laboratory studies may show eosinophilia/uria (due to interleukin-5 activation) as well as hypocomplementemia (likely due to neutrophil activation) in cases of recent atheroembolism.

Patients undergoing coronary angiography are at risk for contrast-induced nephropathy (CIN). Urinalysis in CIN typically shows muddy-brown granular and epithelial cell casts. CIN usually begins to resolve within 3-5 days; renal atheroembolism often shows delayed-onset kidney injury. Moreover, CIN is not associated with multisystem involvement, which favors the diagnosis of cholesterol embolization.

Peripheral Arterial Disease (PAD)

Cardiovascular disease is the major cause of morbidity and mortality in patients with peripheral artery disease (PAD). Patients with PAD and intermittent claudication have an estimated 20% 5-year risk of nonfatal myocardial infarction and stroke and a 15%-30% risk of death due to cardiovascular causes. Only 1%-2% of patients with PAD progress to develop critical limb ischemia with risk of limb amputation.

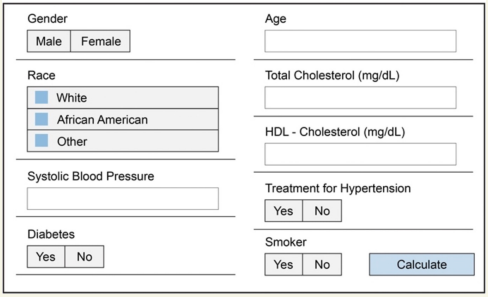
Acute limb ischemia after myocardial infarction suggests embolization of a left ventricular (LV) thrombus. Transthoracic echocardiography should be performed to screen for LV aneurysm and/or residual LV thrombus.

Firstly, start on low-dose aspirin and statin therapy. Then, enroll the patient in a supervised exercise program. Exercise therapy for a minimum of 12 weeks, with 30-45 minutes of exercise at least 3 times a week, is recommended for all patients with claudication. The goal is to reproduce the claudication symptoms during each session. Supervised exercise programs have been shown in multiple clinical trials to reduce symptoms and improve the maximum walking distance in these patients.

Surgical revascularization is reserved for patients with limb-threatening complications (eg, nonhealing ulcers), significant limitation in activities of daily living, or failure to respond to exercise and pharmacologic therapy.

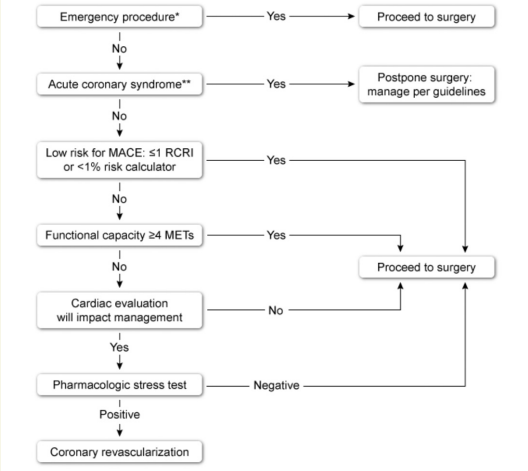
Indications for statin therapy in prevention of ASCVD	
Secondary prevention	◦ Established ASCVD ◦ Acute coronary syndrome ◦ Stable angina ◦ Arterial revascularization (eg, CABG) ◦ Stroke, TIA, PAD
Primary prevention	• LDL ≥190 mg/dL • Age ≥40 with diabetes mellitus • Estimated 10-year risk of ASCVD >7.5%-10%

Sample screenshot of 10-year ASCVD risk calculator



Low-dose aspirin (eg, 81 mg daily) is indicated for secondary prevention in patients with established ASCVD and also for primary prevention of ASCVD in high-risk patients age 50-70. However, it is not typically indicated for primary prevention in patients age <50 because the protective cardiovascular benefit may be too small to outweigh the increased risk of bleeding.

Preoperative evaluation of ischemic heart disease for noncardiac surgery



*Emergency procedure: <6 hours to avoid loss of life/limb.
**Acute coronary syndrome: acute or recent (<60 days) myocardial infarction or unstable angina.
MACE = major adverse cardiac event; **MET** = metabolic equivalent; **RCRI** = Revised Cardiac Risk Index.

Cardiac risk* of selected noncardiac surgical procedures	
Risk level	**Surgery type**
High	Aortic or other major vascular Intrathoracic Open intraperitoneal
Intermediate	Head and neck (eg, thyroidectomy) Orthopedic Prostate
Low	Breast (eg, lumpectomy, mastectomy) Endoscopic procedure Cataract extraction

*Cardiac death, nonfatal cardiac arrest, or nonfatal myocardial infarction.

Estimated cardiac functional capacity by activity (METs*)	
<4 METs	Eat, dress, use toilet Walk indoors in the house Do light housework (eg, vacuuming)
≥4 METs	Climb a flight of stairs Run a short distance Do yardwork (eg, raking leaves) Participate in golf, tennis, or dancing

*1 MET (metabolic equivalent) = volume of oxygen consumed at rest (3.5 mL O_2 uptake/kg/min).

Generally, extensive preoperative cardiac testing is necessary only in patients with significant cardiac conditions undergoing high-risk procedures.

Revised Cardiac Risk Index (RCRI)(cardiovascular risk of noncardiac surgery)	
6 risk predictors	• High-risk surgery (eg, vascular, intrathoracic) • Ischemic heart disease • History of congestive heart failure • History of cerebrovascular disease (stroke *or* TIA) • Diabetes mellitus treated with insulin • Preoperative creatinine >2 mg/dL
Risk of cardiac death,nonfatal cardiac arrest,or nonfatal MI	• 0-1 factor: low risk* • ≥2 factors: elevated risk
*RCRI score of 0-1 originally reported as ≤1% and still accepted as low risk. Slightly higherevent rates of later studies probably due to using troponins (↑ sensitivity) and includingadditional outcomes (eg, all-cause mortality).	

Treatment of hypertriglyceridemia			
Triglycerides	**150-499 mg/dL**	**500-999 mg/dL**	**≥1,000 mg/dL**
Generalmeasures	• Limit dietary sugar/tight glycemic control in diabetes • Limit saturated fat • Regular aerobic exercise • Weight loss of 5%-10% of body weight • Treat with statins based on ASCVD risk		
Specificmeasures	• Limit alcohol intake • Ω-3 acids if high risk of ASCVD	• Abstain from alcohol • Ω-3 acids or fibrates, depending on ASCVD risk	• Abstain from alcohol • Fibrates to reduce pancreatitis risk

The muscle injury associated with statins typically resolves with cessation of the drug. Those who develop rhabdomyolysis, a rare side effect of severe statin-induced myopathy, should discontinue statin use entirely. However, most muscle toxicity is mild (eg, myalgias), and the majority of patients can tolerate a different statin.

Peripheral Venous Disease (PVD)

Chronic Venous Insufficiency (CVI) is a common cause of lower extremity edema that may be accompanied by varicose veins, skin discoloration, and medial skin ulceration. Initial treatment includes conservative measures with leg elevation, exercise, and compression therapy. Patients who do not respond to initial conservative measures should undergo venous duplex ultrasound to confirm the diagnosis of CVI by identification of venous reflux (retrograde venous blood flow) in the deep venous system.

Post-Thrombotic Syndrome	
Epidemiology	• Chronic venous insufficiency following acute DVT • Most cases arise within 2 years of thrombus
Manifestations	• Leg edema, fatigue, pain, superficial venous dilation, venous stasis ulcers • Often worse at the end of the day
Treatment	• Exercise (eg, ankle flexion, walking) • Compression (eg, bandages, stockings)

Approximately 50% of patients with acute DVT develop post-thrombotic syndrome within 2 years due to venous hypertension distal to the site of previous thrombus. This is thought to arise due to venous valve damage from the release of inflammatory mediators and venous lumen stenosis due to wall remodeling.

Long-term anticoagulation is often indicated for those with recurrent thrombus, thrombus in the setting of malignancy, or hypercoagulable state with thrombus. Inferior vena cava (IVC) filter placement is usually indicated for those who have lower extremity thrombus and a contraindication to antithrombotic therapy (eg, gastrointestinal bleed, recent cranial hemorrhage)



Step 2

& Relevant Clinical Step 1

Pulmonology

تَذكَّر:

إنَّ الطِّبَّ وسِيلةٌ.. لا غايَةٌ!

Contact & Updates:

Ehab Alroud

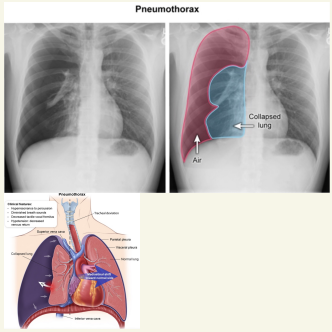
Physical Examination

Breath sounds represent air movement within the lung and tactile fremitus is caused by tissue vibration that occurs during air movement. In general, sound and vibration travel faster and more efficiently in solids or liquids than in air, which results in increased intensity of breath sounds and increased tactile fremitus, as well as egophony (sounds like the letter "A" when the patient says the letter "E"), as in patients with a consolidative process inside the lung (eg, bacterial pneumonia).

Pneumothorax (air) or pleural effusion (fluid) if they present just outside the lung in the thoracic cavity, they can act to insulate sound and vibration originating from the lung, which leads to decreased breath sounds and decreased tactile fremitus.

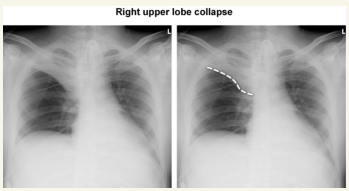
Physical findings in select lung diseases

ABNORMALITY	BREATH SOUNDS	PERCUSSION	FREMITUS	TRACHEAL DEVIATION
Pleural effusion	↓	Dull	↓	None if small Away from side of lesion if large
Atelectasis	↓	Dull	↓	Toward side of lesion
Simple pneumothorax	↓	Hyperresonant	↓	None
Tension pneumothorax	↓	Hyperresonant	↓	Away from side of lesion
Consolidation (lobar pneumonia, pulmonary edema)	Bronchial breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy	Dull	↑	None

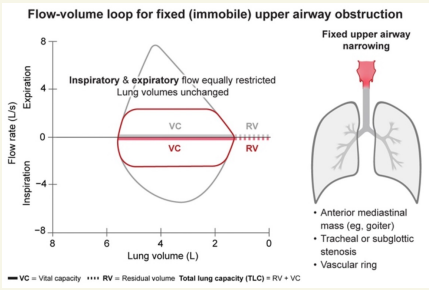


Asthma exacerbations can be associated with mucus hypersecretion (eg, dark-colored sputum), which can result in formation of a mucus plug in the airways. The resultant airway obstruction causes distal air trapping and prevents additional air from entering that portion of the lungs. The trapped air molecules eventually diffuse into the bloodstream, creating a vacuum that leads to alveolar collapse (ie, atelectasis). As the lung collapses, the trachea and other mediastinal structures are pulled toward the side of the atelectasis. Because collapsed lung has a greater density than air-filled lung, dullness to percussion is also present. In addition, the lack of air flow leads to absent or markedly decreased breath sounds and decreased tactile fremitus.

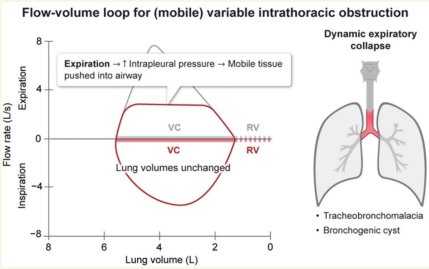
Atelectasis (if large-volume) chest x-ray typically shows opacification of the affected lung area with ipsilateral mediastinal shifting and rib space narrowing.



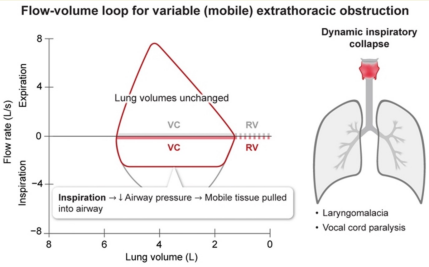
Flow - Volume Loop (FVL)



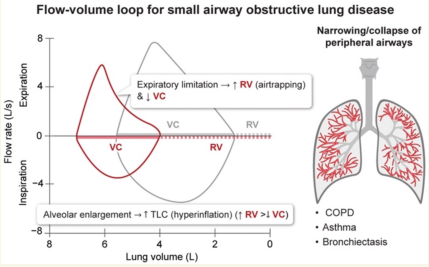
Tracheal stenosis (fixed upper airway obstruction) reduces airflow equally across inspiration and expiration, flattening the flow-volume loop. Prolonged intubation or high endotracheal tube cuff pressure can cause ischemic injury to the tracheal mucosa. The resultant scar formation results in tracheal stenosis, which can evolve months after the initial injury. Flow through the narrowed segment becomes turbulent, generating audible noisy sounds during inspiration and expiration (biphasic stridor).



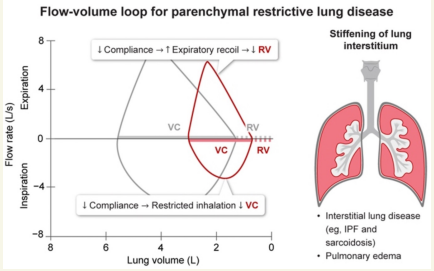
Bronchomalacia refers to structural weakness of the central intrathoracic airways, causing them to collapse with the positive intrapleural pressure that occurs during expiration. This results in a variable intrathoracic obstruction pattern on FVL, with a uniformly flattened expiratory portion. Patients typically have expiratory stridor.



During inspiration, the vocal cords normally open widely (ie, abduct) to keep the airway open. Patients with **Vocal Cord Dysfunction** (ie, paradoxical vocal fold movement [PVFM], inducible laryngeal obstruction) do not keep the airway widely open during inspiration. This produces avariable extrathoracic obstruction pattern on FVL. Patients can have exercise-induced shortness of breath, but they have inspiratory stridor.



Asthma involves reversible bronchospasm of peripheral airways. During an asthma exacerbation, a small airway obstruction pattern would be seen on FVL. Expiratory air trapping leads to a leftward shift of the loop (increased residual volume). Because the small distal airways are affected, the obstruction progressively worsens as the lung empties, leading to a scalloped appearance of the expiratory portion. Patients have expiratory wheezing.

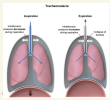


Pulmonary Fibrosis produces a parenchymal restrictive pattern on FVL. It is characterized by supranormal early expiratory airflow (increased recoil of stiff lungs) and loss of lung volume. Therefore, FVL is peaked, narrow, and shifted to lower volumes. Patients typically have inspiratory crackles on lung auscultation.

Paradoxical vocal fold motion (PVFM)

The vocal cords normally abduct (open) during inspiration. During PVFM (also called vocal cord dysfunction) episodes, the vocal cords inappropriately adduct (close) during inspiration, causing laryngeal obstruction. Episodes may be triggered by strong smells, stress, or exercise. A classic scenario is a young, female athlete, particularly in the setting of a transition to a higher level of competition. It's often mimics exercise-induced asthma. In addition to dyspnea and noisy breathing, patients typically report throat tightness and impaired inspiration.
Diagnosing PVFM during an acute episode of respiratory distress is difficult; patients may have a history of repeated intubations. Patients may also pass out (due to hypoxia), after which the vocal cords move normally, and respiratory distress immediately resolves.

Laryngoscopy showing vocal cord adduction during inspiration is diagnostic.
PFT may show flattening of the inspiratory loop but may be normal if done between episodes. Acute episodes are managed by encouraging the patient to sniff or pant, which activates the posterior cricoarytenoid to abduct the vocal cords, or with noninvasive positive-pressure ventilation. Endotracheal intubation ideally should be avoided. Long-term treatment primarily consists of education and therapy with a speech-language pathologist.



Acquired tracheomalacia:

Can present with noisy breathing during periods of increased respiratory effort However, stridor is expiratory. Risk factors for development of tracheomalacia (eg, intubation, recurrent pulmonary infections, relapsing polychondritis).

Bilateral choanal atresia:

Congenital blockage of the posterior nasal aperture, presents shortly after birth with cyclic cyanosis that worsens when newborns cannot breathe through the mouth (eg, during feeding) and improves when they do (eg, while crying). Unilateral choanal atresia commonly presents during childhood as persistent, unilateral nasal obstruction and discharge.

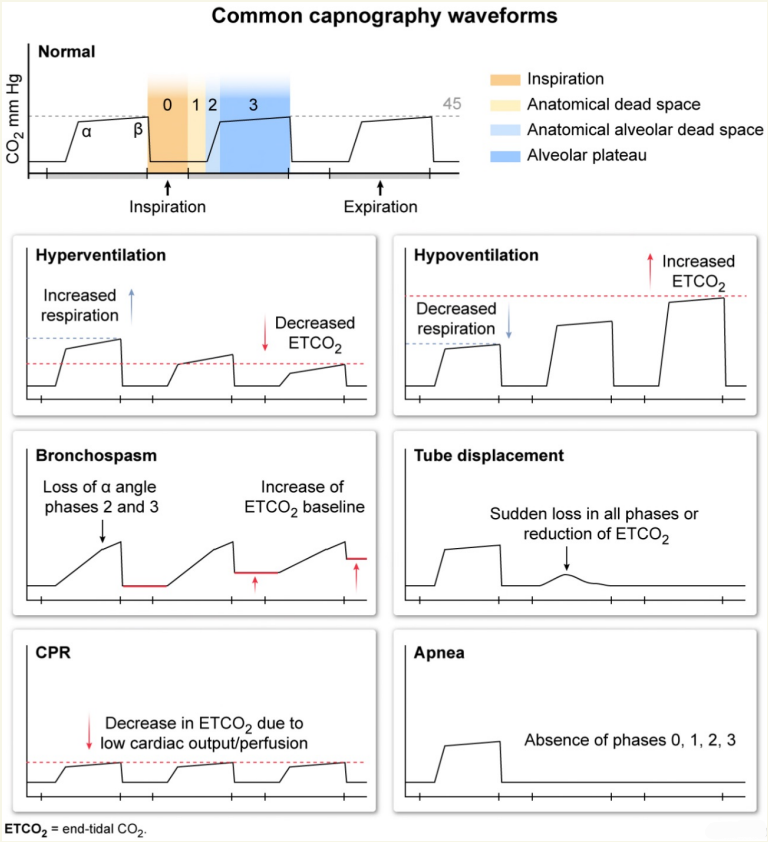
Adenotonsillar hypertrophy may cause airway obstruction but typically manifests as nighttime snoring.

Capnogram

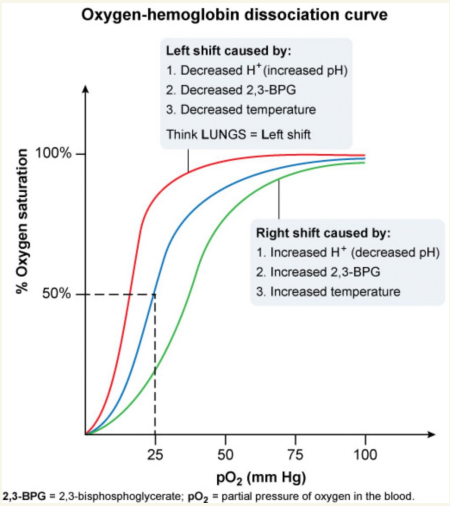
Capnography is the measurement of carbon dioxide concentration over time. It can provide valuable information about ventilation/perfusion and metabolic status and is the most reliable method for verifying endotracheal tube (ETT) placement.

A flat waveform indicates that the sensor (located at the hub of the ETT) is not detecting CO2. This most commonly reflects 2 situations:

- Because CO2 is not produced in the stomach or esophagus, esophageal intubations are classically represented by a flat line, especially in an uncuffed ETT, which can easily become displaced during transport and move the relatively short distance from the trachea to the esophagus. (Uncuffed ETTs are commonly used in children because they are thought to be associated with less mucosal injury)
- In prolonged cardiac arrest (production of CO2 has ceased), a flat waveform can occur.



O2-Hb Dissociation Curve

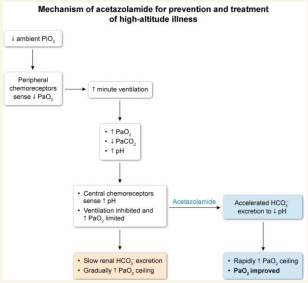


Shifts in oxyhemoglobin dissociation curve (ODC) reflect local tissue oxygen needs. Can be helpful (meets metabolic needs) or harmful (in toxicities, pathophysiologic situations).

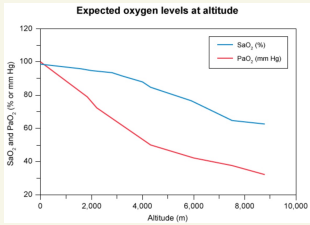
Right shift in ODC reflects ↓ Hb affinity for O_2 → ↑ O_2 unloading at tissue. Physiologically occurs with ↑ O_2 needs: exercise, ↓ pH, ↑ temperature/fever, hypoxia (↑ 2,3-BPG); at the cellular level, caused by ↑ H^+ and ↑ CO_2 created by tissue metabolism (Bohr effect).

Left shift in ODC reflects ↑ Hb affinity for O_2 → ↓ O_2 unloading at tissue. Physiologically occurs with ↓ O_2 needs (↓ temperature) and pregnancy (fetal Hb has higher O_2 affinity than adult Hb, and ↑ O_2 binding due to ↓ affinity for 2,3-BPG → left shift, driving O_2 across placenta to fetus). Pathologically occurs with ↑ CO, ↑ MetHb, genetic mutation (↓ 2,3-BPG). **Left is lower.**

High-altitude illness (HAI) causes fatigue, nausea, headache, lightheadedness, and SOB. These symptoms most commonly occur within 1-2 days of ascent to an elevation >2,500 m (~8,000 ft) and are driven by the hypoxemia that results from low partial pressure of inspired oxygen (PiO2) at high altitude. Acetazolamide is used for treatment and prevention.



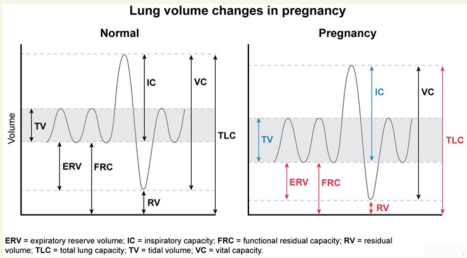
Characteristics of high-altitude pulmonary edema versus multifocal pneumonia	
High-altitude pulmonary edema	**Multifocal pneumonia**
• Recent arrival at high altitude (<1 week) • Absent or mild leukocytosis • Procalcitonin normal • Marked early improvement with O_2	• Persistent stay at high altitude • Leukocytes >15,000 mm^3 with bands • Procalcitonin elevated • Minimal early improvement with O_2



In response to the low partial pressure of inspired oxygen (PiO2) at high altitude (ie, >2500 m), the lungs undergo hypoxic vasoconstriction to optimize alveolar-capillary gas exchange. Some individuals have a genetic predisposition to developing unevenly distributed hypoxic vasoconstriction, which exposes the pulmonary capillaries in relatively less vasoconstricted areas to high perfusion pressure. The regional elevations in perfusion pressure disrupt the alveolar-capillary membrane and lead to patchy, bilateral pulmonary edema (noncardiogenic pulmonary edema).

Hyperventilation syndrome presents with acute onset of deep breathing and/or tachypnea often accompanied by neurologic symptoms. Lung examination is normal. It's a diagnosis of exclusion characterized by intermittent episodes of hyperventilation without any obvious cardiac or pulmonary etiology. Neurologic symptoms may be related to cerebral vasoconstriction or alkalosis-induced hypocalcemia and hypophosphatemia. Education and reassurance are key components of treatment. Patients should be taught abdominal (diaphragmatic) breathing, a retraining maneuver that involves trying to keep the chest still; this maneuver generally takes some practice but resolves most episodes. If the episode does not improve with breathing retraining, a small dose (not a high dose) of a short-acting benzodiazepine (eg, lorazepam) is appropriate second-line therapy. Breathing into a paper bag was previously recommended to improve hypocarbia by rebreathing CO2; however, this can also result in hypoxia and therefore should not be done.

Pulmonary changes in pregnancy	
Pathophysiology	• Progesterone-induced hyperventilation
Clinical features	• Dyspnea of pregnancy • ↑ PaO_2, ↓ $PaCO_2$ (respiratory alkalosis)
Lung volumes	• ↑ Minute ventilation (mostly via ↑ tidal volume) • ↓ Residual volume & functional residual capacity • Normal vital capacity & FEV1



Normal physiologic changes in pregnancy include a progesterone-induced sensation of dyspnea and an increase in minute ventilation, mostly via increased tidal volume and a slight increase in respiratory rate. The hyperventilation increases PaO2 to facilitate oxygen delivery to the fetus and decreases PaCO2 (respiratory alkalosis) to encourage unloading of acidic wastes from the fetus.

Because of the gravid uterus, the resting position of the diaphragm elevates in pregnancy, compressing the lower portion of the lungs. The resulting basilar atelectasis causes decreased residual volume and functional residual capacity (FRC), as well as a slight decrease in total lung capacity. However, diaphragmatic excursion is not impaired and actually increases, which, combined with increased chest wall expansion, allows for larger tidal volume. Although breathing takes place at a lower baseline lung volume (ie, lower FRC), vital capacity is unchanged.

Hypoxemia

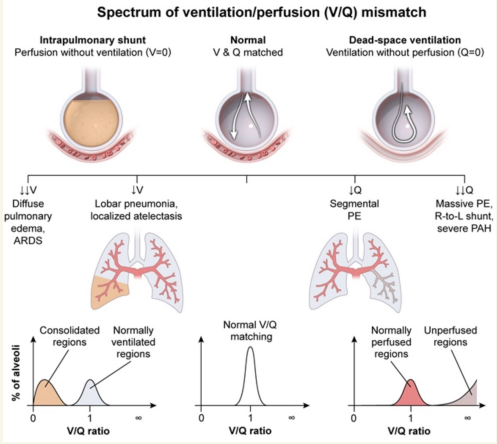
Causes of hypoxemia			
	Examples	**A-a gradient**	**Corrects with supplemental O_2?**
Reduced PiO_2	High altitude	Normal	Yes
Hypoventilation	CNS depression, morbid obesity	Normal	Yes
Diffusion limitation	Emphysema, ILD	Increased	Yes
V/Q mismatch*	Small PE, lobar pneumonia	Increased	Yes
Large intrapulmonary shunt	Diffuse pulmonary edema	Increased	No
Large dead-space ventilation	Massive PE, right-to-left intracardiac shunt	Increased	No

*Caused by localized dead-space ventilation &/or intrapulmonary shunting.
A-a gradient = alveolar-arterial oxygen gradient; **ILD** = interstitial lung disease; **PE** = pulmonary embolism;
PiO_2 = partial pressure of inspired oxygen; **V/Q** = ventilation/perfusion ratio.

Pneumonia causes hypoxemia due to right-to-left intrapulmonary shunting, an extreme form of ventilation/perfusion mismatch. Depending on how much of the lungs are affected by intrapulmonary shunting, the resulting hypoxemia may be difficult to correct with an increase in the fraction of inspired oxygen. Fever induces a hyperdynamic state, which may cause murmur (flow murmur).

Normal arterial blood gas in adults	
pH	7.35-7.45
PaO_2	80-100 mm Hg
$PaCO_2$	35-45 mm Hg
HCO_3	22-26 mEq/L
SaO_2	95%-99%

The A-a gradient is elevated if it is higher than the expected A-a gradient on room air, estimated by (patient age/4 + 4). A-a gradient elevation occurs in processes that cause impaired gas exchange.



Hypercapnea

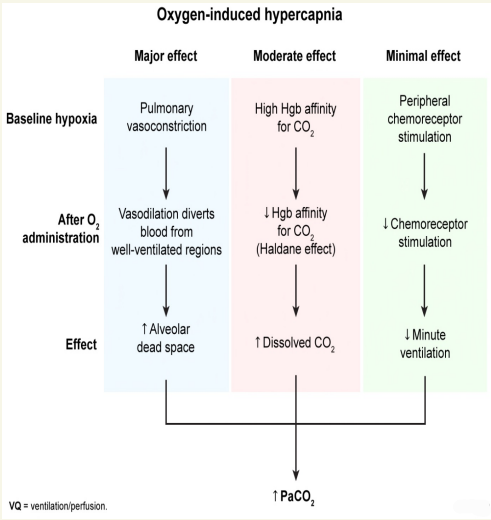
Manifestations of hypercapnia are mainly neurologic and include headache and somnolence. Hypoxemia may be absent; therefore, high clinical suspicion is required to recognize hypercapnia and measure PaCO2 using arterial blood gas analysis.

Causes of hypercapnia	
Mechanism	**Examples**
↓ Central respiratory drive	• Drugs (eg, opioids, benzodiazepines) • CNS trauma, stroke, or encephalitis
↓ Respiratory neuromuscular function	• Spinal cord lesions • Amyotrophic lateral sclerosis • Myasthenia gravis
↓ Thoracic cage or pleural function	• Obesity hypoventilation syndrome • Pneumothorax • Rib fractures, flail chest
Airway obstruction	• Obstructive sleep apnea (upper airway) • Chronic obstructive pulmonary disease (lower airway)
Impaired gas exchange	• Cardiogenic pulmonary edema • Interstitial lung disease

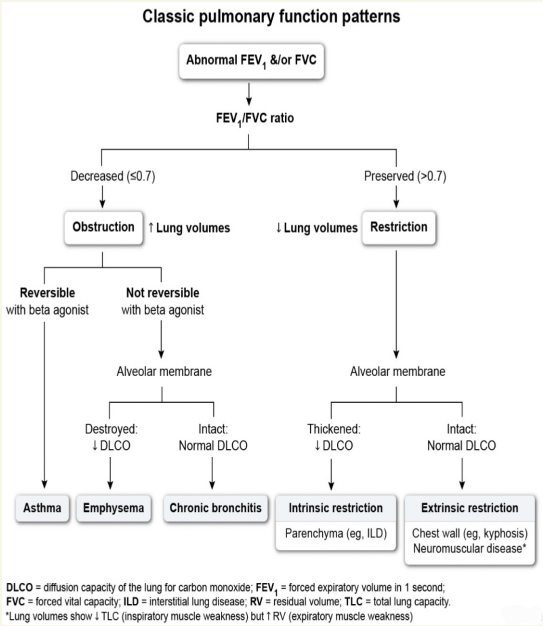
Benzodiazepines bind to the GABA A receptor and increase the inhibitory effects of GABA in the CNS; in cases of severe overdose, this can depress central respiratory drive. This effect is potentiated by alcohol, a common coingestant.
Management of patients with acute benzodiazepine intoxication should first involve protection of the airway and ventilatory support as needed. Flumazenil, a nonspecific competitive antagonist, is sometimes given as a reversal agent; however, it does not consistently reverse respiratory depression and can potentiate seizures in patients who have developed a tolerance to benzodiazepines

Patients with advanced chronic obstructive pulmonary disease are prone to oxygen-induced hypercapnia due to reversal of hypoxic pulmonary vasoconstriction, which increases alveolar dead space. Severe hypercapnia causes neurologic dysfunction (eg, encephalopathy) and can be prevented by maintaining SaO2 at 88%-92%.

The body compensates for chronic hypercapnia (respiratory acidosis) by increasing renal bicarbonate retention and creating a compensatory chronic metabolic alkalosis. The baseline PaCO2 and serum HCO3- are shifted accordingly.



PFT



Differential diagnosis based on DLCO			
	Obstructive pattern(FEV1/FVC <70% predicted)	Restrictive pattern(FEV1/FVC >70% predicted,FVC <80% predicted)	Normal spirometry
LowDLCO	• Emphysema	• Interstitial lung diseases • Sarcoidosis • Asbestosis • Heart failure	• Anemia • Pulmonary embolism • Pulmonary hypertension
NormalDLCO	• Chronic bronchitis • Asthma	• Musculoskeletal deformity • Neuromuscular disease	
IncreasedDLCO	• Asthma	• Morbid obesity	• Pulmonary hemorrhage • Polycythemia
DLCO = diffusing capacity of the lung for carbon monoxide.			

COPD is associated with reduced DLCO due to alveolar destruction, whereas severe asthma is associated with increased DLCO due to increased thoracic blood flow caused by increased negative intrathoracic pressures during inspiration.

Pulmonary function tests						
Type	Normal	Obstructive lung disease			Restrictive lung disease	
		Emphysema	*Chronic bronchitis*	*Asthma*	*Intrinsic*	*Extrinsic*
DLCO*	Normal	Normal to decreased	Normal	Normal to high	Decreased	Normal
FEV_1	> 80% (of predicted)	Decreased			Decreased	
FEV_1/FVC	> 70%	Decreased			Normal to increased	
FVC	> 80% (of predicted)	Normal to decreased			Decreased	
*DLCO is directly proportional to alveolar surface area and solubility of the gas (eg, more blood volume). DLCO is inversely proportional to membrane thickness.						

Pulmonary function tests in chronic lung disease					
	Asthma	COPD	Interstitial lung diseases	Pulmonary arterial hypertension	Restrictive chest wall disease
TLC	Normal/↑	↑	↓	Normal	↓
FEV1/FVC	↓*	↓	Normal	Normal	Normal
DLCO	Normal/↑	↓†	↓	↓	Normal

COPD = chronic obstructive pulmonary disease; **DLCO** = diffusing capacity for carbon monoxide; **TLC** = total lung capacity.

*With positive bronchodilator response.

†Normal in early COPD.

ILD

Common etiologies	• Sarcoidosis, amyloidosis, alveolar proteinosis • Vasculitis (eg, granulomatosis with polyanglitis) • Infection (eg, fungal, tuberculosis, viral pneumonia) • Environmental exposure (eg, silicosis, HP) • Connective tissue disease (eg, SLE, scleroderma) • IPF, cryptogenic organizing pneumonia
Clinical presentation	• Progressive exertional dyspnea, dry cough • >50% of patients have significant smoking history • Fine inspiratory crackles ± digital clubbing
	• Chest x-ray: reticulonodular interstitial opacities • HRCT: fibrosis, honeycombing, traction bronchiectasis • PFT: restrictive pattern with ↓ DLCO

Restrictive lung disease:

1- Altered respiratory mechanics (extrapulmonary, normal DLCO, normal A-a gradient):

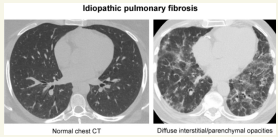
- Respiratory muscle weakness—polio, myasthenia gravis, Guillain-Barré syndrome, ALS
- Chest wall abnormalities—scoliosis, severe obesity, ankylosing spondylitis (functional residual capacity (FRC) and residual volume (RV) are normal or increased due to fixation of the rib cage in an inspiratory position)

2- Diffuse parenchymal lung diseases, also called interstitial lung diseases (pulmonary, decreased DLCO, increased A-a gradient). Inspiratory "Velcro" (eg, fine, dry) crackles are sensitive for interstitial fibrosis, which is present in many forms of ILD. They are typically audible long before abnormalities on chest x-ray (CXR) or pulmonary function testing emerge, underscoring the value of careful auscultation:

- Pneumoconioses
- Sarcoidosis
- Idiopathic pulmonary fibrosis (IPF)
- Granulomatosis with polyangiitis (Wegener granulomatosis)
- Hypersensitivity pneumonitis (HS)
- Drug toxicity (eg, bleomycin, busulfan, amiodarone, methotrexate, nitrofurantoin)
- Acute respiratory distress syndrome (ARDS)
- Radiation-induced lung injury: may be asymptomatic but most common symptoms are dry cough and dyspnea +/– low-grade fever. Acute radiation pneumonitis develops within 3–12 weeks. Radiation-induced fibrosis: dyspnea, nonproductive cough, and chest pain typically develop 4-24 months after therapy. Chest x-ray usually shows volume loss with coarse opacities.

Acute nitrofurantoin-induced pulmonary injury is due to a hypersensitivity that can present with fevers, shortness of breath, dry cough, and erythematous rash. Symptoms usually begin 3-9 days from medication initiation. Bilateral basilar opacities and pleural effusions are common. Both short- and long-term use of nitrofurantoin can result in lung injury. Short-term use is associated with an acute hypersensitivity involving the lungs, whereas long-term use can lead to interstitial lung disease. Pleural effusions also occur and are typically unilateral. Management involves cessation of the drug, which typically leads to symptomatic improvement within 1-2 days.

There is no specific diagnostic test for methotrexate (MTX) pneumonitis. Infection must be excluded first, often through bronchoalveolar lavage (BAL). Empiric antimicrobials are often administered while awaiting culture data. Systemic corticosteroids are sometimes indicated if respiratory status does not improve with MTX cessation.



Idiopathic pulmonary fibrosis (IPF)

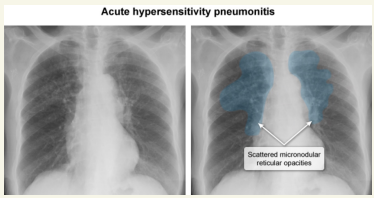
is characterized by slowly progressive dyspnea, dry cough, and fine crackles and commonly occurs in patients age 50-70. Most patients have a history of smoking. It is associated with a restrictive profile and reduced diffusion capacity on pulmonary function. In addition to fine bibasilar crackles, patients in advanced disease may develop end-inspiratory squeaks, digital clubbing, and an abnormal S2 (eg, loud P2; fixed, split S2) due to pulmonary hypertension. Those without an identifiable environmental, infectious, or autoimmune etiology are typically diagnosed with IPF (it's a dx of exclusion). Chest x-ray typically demonstrates nonspecific reticular infiltrates, but chest CT findings such as peripheral or basilar reticular infiltrates and honeycombing are more helpful in establishing the diagnosis. If imaging is nondiagnostic or the clinical picture is atypical, a biopsy can confirm the diagnosis. Antifibrotic agents (eg, pirfenidone) are used for IPF, which is characterized by fibrotic interstitial pneumonia (ie, predominant honeycombing without consolidations) without an underlying autoimmune disorder (ie, no RA).

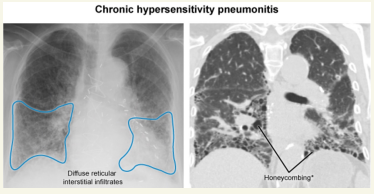
Hypersensitivity pneumonitis (HP),

if acute, the symptoms will be self-limiting and resolve after several days with removal of antigen exposure, but if chronic it will often be irreversible.
Patients with a history of atopy (eg, asthma, eczema) are more likely to develop HP, and smoking decreases the risk of developing HP, possibly due to blunting of the pulmonary immunologic response.

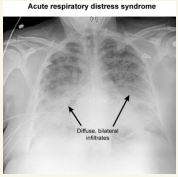
Etiology	• Immunologic response to inhaled antigen (eg, mold, animal protein)
Clinical presentation	**Acute** • Abrupt-onset fever, chills, cough, dyspnea, fatigue, leukocytosis • Episodes often recurrent and self-resolving • Chest x-ray: scattered micronodular interstitial opacities **Chronic** • Progressive cough, dyspnea, fatigue, weight loss • Hypoxemia that worsens with exertion • Chest x-ray: diffuse reticular interstitial opacities
Diagnosis	• PFT: restrictive pattern, ↓ DLCO (chronic only) • BAL: high relative lymphocyte count • Lung biopsy: lymphocytic infiltrate, poorly formed noncaseating granulomas, interstitial inflammation or fibrosis (chronic only)
Treatment	• Remove antigen exposure (resolves acute disease) • Glucocorticoids and/or lung transplantation (chronic only)

Common types of hypersensitivity pneumonitis	
Condition	**Causative agent**
Farmer's lung	Moldy hay (thermophilic actinomycetes, Aspergillus spp)
Bird fancier's lung	Proteins in avian droppings or feathers
Hot tub lung	Mycobacterium avium complex, Cladosporium spp
Mushroom worker's lung	Thermophilic actinomycetes
Potato riddler's lung	
Wine maker's lung	Botrytis spp
Cheese maker's lung	Penicillium spp, Aspergillus spp
Chemical worker's lung	Spray paints, dyes, varnishes





ARDS



Acute respiratory distress syndrome can develop due to direct (eg, aspiration, pneumonia) or indirect (eg, trauma, sepsis, pancreatitis) lung injury. In ARDS, severe hypoxemia is due mainly to an intrapulmonary shunt effect caused by neutrophilic lung inflammation and flooding of fibrinous proteinaceous fluid into alveoli.

Risk factors &pathogenesis	• Direct (eg, pneumonia, inhalation) or indirect (eg, sepsis, pancreatitis, trauma) lung injury • Inflammatory cell activation & ↑ permeability of fluid & cytokine leakage into alveoli
Pathophysiology	• ↓ Lung compliance (alveolar flooding) → ↑ work of breathing • Severe V/Q mismatch (intrapulmonary shunt) → severe hypoxemia • ↑ Hypoxic pulmonary vasoconstriction → ↑ RV afterload & acute PHTN
Diagnosis	• New bilateral alveolar opacities within 1 week of inciting insult • Edema not explained by cardiac failure or volume overload • Hypoxemia with PaO_2/FiO_2 ≤300

Mechanical ventilation	• Lung protection: limit alveolar distending volume (V_T 6 mL/kg) & pressure (Pplat ≤30 cm H_2O) • Ventilation: tolerate permissive hypercapnia (ie, ↑ $PaCO_2$ & ↓ pH acceptable) to avoid excessive V_T • Oxygenation: set lowest feasible FiO_2 (goal SpO_2 92%-96%) to avoid O_2 toxicity
Supportive care	• Treat underlying etiology: source control (eg, sepsis) • Prevent iatrogenic harm: negative fluid balance, timely extubation (eg, minimize sedation) • ± Corticosteroids: select patients with moderate-to-severe early ARDS
Prognosis	• Mortality rate: 40% in hospital, death mostly due to multiorgan failure • Morbidity rate: 50% with chronic cognitive impairment & physical debility, 25% with chronic pulmonary dysfunction (restriction & ↓ DLCO)

A negative fluid balance decreases the formation of pulmonary edema and accelerates recovery from acute respiratory distress syndrome. Fluid balance refers to the net sum of all fluid intake and output from the time of admission. Patients with ARDS often have an initial positive fluid balance (eg, volume resuscitation for sepsis, blood transfusion for trauma). During hospitalization, a conservative fluid strategy aimed at achieving a neutral or negative fluid balance accelerates recovery from ARDS, with a trend toward improved survival rate ("dry lungs = happy lungs"). This goal is accomplished by:

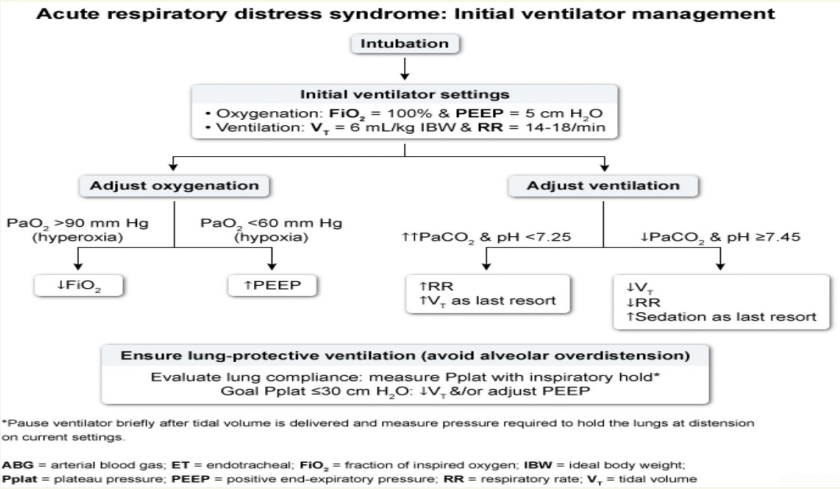
- Minimizing intake: avoiding unnecessary fluid boluses, concentrating IV drips
- Promoting removal: diuretics, renal replacement therapy.

Patients with refractory hypotension (eg, septic shock) should be assessed for fluid-responsiveness prior to blind volume loading (eg, via passive leg raise to simulate a fluid bolus). Vasopressors (eg, norepinephrine) may be required to support hemodynamics to permit volume removal.

Deep sedation may be required to promote patient-ventilator synchrony (ie, matching patient respiratory efforts to the mechanical ventilator breaths), which decreases oxygen consumption and self-inflicted barotrauma. However, excessive sedation increases the risk of delirium, deconditioning, and prolonged intubation. Sedation should be routinely tapered off (ie, daily sedation holiday) as soon as feasible to promote wakefulness and eventual extubation. For example: All mechanically ventilated patients on continuous sedation will undergo a daily sedation holiday unless contraindicated. Sedatives will be held until the patient awakens or becomes agitated/distressed, then restarted at 50% of the previous dose.



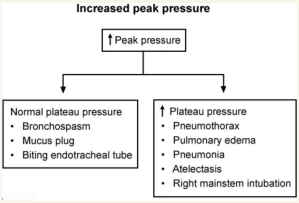
Management of ARDS involves mechanical ventilation to provide adequate oxygenation and ventilation without causing further injury to the lungs. In ARDS, a significant number of the alveoli remain collapsed despite positive airway pressure, and any tidal volume delivered by the ventilator is distributed to those remaining open (functional "baby lung"). Low tidal volume ventilation (LTVV) prevents overdistension of these alveoli. Prone positioning also decreases mortality, likely by homogenizing ventilation throughout the lungs.



Oxygenation in mechanically ventilated patients is determined by the FiO2 and positive end-expiratory pressure (PEEP). Increasing PEEP recruits collapsed alveoli in acute respiratory distress syndrome (ARDS), reducing intrapulmonary shunting and allowing reduction of FiO2. Optimal PEEP settings may improve mortality rates in patients with severe ARDS.

Elevated PEEP levels (eg, ≥10 cm H2O) are frequently required in ARDS. Increasing PEEP must be carefully done because it can increase the risk of barotrauma. Oxygenation can also be improved by increasing the FiO2; patients are often provided high (≥60% or 0.6) FiO2 immediately after intubation. However, FiO2 is usually weaned to <60% as quickly as possible to avoid potential oxygen toxicity.

Peak airway pressure is the sum of airway resistance and plateau pressure. The plateau pressure is the sum of the elastic pressure and positive end-expiratory pressure (PEEP) and is calculated by performing the end-inspiratory hold maneuver. PEEP is calculated with the end-expiratory hold maneuver.
The alveolar end-expiratory pressure is typically equal to the atmospheric pressure. In obstructive lung disease, however, the alveoli cannot empty completely, resulting in higher than normal end-expiratory pressures. This is called intrinsic, or auto-PEEP.



Mechanical ventilation with intubation is associated with a number of serious complications (eg, pneumonia, pulmonary barotrauma); therefore, its duration should be minimized as much as possible. The initial criteria for extubation readiness include:

- pH >7.25
- Adequate oxygenation (eg, PaO_2 ≥60 mm Hg) on minimal support (ie, fraction of inspired oxygen [FiO_2] ≤40% and positive end-expiratory pressure [PEEP] ≤5 cm H_2O)
- Intact inspiratory effort and sufficient mental alertness to protect the airway

Because there is short-term risk of recurrent respiratory failure requiring reintubation, most patients who meet the above criteria should undergo a spontaneous breathing trial (SBT) to help confirm readiness for extubation. During an SBT, patients remain intubated but ventilatory support is turned off.

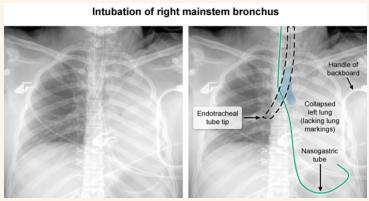
Candidacy for successful extubation may be further assessed during an SBT using the rapid shallow breathing index (RSBI), which is calculated by dividing respiratory rate (per minute) by tidal volume (liters). Patients with a high RSBI (eg, >105) are breathing fast and shallow and are unlikely to do well without continued ventilatory support.

Because an endotracheal tube can cause damage to the larynx and upper trachea over time (eg, tracheal stenosis), tracheostomy is indicated when prolonged intubation (eg, >7-10 days) is required.

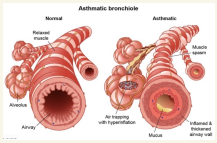
Complications of positive pressure ventilation: Alveolar damage, pneumothorax, and hypotension. Pneumothorax presents with sudden-onset shortness of breath, hypotension, tachycardia, tracheal deviation, and unilateral absence of breath sounds.

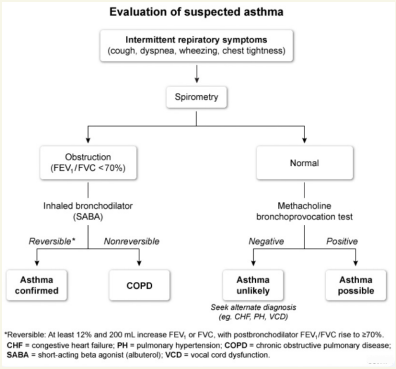
The ideal location of the distal tip of the endotracheal tube is 2-6 cm above the carina.

Right mainstem bronchus intubation is a relatively common complication of endotracheal intubation. It causes asymmetric chest expansion during inspiration and markedly decreased or absent breath sounds on the left side on auscultation. Repositioning the endotracheal tube by pulling back slightly will move the tip between the carina and vocal cords and solve the problem.



Asthma





Obstructive lung diseases:

- COPD (chronic bronchitis and emphysema)
- Asthma
- Bronchiectasis.

Although asthma most commonly begins in early childhood, it can remain undiagnosed and become symptomatic in adulthood.

In patients with intermittent asthma, lung sounds may be normal during calm tidal breathing in intermittent asthma, although wheezing can sometimes be elicited by forceful exhalation, reflecting residual airway inflammation and spasticity.

IL-5 is a T helper type 2 (Th2) cytokine that plays a central role in the pathogenesis of intrinsic asthma (eg, in response to weather, exercise) and chronic rhinosinusitis with nasal polyposis (aspirin-exacerbated).

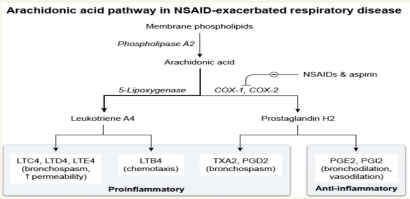
Bronchodilator-responsive airflow obstruction (≥12% increase in FEV1 or FVC) suggests asthma, regardless of age. Because late adult-onset asthma features greater airway remodeling, the FEV1/FVC ratio may not fully normalize.

Exercise-induced bronchoconstriction (EIB): bronchoprovocation testing reveals an exercise-induced decline in expiratory airflow of >15% (normal: <10%). A role for leukotrienes and T-helper cell 2–predominant inflammation has been identified in patients with recurrent episodes of EIB. Therefore, EIB is often considered to be a subtype of intermittent asthma, and premedication is recommended with an inhaled corticosteroid (ICS) and beta agonist.

Exercise-induced bronchoconstriction	
Pathophysiology	• Hyperventilation → incomplete heating & humidification of inspired air → cooler, dry air triggers mast cell degranulation & bronchospasm • Can occur in isolation or in underlying asthma
Clinical features& diagnosis	• ↓ Exercise tolerance; asthma symptoms appear within 5-10 min & improve* after 20 min of exercise • Diagnosis: ◦ Supportive: empiric response to preexercise bronchodilator ◦ Confirmatory: bronchoprovocation testing (eg, spirometry before & after exercise) showing ≥15% decline in FEV_1
Management	• Improve control of underlying asthma (ie, step-up therapy) • Premedicate before exercise: ICS-formoterol (10 min prior) preferred over SABA, LTRA (2 hr prior) • Daily ICS-beta agonist or LTRA may be needed for frequent, prolonged exercise
*Refractory period (↓ preformed mast cell mediators & ↑ inhibitory prostaglandins).	

Aspirin-exacerbated respiratory disease (AERD): is a nonimmunologic reaction that occurs when cyclooxygenase inhibitors (eg, aspirin, other nonsteroidal anti-inflammatory drugs [NSAIDs]) promote the imbalanced production of leukotrienes over prostaglandins. The classic triad (Samter triad) includes asthma, chronic rhinosinusitis with nasal polyposis, and NSAID sensitivity. It is usually occurring 30 minutes to 3 hours after NSAID ingestion. Unlike anaphylactic reactions, these pseudoallergic reactions are not IgE-mediated.

Treatment includes avoidance of NSAIDs. If NSAIDs are absolutely required, desensitization is sometimes necessary. Leukotriene pathway inhibitors (eg, zileuton, montelukast) can also improve respiratory and nasal symptoms



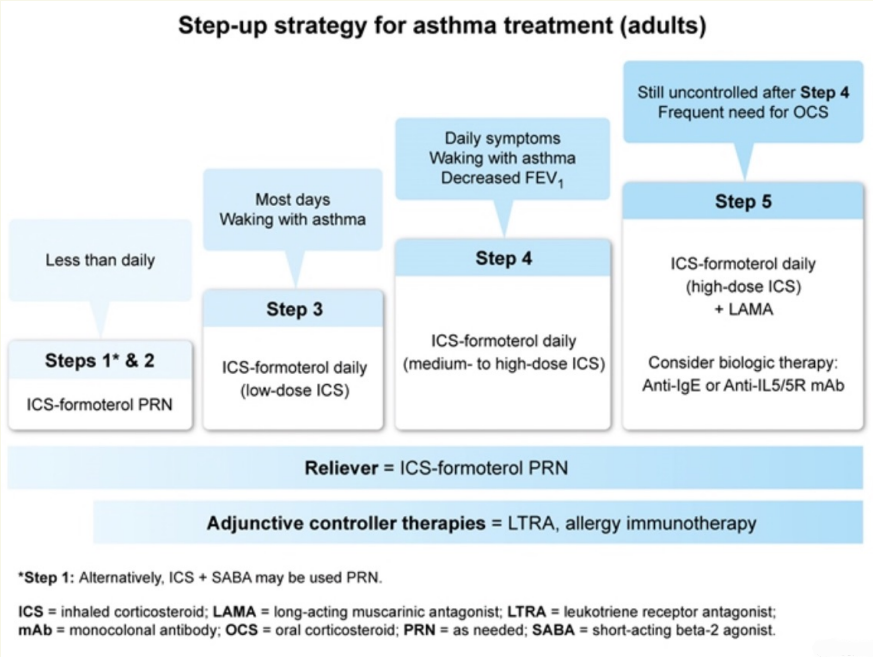
IgE is the primary upstream player in type 1 (immediate) hypersensitivity reactions such as anaphylaxis, angioedema, extrinsic allergic asthma (eg, dust mites, pollen), and allergic rhinitis and conjunctivitis (ie, hay fever). However, it is not involved in the pathogenesis of AERD.

Occupational asthma is induced by workplace antigen exposure (eg, animal proteins, isocyanates). Chronic occupational asthma may produce persistent airway inflammation and bronchoconstriction that subside only after prolonged absence from work.

Once asthma is diagnosed (eg, baseline spirometry), occupational asthma is confirmed by demonstrating workplace-specific worsening of airflow obstruction (eg, fall in peak expiratory flow). Patients record their PEFR at home and at work (along with their symptoms):
a PEFR decline by ≥20% at the workplace relative to at home is consistent with occupational asthma.

Pathogenesis& high-riskoccupations	• Workplace antigens → inflammation (IgE-dependent or independent) → bronchoconstriction • Classic antigens: animal proteins (eg, animal workers, seafood processors), grain carbohydrates (eg, bakers), isocyanates (eg, painters), metals (eg, welders) • Latency (months/years) due to gradual sensitization
Clinicalfeatures	• Initially, symptoms clearly exacerbated at workplace & relieved at home • Over time, symptoms persist throughout week & subside only after sustained work absence • Diagnosis: confirm asthma or BHR (eg, methacholine bronchoprovocation) → confirm workplace-specific worsening of obstruction (eg, serial PEFR at home & work)
Management	• Antigen avoidance (change of workplace if possible) or reduction (eg, respirator, shift rotation) • Bronchodilators & inhaled corticosteroids • Desensitization (immunotherapy)

BHR = bronchial hyperresponsiveness; **PEFR** = peak expiratory flow rate.



- Montelukast (LTRA) for aspirin/exercise-induced asthma
- Omalizumab (anti-IgE) for allergic/occupational asthma
- Mepolizumab (anti-IL5) for eosinophilic asthma

Many patients may be falsely reassured that their asthma is well controlled because their symptoms do not interfere with daily life and are alleviated with acute reliever therapy alone. Therefore, they may self-treat intermittently despite having persistent asthma, which leads to chronic undermedication and poor long-term control. Undertreatment of persistent asthma is associated with greater lung function decline and a higher likelihood of severe acute exacerbations.

Initial pharmacotherapy for acute asthma exacerbation		
Class	**Medication**	**Use**
Short-acting β_2-agonist	• Inhaled albuterol	• Bronchodilator • Continuous (if severe) or repeated dosing
Anticholinergic	• Inhaled ipratropium bromide	• Bronchodilator • Repeated dosing only in acute setting & in conjunction with albuterol
Glucocorticoid	• Prednisone, methylprednisolone, dexamethasone (oral/intravenous)	• Anti-inflammatory • Delayed effect (6 hr) • Multiday dosing for control of late-phase inflammation

In patients with significant respiratory distress (eg, accessory muscle use), ipratropium (inhaled anticholinergic) may be used in conjunction with albuterol in the acute setting for additional bronchodilation.

Corticosteroids are continued at home (eg, prednisone 40-60 mg daily for 5-7 days) to prevent relapse and decrease the need for hospitalization.

Features of respiratory failure in acute asthma	
Clinical features	• Absent/minimal wheezing (poor air movement → silent chest) • Accessory muscle use • Altered mental status
Laboratory findings	• ABG*: poor ventilation (↑ $PaCO_2$ & ↓ pH), poor oxygenation (↓ PaO_2) • Lactate: transient ↑ due to muscle WOB (type A) &/or β-agonist–induced (type B) • K^+: transient ↓ due to β-agonist &/or respiratory alkalosis
Management	• Nebulized albuterol & ipratropium, IV corticosteroids ± IV magnesium • Short trial (<2 hr) of NIPPV • Low threshold for intubation & invasive mechanical ventilation
***Impending respiratory failure:** ↑↑ respiratory effort to maintain normal/borderline $PaCO_2$ & pH. **ABG** = arterial blood gases; **IV** = intravenous; **NIPPV** = noninvasive positive pressure ventilation; **WOB** = work of breathing.	

Respiratory compensation for the marked acidemia that occurs with profound metabolic acidosis (eg, septic shock, severe acute renal failure) creates high ventilatory demand that some patients (especially those age >60) are unable to meet. Respiratory muscle fatigue leads to acute respiratory failure, recognized by higher-than-expected PaCO2 (ie, mixed primary metabolic acidosis and respiratory acidosis).

Fatal asthma: risk factors	
Patient history	• Prior respiratory failure: NIPPV, intubation, ICU admission • Poor asthma control: ↑ inhaler use, frequent oral corticosteroids or acute care visits
Clinical status (impending respiratory failure)	• Examination: respirations >30/min, SaO_2 ≤90%, accessory muscle use, AMS, "silent chest" • ABG: ↑ or inappropriately normal $PaCO_2$ relative to WOB • Peak flow: ≤50% of baseline

The greatest risk factor for life-threatening asthma is a history of respiratory failure, defined as prior intubation or need for mechanical ventilation. Both inspiratory and expiratory wheezing are common during asthma exacerbations. In contrast, the absence of wheezing (ie, "silent chest") due to tight bronchospasm causing diminished air flow is another concerning sign of impending respiratory failure.

* High doses of inhaled beta-2 agonists used in asthma treatment can drive potassium into cells and cause hypokalemia. Severe hypokalemia can present with muscle weakness, hyporeflexia, and life-threatening arrhythmias.

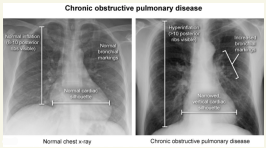
Adverse effects of inhaled corticosteroids	
Local	~75% of dose deposited in oropharynx • **Dysphonia:** steroid-induced laryngeal myopathy; common (50%) & usually minor • **Thrush:** affects tongue & pharynx (esophagus: very rarely); prevent by rinsing & gargling with water, using spacer (decrease local deposition) • **Other:** contact dermatitis (budesonide hypersensitivity); cough & reflex bronchoconstriction
Systemic*	~25% of dose deposited in peripheral lung & systemically absorbed • **HPA axis:** secondary adrenal insufficiency (usually subclinical); can coexist with ICS-induced Cushing syndrome • **Skeletal:** small ↑ osteoporosis & fracture risk • **Other:** dermal thinning (fragile skin, purpura), ocular effects (cataract formation, ↑ IOP), small ↑ CAP risk in COPD patients
∗Uncommon. Typically only seen with prolonged (years) of high-dose ICS, superimposed oral glucocorticoid use, or concurrent administration of potent cytochrome P-450 3A4 inhibitor. **CAP** = community-acquired pneumonia; **COPD** = chronic obstructive pulmonary disease; **HPA** = hypothalamic-pituitary-adrenal; **ICS** = inhaled corticosteroid; **IOP** = intraocular pressure.	

ICS has low systemic bioavailability overall (~25% at most), particularly because any locally deposited steroid that is eventually swallowed is inactivated by first-pass metabolism in the liver. systemic adverse effects are typically seen only in patients taking very high doses of an ICS (ie, ≥800 mcg/day fluticasone equivalent) for prolonged durations (ie, several years to decades).

Glucocorticoid use causes a leukocytosis due to the following:

- Mobilization of marginated neutrophils into the bloodstream (predominant mechanism): Marginated neutrophils are attached to the endothelium of blood vessels; glucocorticoid-induced mobilization of these neutrophils leads to a higher number of circulating neutrophils
- Stimulation of release of immature neutrophils from the bone marrow (as evidenced by increased % of bandforms in some patient)
- Inhibition of neutrophil apoptosis

In contrast, glucocorticoids decrease the number of circulating lymphocytes and eosinophils through a combination of increased apoptosis, increased emigration into the tissues, and decreased production.



COPD

Chronic obstructive pulmonary disease (COPD) encompasses a spectrum of chronic bronchitis and emphysema. The diffusing capacity of the lung for carbon monoxide is normal in chronic bronchitis-predominant COPD and decreased in emphysema-predominant COPD.

Chronic bronchitis x-ray reflects airway inflammation, including prominent thickened bronchovascular markings. In contrast, chest x-ray findings in emphysema reflect obliteration of the alveolar septa and include decreased lung tissue density (hyperlucency) and bullae. COPD patients usually have distant heart sounds due to hyperinflated lungs.

Emphysema: alveolar wall destruction (appears on x-ray as hyperinflated hyperlucent lung tissue with bulla) due to smoking or AAT deficiency.

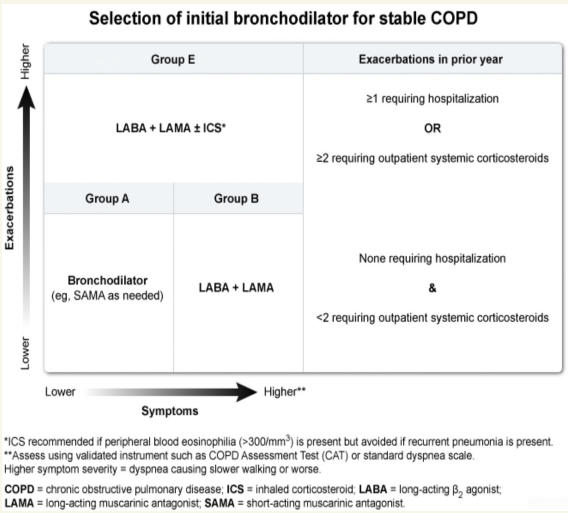
Alpha-1 antitrypsin (AAT) deficiency-related lung disease presents similarly to other forms of chronic obstructive pulmonary disease (COPD) but results in panacinar (panlobular) emphysema. Smoking-induced centriacinar (centrilobular) emphysema most commonly causes disease in the upper lobes of the lungs, whereas the panacinar emphysema of AAT deficiency classically results in greater destruction of the lower lobes. On average, smokers present in their 30s, whereas nonsmokers present in their 40s. AAT deficiency is frequently associated with liver disease, most commonly resulting in neonatal hepatitis, cirrhosis, or hepatocellular carcinoma. family history of emphysema or liver disease is common.

AAT deficiency should be considered in patients with:

- COPD at a young age (age ≤45)
- COPD with minimal or no smoking history
- basilar-predominant COPD
- history of unexplained liver disease

Diagnosis is confirmed by measuring serum AAT levels, and pulmonary function testing should also be performed. Treatment includes intravenous supplementation with human AAT in addition to bronchodilators and corticosteroids as needed. Individuals with severe lung disease are candidates for lung transplantation, whereas those in hepatic failure can be treated with liver transplantation.

Patients with liver disease may be asymptomatic up until the point of endstage disease, and cirrhosis is the 2nd most common cause of death in these patients.



Management of stable chronic obstructive pulmonary disease	
Nonpharmacologic	• Smoking cessation* • Pulmonary rehabilitation* • Vaccination (influenza*, pneumococcal, COVID-19) • Long-term oxygen therapy* if SaO_2 ≤88% at rest • Nocturnal noninvasive ventilation if daytime hypercapnia*
Surgical	• Lung volume reduction or lung transplantation for advanced disease*
Medications	• Bronchodilators (LAMA, LABA) ± ICS • Long-term macrolide (eg, azithromycin 3× weekly)** • PDE4 inhibitor (eg, roflumilast)** • Biologic therapy (eg, anti–IL-5 mAb) if eosinophilic/asthma overlap**

*Reduces mortality.

**Reduces hospitalizations for patients with frequent exacerbations.

ICS = inhaled corticosteroid; **LABA** = long-acting β_2 agonist; **LAMA** = long-acting muscarinic antagonist; **mAb** = monoclonal antibody; **PDE4** = phosphodiesterase 4.

The ICS more effectively suppresses Th2 airway inflammation (asthma), whereas a LAMA more effectively suppresses goblet cell hyperplasia (COPD).

Patients with COPD who have resting arterial oxygen tension (PaO2) ≤55 mm Hg or pulse oxygen saturation (SaO2) ≤88% are candidates for long-term home oxygen treatment. Those with signs of right heart failure (cor pulmonale) or hematocrit >55% should be started on home oxygen if PaO2 ≤59 mm Hg or SaO2 ≤89%. The dose of supplemental oxygen should be titrated so that SaO2 is maintained at >90% during sleep, normal walking, and at rest. Survival benefits of home oxygen therapy are significant when it is used for ≥15 hours a day.

Active smoking increases the risk of postoperative pulmonary complications (eg, pneumonia, respiratory failure requiring mechanical ventilation), especially in patients with underlying lung disease (eg, chronic obstructive pulmonary disease). Smoking cessation is recommended >4-8 weeks prior to elective surgery as it has been shown to reduce the risk of postoperative pulmonary complications.

Patient with COPD has functional limitation due to severe dyspnea and fatigue. These are the 2 most disabling symptoms of COPD, often leading to sedentary behavior, deconditioning of peripheral and respiratory muscles, and worsening dyspnea/fatigue in a vicious cycle. Pulmonary rehabilitation is a multidisciplinary program designed to interrupt this cycle; it consists of 4 components delivered over 12 weeks:

- Supervised exercise: intended to build muscle mass and increase the efficiency of peripheral muscle oxygen use, leading to improved exercise capacity although lung function is unchanged
- Disease management education: includes inhaler technique teaching, breath training (eg, pursed lip), counseling on vaccinations, COPD action planning (early treatment of exacerbations)
- Nutritional intervention: includes a dietary plan to address nutritional comorbidities very frequently associated with COPD (eg, excessive weight, pulmonary cachexia, glycemic control)
- Psychosocial support: support for psychological comorbidities (eg, anxiety, depression), and identification of financial and social resources (eg, medication assistance, peer group)

There is no evidence that preoperative antibiotics active against respiratory pathogens (eg, moxifloxacin) decrease the risk of pneumonia, COPD exacerbation, or other postoperative pulmonary complications.

Multifocal atrial tachycardia (MAT) is a supraventricular tachyarrhythmia characterized by distinct P waves with >3 different morphologies, atrial rate >100/min, and an irregular rhythm. It is usually precipitated by acute respiratory illness in patients with underlying lung disease. Treatment should be directed at correcting the underlying inciting disturbance. Pharmacologic rate control with calcium channel blockers (eg, verapamil) or cardioselective beta blockers (eg, metoprolol) is indicated for MAT only when rapid ventricular rate leads to myocardial ischemia or congestive heart failure or when the arrhythmia persists despite management of the underlying disturbance. Beta blockers may worsen bronchospasm in patients with exacerbation of COPD and should be used with caution. Unlike A-Fib, MAT does not create an increased risk of atrial thrombus formation and thromboembolism; therefore, anticoagulation is not recommended.

Theophylline is a nonselective PDE inhibitor that causes bronchodilation and is occasionally used in the management of COPD. Toxicity typically results from reduced hepatic clearance of the drug (eg, coadministration of a cytochrome P450 inhibitor), with patients experiencing CNS (eg, tremor, seizure), cardiovascular (tachyarrhythmia, hypotension), and gastrointestinal (eg, vomiting) manifestations.

Acute exacerbation of chronic obstructive pulmonary disease	
Precipitants	• Infectious (70%): respiratory viruses (eg, rhinovirus) & commensal bacteria (eg, nontypable *Haemophilus influenzae*) • Noninfectious (30%): sterile inflammation (underlying disease), pulmonary embolism, inhaled irritants
Pathophysiology & presentation	• Bronchial inflammation: systemic response (eg, fever, leukocytosis) usually absent • Cardinal symptoms: ↑ dyspnea, ↑ sputum volume, ↑ sputum purulence • ↑ WOB (hyperinflation) & impaired gas exchange (hypoxemia [↓ V/Q], hypercapnia [↑ V_D])
Management	• Maximize expiratory flow: inhaled bronchodilators • Reduce airway inflammation: systemic glucocorticoids • Treat underlying triggers: ± antibiotics* &/or antivirals (influenza, COVID-19) • Maintain adequate oxygenation: SpO_2 target 88%-92% • Maintain adequate ventilation: NIPPV or invasive mechanical ventilation
*Antibiotics generally indicated if: (1) increased sputum purulence + ≥1 other cardinal symptoms; or (2) patient requires hospitalization. **NIPPV** = noninvasive positive pressure ventilation; **V_D** = alveolar dead space ventilation; **V/Q** = ventilation/perfusion ratio; **WOB** = work of breathing.	

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is characterized by a change in ≥1 of the following:

- Cough severity or frequency
- Volume or character of sputum production
- Level of dyspnea

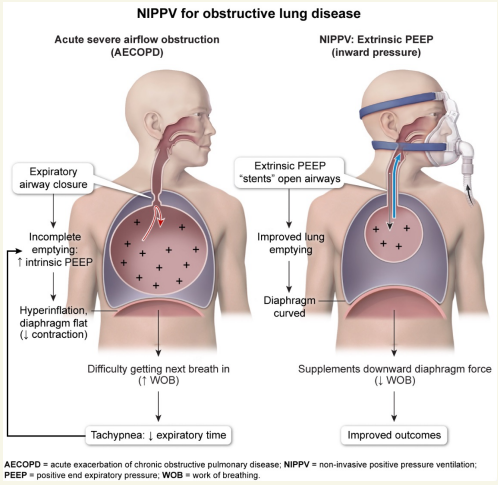
Inflammation in COPD is usually out of proportion to the bacterial load such that significant symptoms can develop even with bacterial counts far below the culture threshold. Therefore, respiratory cultures are of limited diagnostic utility and antibiotic therapy is empiric for moderate/severe AECOPD. Roflumilast is a selective phosphodiesterase-4 inhibitor with anti-inflammatory properties. It is effective for AECOPD prophylaxis in high-risk patients (ie, frequent exacerbations), but it has no role in acute treatment.

A typical treatment duration is 5-7 days; oral and intravenous administration is considered equivalent, but the latter may be required for patients who are too dyspneic to swallow. Systemic glucocorticoids should be administered even when there is an underlying infectious trigger because respiratory dysfunction is mostly driven by the infection-elicited inflammatory response rather than the pathogen itself.

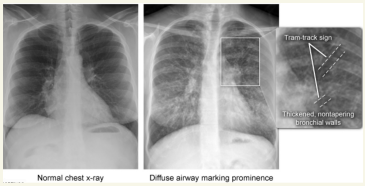
A trial of NIPPV is warranted prior to intubation. If this patient is not improved after a 2-hour trial of NIPPV (eg, worsening respiratory distress, decreased consciousness, and/or acidosis), intubation should be considered. Noninvasive positive pressure ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease helps to unload the work of breathing and decreases mortality and need for intubation.

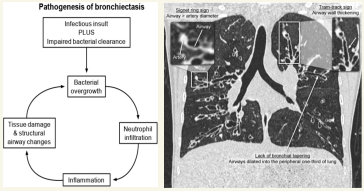
NIPPV instantly improves COPD-related hyperinflation, in which collapsible airways can be stented open by extrinsic pressure. In contrast, severe asthma is marked by concentric smooth muscle hypertrophy, and exacerbations typically involve inflammatory edematous airway closure that is not as readily relieved by positive pressure. Therefore, there is a low threshold to intubate and begin mechanical ventilation.

Noninvasive positive pressure ventilation	
Indications (strongest evidence)	COPD (severe exacerbation, prevent extubation failure) Cardiogenic pulmonary edema Acute respiratory failure Postoperative hypoxemic respiratory failure Immunosuppressed patients Facilitate early extubation
Contraindications	**Medical instability** Cardiac or respiratory arrest (or impending arrest) Severe acidosis (pH <7.1) Acute respiratory distress syndrome Nonrespiratory organ failure Unstable cardiac arrhythmia/hemodynamic instability Encephalopathy (Glasgow Coma Score <10) Gastrointestinal bleed **Inability to protect airway** Uncooperative or agitated Inability to clear secretions/high aspiration risk **Mechanical issues** Recent esophageal anastomosis Facial or neurologic surgery, deformity, or trauma Upper airway obstruction



Bronchiectasis





Clinical features	• Pathophysiology: airway insult (eg, infection, inhalation) with impaired clearance (eg, mucostasis, immunodeficiency) • Chronic: daily production of voluminous, thick ± blood-tinged mucus • Acute exacerbations: recurrent infections with mucopurulent sputum ± frank hemoptysis
Etiologies/contributory conditions	• Airway obstruction (eg, cancer, foreign body) & mucostasis (eg, CF, ABPA) • Immunodeficiency (eg, ↓Ig) & autoinflammatory disease (eg, Sjögren syndrome) • Chronic/past infection (eg, mycobacteria) or toxic inhalation
Evaluation	• High-resolution CT scan of the chest (needed for diagnosis): airway dilation • Pulmonary function testing: obstructive pattern • Investigation of etiologies (eg, Ig levels, respiratory cultures, bronchial obstruction)
Treatment	• Address underlying disorders (eg, Ig replacement) • Airway clearance (eg, chest physiotherapy), mucolytics • Antibiotics to suppress bacterial overgrowth & treat exacerbations

ABPA = allergic bronchopulmonary aspergillosis; **CF** = cystic fibrosis; **Ig** = immunoglobulin; **RA** = rheumatoid arthritis.

Chest x-ray is not diagnostic for bronchiectasis but can reveal suggestive findings, such as dilated and thickened airways (prominent bronchial markings, ring shadows when viewed head on). High-resolution CT (HRCT) scanning of the chest is required to diagnose bronchiectasis because it clearly visualizes the bronchial wall thickening (tram tracking), lack of distal airway tapering, and bronchial dilation (bronchial diameter larger than adjacent pulmonary artery, a finding referred to as the "signet ring" sign). Chronic airway wall inflammation leads to submucosal erosion, producing bronchial arteriolar bleeding that ranges from chronic minimal streaking to acute life-threatening frank hemoptysis. Worsening hemoptysis may indicate an exacerbation of bronchiectasis. In most instances, treatment of superinfection (eg, antibiotics) and mucus retention (eg, airway clearance, mucolytics) resolves the hemoptysis. However, bronchoscopy or bronchial artery embolization is occasionally necessary for severe cases.

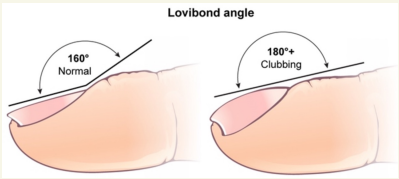
Approximately 7% of patients with cystic fibrosis (CF) are diagnosed at age >18, and testing for CF is recommended in the evaluation of bronchiectasis. A mutation of the CF transmembrane conductance regulator (CFTR) gene results in defective chloride and sodium transport and leads to thick secretions and impaired mucociliary clearance. Chronic bacterial infection ensues, leading to enhanced neutrophil recruitment and excessive release of elastase, which contributes to bronchial airway damage. Pseudomonas aeruginosa is a characteristic finding in the sputum. In addition, upper lung lobe involvement (evidenced by upper lung field crackles and right upper lobe infiltrate) is characteristic of bronchiectasis due to CF and helps differentiate it from bronchiectasis due to other causes.

Hypertrophic osteoarthropathy (HOA) is a condition where digital clubbing is accompanied by sudden-onset arthropathy, commonly affecting the wrist and hand joints. Hypertrophic pulmonary osteoarthropathy (HPOA) is a subset of HOA where the clubbing and arthropathy are attributable to underlying lung disease like lung cancer, tuberculosis, bronchiectasis, or emphysema; therefore a chest x-ray is indicated.

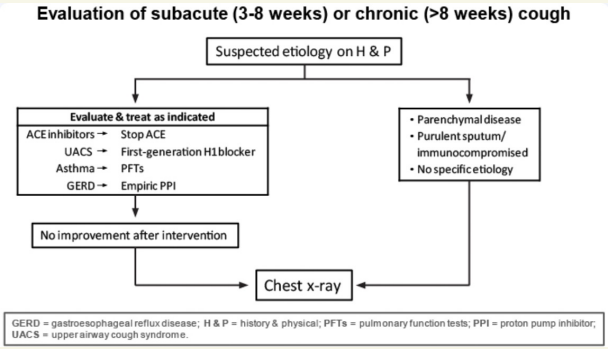
Malignancies, cystic fibrosis, and right-to-left cardiac shunts are the most common causes of secondary digital clubbing. COPD (with or without hypoxemia) does not cause digital clubbing, and the presence of clubbing should prompt a search for occult malignancy. HOA refers to digital clubbing along with painful joint enlargement, periostosis of long bones, and synovial effusions. Pathophysiology involves megakaryocytes that skip the normal route of fragmentation within pulmonary circulation (due to circulatory disruption from tumors, chronic lung inflammation) to enter systemic circulation. Megakaryocytes become entrapped in the distal fingertips due to their large size and release platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). PDGF and VEGF have growth-promoting properties that increase connective tissue hypertrophy and capillary permeability and vascularity, ultimately leading to clubbing.

Conditions commonly associated with digital clubbing	
Intrathoracicneoplasms	• Bronchogenic carcinoma • Metastatic cancers • Malignant mesothelioma • Lymphoma
Intrathoracicsuppurativediseases	• Lung abscess • Empyema • Bronchiectasis • Cystic fibrosis • Chronic cavitary infections (eg, fungal, mycobacterial)
Lung diseases	• Idiopathic pulmonary fibrosis • Asbestosis • Pulmonary arteriovenous malformations
Cardiovasculardisease	• Cyanotic congenital heart disease





Chronic Cough



Common etiologies of chronic cough	
Upper airway disorders	Upper airway cough syndrome (postnasal drip) Chronic sinusitis
Lower airway & parenchymal disorders	Asthma Post–respiratory tract infection Chronic bronchitis Bronchiectasis Lung cancer Nonasthmatic eosinophilic bronchitis
Other causes	Gastroesophageal reflux ACE inhibitors

Subacute (3-8 weeks) and chronic (>8 weeks) cough is seen frequently in adults. Upper-airway cough syndrome (UACS) (eg, postnasal drip), gastroesophageal reflux disease (GERD), and asthma cause >90% of chronic cough in nonsmokers without pulmonary disease.

For patients with, UACS, cough following upper respiratory infection (primarily at night) and an oropharyngeal cobblestoning on physical examination, initial empiric treatment includes oral first-generation antihistamine (eg, chlorpheniramine) or combined antihistamine-decongestant (eg, brompheniramine and pseudoephedrine). Despite their sedating effects, first-generation antihistamines are used because they are more effective. This approach differs from that used for symptoms thought to be due to rhinitis, in which intranasal glucocorticoids are first-line. Patients who do not respond after 2-3 weeks may require further investigation.

Chronic nonproductive cough is a common side effect of ACE inhibitors (eg, lisinopril) that is likely due to increased circulating levels of kinins, substance P, prostaglandins, and thromboxane. It occurs in up to 20% of patients, and onset of the cough is typically within a week of drug initiation or dosage increase (although onset may be delayed for months).

Gastroesophageal reflux disease (GERD) manifests as dysphagia, chest pain/ heartburn, and sensation of regurgitation. Comorbid GERD is common in patients with asthma and can worsen asthma symptoms as a result of microaspiration, leading to an increase in vagal tone and bronchial reactivity (wheezing). In asthma patients with signs and/or symptoms suggestive of comorbid GERD, proton-pump inhibitor therapy has shown benefit in improving asthma symptoms and peak expiratory flow rate. GERD can also cause laryngeal irritation, contributing to vocal cord dysfunction (VCD) that manifests as episodic dysphonia and inspiratory stridor.

OSA

STOP-Bang survey for obstructive sleep apnea (OSA)	
1 point for each characteristic present	**S**noring Excessive daytime **t**iredness **O**bserved apneas or choking/gasping High blood **p**ressure **B**MI >35 kg/m^2 **A**ge >50 **N**eck size: men >17 in (43.2 cm), women >16 in (40.6 cm) Male **g**ender
Scoring: 0-2 points: low risk; 3-4 points: intermediate risk; ≥5 points: high risk.	
Sequelae	• Systemic hypertension • Pulmonary hypertension & right-sided heart failure

Polysomnography is used to diagnose OSA, which it's an upper airway obstruction (due to pharyngeal muscle relaxation during sleep) causes progressive hypoxia and hypercapnia until chemoreceptors in the carotid body and brainstem trigger arousal (by the production of catecholamines), which restores pharyngeal tone.

OHS

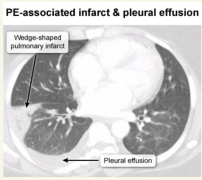
Diagnostic criteria	• Obesity with BMI ≥30 kg/m^2 • Awake daytime hypercapnia ($PaCO_2$ >45 mm Hg) • No alternate cause of hypoventilation
Workup	• ABG on room air (hypercapnia, normal A-a gradient) • No intrinsic pulmonary disease on chest x-ray • Restrictive pattern on PFTs • Normal TSH • Polysomnography
Treatment	• Nocturnal positive pressure ventilation as first-line therapy • Weight loss (bariatric surgery in select cases) • Avoidance of sedative medications • Respiratory stimulants (eg, acetazolamide) as last resort

Patients with combined OHS and OSA can develop chronic hypoxia and hypercapnia (with a compensatory metabolic alkalosis), secondary erythrocytosis, pulmonary hypertension, and cor pulmonale.

In obesity hypoventilation syndrome (OHS), there are several mechanisms likely contribute to hypoventilation and resultant hypercapnia. Obesity reduces chest wall and lung compliance, leading to a decrease in tidal volumes and total lung capacity and an increase in airway resistance. As a result, higher levels of ventilatory drive are required to maintain normocapnia, but there is an inability to exhale excess CO2 during the day (due to persistent restriction). This leads to CO2 accumulation overnight, with subsequent chronic respiratory acidosis. Renal bicarbonate excretion is decreased as a compensatory mechanism; this blunts the ventilatory response to the increased CO2 and contributes to hypoventilation. In sum, patients with OHS "can't breathe" (due to excess weight and altered lung mechanics) and "won't breathe" (due to decreased chemosensitivity to hypercapnia from persistent nocturnal hypoventilation). Arterial blood gas will show hypercapnia, hypoxemia, and respiratory acidosis.

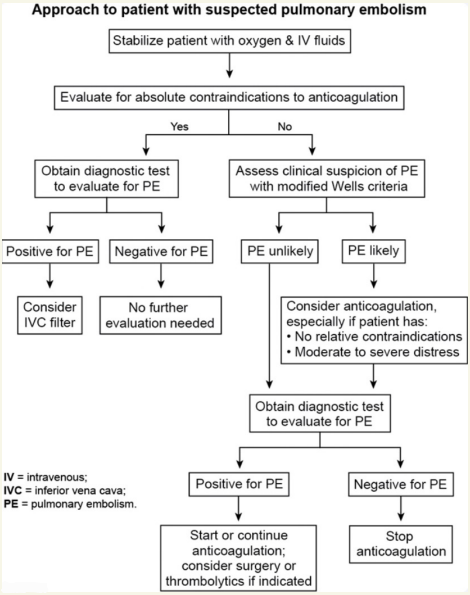
Study PE in Cardiology, page 31

PE



The manifestations of pulmonary embolism (PE) are nonspecific and variable. Acute-onset dyspnea and pleuritic chest pain are the most common symptoms, occurring in 73% and 66% of patients, respectively. Hemoptysis occurs in <20% and symptoms of deep venous thrombosis (DVT) in <30%. There are physical examination findings consistent with PE, including tachypnea (~55%), tachycardia, hypoxemia, low-grade fever (~5%), and jugular venous distension (~15%). Bilateral wheezing can occur in acute PE due to cytokine-induced bronchoconstriction in response to hypoxia and infarction. The classic findings of PE on ECG include: prominent S in lead I, Q in lead III, and inverted T in lead III [S1Q3T3].

Atrial fibrillation (A-Fib) is commonly associated with PE and may result from PE-induced right atrial dilation or increased sympathetic tone. In some cases, the atrial fibrillation may be the cause (rather than result) of PE due to embolization of thrombus from the right atrial appendage into the pulmonary circulation. Hypoxemia and atrial fibrillation are both associated with poor prognosis in PE.



Patients with massive PE usually present with signs of low arterial perfusion (eg, hypotension, syncope) and acute dyspnea, pleuritic chest pain, and tachycardia. The thrombus increases pulmonary vascular resistance and right ventricular pressure, causing right ventricular hypokinesis and dilation and hypotension.

It may be difficult to differentiate PE from RV myocardial infarction (RVMI), which can also cause RV dysfunction; however, RVMI is less likely to cause dyspnea or syncope and more likely to cause bradycardia or arrhythmias.

Lower extremity venous ultrasound is used to diagnose lower extremity DVT. However, a negative result does not rule out acute PE in a patient with high clinical suspicion.

Early and effective anticoagulation decreases mortality risk of acute PE from 30% to ~2%-8%.

Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) results from intimal hyperplasia of the pulmonary arteries and typically presents with progressive dyspnea. It can also cause chest tightness and wheezing due to stretching of the pulmonary vessels and lung mechanoreceptors. It most frequently affects young adult women and often masquerades as asthma for many years prior to diagnosis. However, PAH is associated with a low DLCO value (decreased distal lung perfusion) and does not cause airflow obstruction. It is common in systemic sclerosis (SS) especially in the limited cutaneous subtype, which commonly affect African American patients.

Classification	Pulmonary arterial hypertension (WHO group 1) Due to left heart disease (group 2) Due to chronic lung disease or hypoxemia (eg, COPD, OSA) (group 3) Due to chronic thromboembolic disease (group 4) Due to other causes (eg, sarcoidosis) (group 5)
Symptoms	↓ Cardiac output: exertional syncope/presyncope, fatigue, weakness ↑ PA pressure: chest tightness, hemoptysis (rare) RV demand ischemia: exertional angina/tightness Venous congestion: abdominal distension (bowel edema), early satiety
Signs	Precordial heave due to RV hypertrophy Loud P2, right-sided S3 &/or S4 Holosystolic murmur of tricuspid regurgitation JVD, ascites, peripheral edema, hepatomegaly

- Systemic venous congestion: Poor RV function leads to elevated right atrial pressure and central venous pressure, producing abdominal distension, early satiety (due to GI edema), ascites, congestive hepatopathy, and oliguria (ie, cardiorenal syndrome).

- Limited cardiac output: Because of the obstructive physiology and RV dysfunction, cardiac output cannot be sufficiently increased, leading to exertional fatigue. Patients are also especially susceptible to presyncope or syncope due to diminished venous return; furthermore, right atrial dilation predisposes to mechanoreceptor-induced reflex vagal bradycardia (eg, defecation, cough, tying shoes).

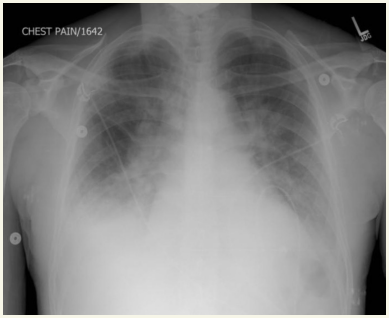
Management of pulmonary hypertension	
Group 1PAH	• Evaluate for autoimmune CTD, toxins (eg, amphetamines), HIV, schistosomiasis, etc. • Pulmonary vasodilator therapy, treat underlying (eg, autoimmune) cause
Group 2 Left-sidedheart disease	• Echocardiography (± RHC if diagnosis unclear) • Optimize left ventricular function (eg, heart failure therapy), treat significant valve disease
Group 3 Lung disease &/orchronic hypoxemia	• Pulmonary function tests, chest imaging, polysomnography • Treat underlying respiratory condition (eg, obstructive sleep apnea)
Group 4CTEPH	• V/Q scan, pulmonary angiography • Pulmonary thromboendarterectomy surgery (curative), anticoagulation
Generalmeasures	• Refer to accredited PH center • Maintain normoxia, euvolemia & sinus rhythm • Contraceptive counseling, immunization, cardiac rehabilitation • Refractory PH: bilateral lung transplant

CTD = connective tissue disease (eg, scleroderma); **CTEPH** = chronic thromboembolic pulmonary hypertension; **PAH** = pulmonary arterial hypertension; **PH** = pulmonary hypertension; **RHC** = right-sided heart catheterization; **V/Q** = ventilation-perfusion.

Pulmonary hypertension is also a serious complication of sickle cell disease (SCD). It involves chronic intravascular hemolysis, causing pulmonary vascular remodeling. Symptoms include exertional dyspnea and signs of right-sided heart failure (eg, hepatomegaly, edema). DLCO is low due to loss of the vascular bed.

Diffuse Alveolar Hemorrhage

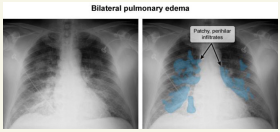
Diffuse airspace opacification	
Definition: Alveolar filling processes that can involve multiple lobes	
Fluid	Transudative edema: cardiogenic Exudative edema: noncardiogenic (ARDS)
Cells	Neutrophils (pus): infectious pneumonia Lymphocytes & macrophages: hypersensitivity pneumonitis Eosinophils: acute eosinophilic pneumonia Malignant cells: carcinomatosis
Blood	Diffuse alveolar hemorrhage Aspirated nonalveolar hemorrhage
Others	Fat: lipoid pneumonia (eg, vaping oils) Protein: pulmonary alveolar proteinosis



Diffuse alveolar hemorrhage	
Etiology & pathogenesis	• Pulmonary capillaritis: ANCA vasculitis, SLE, antiphospholipid antibodies • Bland hemorrhage: mitral stenosis, anticoagulation • Alveolar damage: viral pneumonitis, ARDS, drug-induced (eg, cocaine, amiodarone)
Clinical presentation & diagnosis	• Dyspnea, hypoxemia, hemoptysis (absent in ~50%) & blood loss anemia • CXR or CT: diffuse ground-glass opacities • Bronchoscopy: progressive blood on serial lavage
Management	• Treat underlying (eg, rheumatologic, infectious) cause • Supportive care: oxygen, mechanical ventilation; avoid anticoagulation

In diffuse pulmonary or alveolar hemorrhage (eg, pulmonary vasculitis), an abnormal increase in hemoglobin within the alveolar space increases carbon monoxide transfer, resulting in increased DLCO.

Because the bleeding occurs deep in the lungs, hemoptysis may be absent in half of the patients.

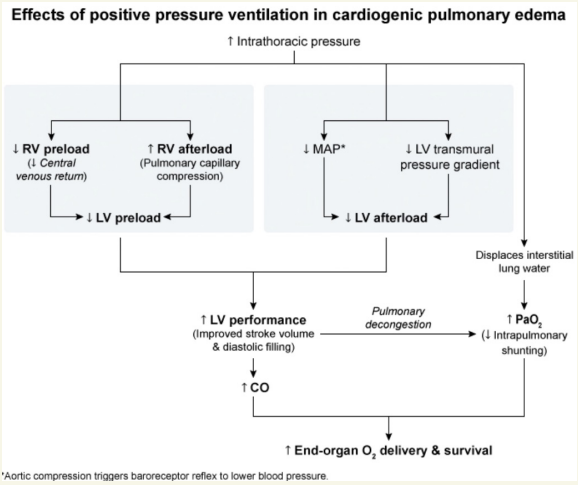


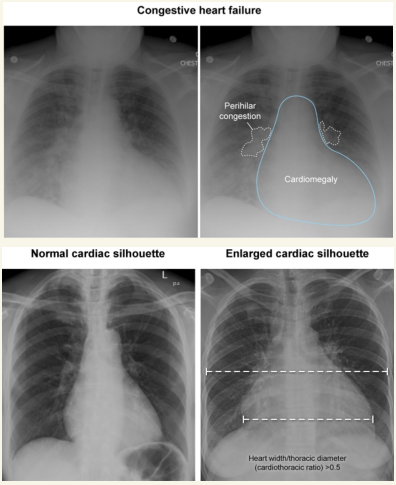
Pulmonary Edema

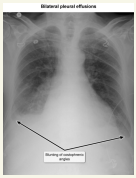
Pulmonary venous congestion from fluid overload can cause dyspnea and hypoxia. However, jugular venous distension (and possibly peripheral edema) is typical, and chest x-ray would reveal peribronchial thickening; prominent pulmonary vascular markings; and patchy, perihilar opacities.

Congestive heart failure exacerbation can cause tachypnea as left ventricular dysfunction allows fluid to pool in the lungs, causing a pleural effusion and hypoxemia due to reduced ventilation. Tachypnea causes hypocapnia and respiratory alkalosis. Examination typically shows signs of fluid overload, S3 and S4 gallops, cardiomegaly, and bibasilar crackles in the lungs. More specific testing for CHF would include assessment of the B-type natriuretic peptide (BNP) and the pulmonary capillary wedge pressure.

Positive pressure ventilation (PPV) is a mainstay lifesaving treatment for acute cardiogenic pulmonary edema. PPV lowers left ventricle (LV) preload and afterload to promote LV diastolic filling and systolic ejection, decreasing pulmonary congestion and enhancing oxygen delivery.







Pleural Effusion

Pleural effusions are divided into transudates and exudates.
Transudative effusions are due to an imbalance between hydrostatic and oncotic pressures that increases fluid movement across the capillaries into the visceral pleura and pleural space. They requires no further intervention except for treatment directed at the underlying disease.
Exudative effusions are due to pleural and lung inflammation resulting in increased capillary and pleural membrane permeability.

Common causes of pleural effusions	
Transudate	**Exudate**
• Congestive heart failure • Cirrhosis • Nephrotic syndrome • Peritoneal dialysis	• Infections • Malignancy • Connective tissue diseases • Inflammatory disorders • Movement of fluid from abdomen to pleural space • Coronary artery bypass surgery • Pulmonary embolism (usually)

Exudative effusions require more extensive diagnostic investigation.
The Light criteria define an exudate as having at least one of the following:

- Pleural fluid protein/serum protein ratio >0.5
- Pleural fluid lactate dehydrogenase (LDH)/serum LDH ratio >0.6
- Pleural fluid LDH >2/3 of the upper limit of normal for serum LDH

Low pleural glucose indicates an exudative pleural effusion. Pleural fluid glucose <60 mg/dL or pleural fluid/serum glucose ratio <0.5 is usually due to rheumatoid pleurisy, complicated parapneumonic effusion or empyema, malignant effusion, tuberculous pleurisy, lupus pleuritis, or esophageal rupture. (Pleural glucose <30 mg/dL in particular suggests an empyema or rheumatic effusion). Glucose concentration in empyema is decreased due to the high metabolic activity of leukocytes (and/or bacteria) in the fluid. Transudates and all other exudative effusions usually have pleural fluid glucose similar to blood glucose concentration.

*Extremely high yield for USMLE!!!

* Undiagnosed pleural effusion is best evaluated with thoracentesis, except in patients with clear-cut evidence of congestive heart failure, where a trial of a diuretic is warranted.

Pleural fluid analysis provides decision-making information in 90% of cases. If a diagnostic thoracentesis shows exudative pleural fluid, further diagnostic investigations are indicated. Lung carcinoma, breast carcinoma, and lymphoma are the three tumors that cause approximately 75% of all malignant pleural effusions.

Increased capillary hydrostatic pressure is the mechanism responsible for transudative pleural effusions.

Inflammatory conditions cause pleural effusions by increasing the pleural membrane and capillary permeability.

Increased permeability of the right hemidiaphragm leads to right-sided pleural effusions in cirrhosis, also known as a hepatic hydrothorax. Effusions due to cirrhosis are typically transudates.

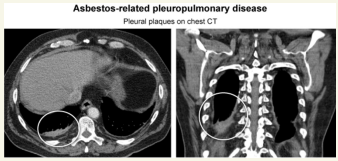
Elevated pleural amylase concentrations are found in pleural effusions due to esophageal rupture or pancreatitis.

PE can cause pleural effusions (typically small, exudative, and bloody).

Congestive heart failure commonly causes transudative effusions (bilateral 61%, unilateral right-sided 27%, and unilateral left-sided 12%).

Normal pleural fluid pH is approximately 7.60.
Transudative fluid is usually due to systemic factors (eg, increased hydrostatic pressure or hypoalbuminemia) and has a pleural fluid pH of 7.4-7.55.
Exudate is usually due to inflammation with a pleural fluid pH of 7.30-7.45.
Pleural fluid pH <7.30 (with normal arterial pH and low pleural glucose) is usually due to increased acid production by pleural fluid cells and bacteria (eg, empyema) or decreased hydrogen ion efflux from the pleural space (eg, pleuritis, tumor, pleural fibrosis).

Pneumoconioses



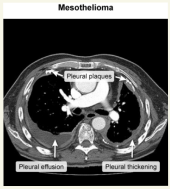
- Asbestosis (shipbuilding, mining, roofing/insulation, plumbing/pipe-work)
- Silicosis (sandblasting)
- Coal-workers' pneumoconioses (black lung disease)
- Berylliosis (beryllium in aerospace and manufacturing industries)

Asbestos is from the roof, but affects the base (lower lobes).
Silica, coal, and berries are from the base (earth), but affect the roof (upper lobes).

Clinical features of asbestosis	
Clinical presentation	• Prolonged asbestos exposure (eg, shipyard, mining) • Symptoms develop ≥20 years after initial exposure • Progressive dyspnea, basilar fine crackles, clubbing • Increased risk for lung cancer & mesothelioma
Diagnostic evaluation	• Pleural plaques on chest imaging • Imaging, PFT & histology consistent with pulmonary fibrosis

Asbestos exposure alone (without smoking) increases the risk of lung cancer by almost 6-fold. Smoking adds a synergistic effect, and smokers with asbestos exposure have an almost 59-fold increased risk of bronchogenic carcinoma. Asbestosis is the only known risk factor for malignant pleural mesothelioma, but bronchogenic carcinoma is more common in patients with asbestos exposure, especially smokers. Pleural plaques are consistent with asbestosis but do not necessarily suggest mesothelioma.

Mesothelioma



Mesothelioma is a malignant neoplasm derived from the mesothelial lining of the thoracic cavity. It is strongly linked to asbestos exposure (tobacco smoking is not a risk factor) and usually presents with cough, chest pain, and dyspnea.
Chest imaging typically reveals unilateral pleural thickening with a large effusion.

Bronchogenic Carcinoma

Lung CA is a leading cause of cancer death. Presented with cough, hemoptysis, bronchial obstruction, wheezing, and pneumonic “coin” lesion on CXR or noncalcified nodule on CT. In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.

SPHERE of complications: Superior vena cava/ thoracic outlet syndromes, Pancoast tumor, Horner syndrome, Endocrine (paraneoplastic), Recurrent laryngeal nerve compression (hoarseness), Effusions (pleural or pericardial).

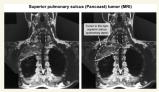
Risk factors include tobacco smoking, secondhand smoke, radiation, environmental exposures (eg, radon, asbestos), pulmonary fibrosis, family history.

Lung cancer			
Tumor type	**Incidence**	**Location**	**Clinical associations**
Adenocarcinoma	40%-50%	Peripheral	• Clubbing • Hypertrophic osteoarthropathy
Squamous cell carcinoma	20%-25%	Central	• Hypercalcemia • Necrosis & cavitation
Small cell carcinoma	10%-15%	Central	• Cushing syndrome • SIADH • Lambert-Eaton syndrome
Large cell carcinoma	5%-10%	Peripheral	• Gynecomastia • Galactorrhea

Smoking is the single greatest risk factor for lung cancer in all patient populations. However, ~50% of women who develop lung cancer have no history of smoking. The most common type of lung cancer in never-smokers is adenocarcinoma, which typically arises in the lung periphery. Patients frequently have chest pain or pleural effusion (eg, dyspnea) due to erosion of the tumor into surrounding structures. Hemoptysis and cough also frequently occur, particularly as the tumor grows.

Bronchial carcinoid tumors account for 1%-2% of total lung malignancies. However, they are the leading cause of lung cancer in adolescents and young adults (particularly in those who do not smoke). These tumors are typically slow-growing.

Bronchial carcinoid tumor	
Epidemiology	• Most common lung cancer in adolescents/young adults • Neuroendocrine tumor derived from bronchial Kulchitsky cells
Manifestations	• Proximal airway obstruction (eg, dyspnea, wheezing, cough) • Recurrent pneumonia distal to obstruction • Hemoptysis • Carcinoid syndrome less common than with midgut carcinoid
Diagnosis	• Chest imaging: contrast enhanced (vascular) tumor with endobronchial component • Bronchoscopy with biopsy



Pancoast tumor (superior sulcus tumor): carcinoma that occurs in the apex of lung may cause Pancoast syndrome by invading/compressing local structures. Compression of locoregional structures may cause array of findings:

- Recurrent laryngeal nerve; hoarseness
- Stellate ganglion; Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)
- Superior vena cava (SVC) syndrome
- Brachiocephalic vein; brachiocephalic syndrome (unilateral symptoms)
- Brachial plexus; shoulder pain, sensorimotor deficits (eg, atrophy of intrinsic muscles of the hand)
- Phrenic nerve; hemidiaphragm paralysis (hemidiaphragm elevation on CXR)

Recommendations for lung cancer screening	
Recommendedtest	• Low-dose CT scan of the chest
Recommended interval	• Yearly
Age forscreening	• 50-80
Eligibility	• ≥20-pack-year history**&** • Currently smoking or quit smoking within the past15 years
Termination of screening	• Patient successfully quit smoking for ≥15 years**OR** • Patient has medical conditions that significantly limit life expectancy

Patients with Hodgkin lymphoma who are treated with chemotherapy and radiation are at high risk for secondary malignancy later in life (generally >10 years after therapy). Solid tumors in the lung (especially in smokers), breast, and gastrointestinal system (eg, colorectal, esophageal, gastric tumors) are most common.

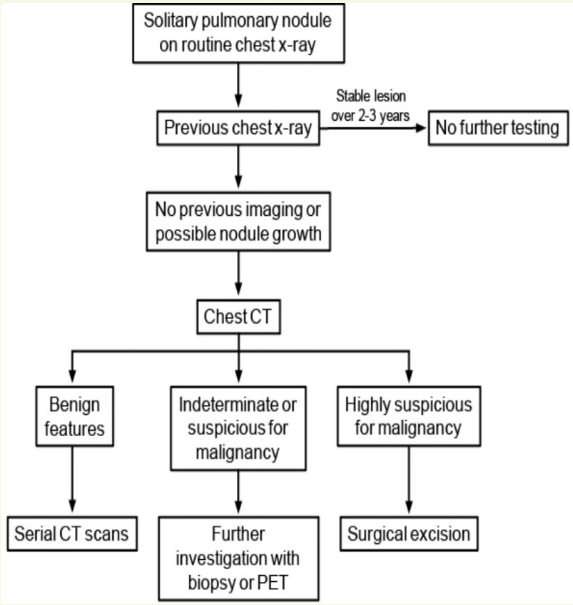
Solitary Pulmonary Nodule

Solitary Pulmonary Nodule (SPN) is defined as a round opacity up to 3 cm in diameter within and surrounded by pulmonary parenchyma. By convention, there must be no associated pleural effusion, adenopathy, or atelectasis. SPN is often discovered incidentally on chest x-ray. Evaluation of a solitary pulmonary nodule detected on chest x-ray includes comparison with old imaging studies, if available, followed usually by chest computed tomography.

The decision to observe, biopsy, or surgically resect the nodule is based on its size and characteristics as well as the patient's age and smoking history. Nodules <0.8 cm with smooth margins are less likely to be malignant; large nodule size, low density, spiculated borders, and eccentric calcification favor carcinoma. Other clinical characteristics suggesting malignancy include age >40, history of smoking, weight loss, and previous malignancy. Nodules with high overall risk for malignancy should be excised. Ground-glass lesions have a higher malignancy risk and likely require yearly assessment, even with stable appearance and size.

Lesions that appear less likely to be malignant on CT scans can be followed with serial CT scans for 2 to 3 years to monitor for growth.

Bronchoscopy is best for biopsy of centrally located lesions, and CT-guided percutaneous biopsy (more sensitive) is best for peripheral lesions.



Causes of solitary pulmonary nodules	
Primary lung cancer	Squamous cell, adenocarcinoma, small cell, large cell & carcinoid
Metastatic cancer	Melanoma, breast, head, neck, renal cell, colon, germ cell & sarcoma
Benign infectious granulomas	Tuberculosis, histoplasmosis, atypical mycobacteria, coccidioidomycosis, *Cryptococcus* & blastomycosis
Benign neoplasms	Lipoma, hamartoma & fibroma
Vascular	Arteriovenous malformations

Assessment of malignancy risk for solitary pulmonary nodule			
Variable	**Low risk**	**Intermediate risk**	**High risk**
Nodule size (cm)	<0.8	0.8-2.0	≥2.0
Age (yr)	<40	40-60	>60
Smoking status	Never smoked	Current	Current
Smoking cessation (yr)	>15	5-15	<5
Nodule margin characteristics	Smooth	Scalloped	Corona radiata or spiculated

Acute Bronchitis

Etiology	• Preceding respiratory illness (90% viral)
Clinical presentation	• Cough for >5 days to 3 weeks (± purulent sputum) • Absent systemic findings (eg, fever, chills) • Wheezing or rhonchi, chest wall tenderness
Diagnosis & treatment	• Clinical diagnosis, CXR only when pneumonia suspected • Symptomatic treatment (eg, NSAIDs &/or bronchodilators) • Antibiotics **not** recommended

Acute bronchitis is a self-limited infection that can last for 3-4 weeks.
Cough lasting >5 days is characteristic of acute bronchitis, and a viral URI is the usual cause. Sputum production occurs in roughly half of patients; the typical yellow/purulent sputum is due to epithelial sloughing and is not a sign of bacterial infection. Small amounts of blood in the sputum can occur due to inflammation and epithelial damage. Mild dyspnea and chest wall discomfort are common, and physical examination often shows wheezing as well as crackles that clear with cough, suggesting that secretions are easily mobilized (unlike in pneumonia).

Fever is not typical and, when present, should raise suspicion for bacterial pneumonia or influenza.

Pneumonia

Pneumonia is classified as follows:

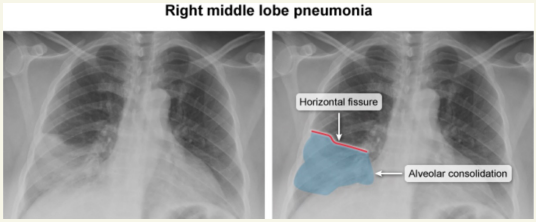
- Community-acquired (CAP)– develops in a nonhospitalized setting
- Hospital-acquired (HAP)– develops ≥48 hours after admission to the hospital
- Ventilator-acquired (VAP)– develops ≥48 hours after endotracheal intubation

The most common cause of CAP is Streptococcus pneumoniae. This organism is acquired by aerosol inhalation and colonizes the nasopharynx. Most patients remain asymptomatic and clear the inoculation within 4-6 weeks. However, those with aggressive serotypes or certain underlying risk factors (eg, age >65, immunosuppression) are more likely to develop invasive disease (eg, pneumonia, meningitis, endocarditis).

Pseudomonas aeruginosa is a common cause of HAP but a rare cause of CAP. Patients with immunocompromise or structural lung disease (eg, cystic fibrosis) can sometimes develop P aeruginosa in the community setting.

Clinical and physical findings are notoriously poor at predicting the presence of pneumonia (<50% sensitivity). Therefore, the diagnosis of CAP requires the presence of a lobar, interstitial, or cavitary infiltrate on chest imaging (eg, chest x-ray). Sputum and blood cultures are typically not required in the outpatient setting as empiric oral antibiotics are almost always curative.

Risk factors for community-acquired pneumonia	
Impaired immunity	• Age >65 • HIV • Diabetes mellitus
Impaired pulmonary function	• Chronic obstructive pulmonary disease • Bronchiectasis/cystic fibrosis • Recent upper respiratory viral infection • Smoking
Increased microaspiration	• Substance/alcohol use disorder • Seizure disorder or stroke • Esophageal dysmotility
Medications	• Acid suppressants • Sedatives • Immunomodulatory agents



Common causes of recurrent pneumonia	
Samelung lobe*	**Bronchial obstruction** • Extrinsic: neoplasm, adenopathy • Intrinsic: bronchiectasis, foreign body **Recurrent aspiration** • Altered consciousness: seizure, sedatives, antipsychotics, alcohol, illicit drugs • Dysphagia: neurologic disorder, esophageal motility issue • Poor dental hygiene • Gastroesophageal reflux
Differentlung lobes	• Immunodeficiency: HIV, leukemia, CVID • Sinopulmonary disease: cystic fibrosis, immotile cilia • Noninfectious: vasculitis, BOOP
*Recurrent aspiration can lead to pneumonia in different dependent regions of the lung depending on the position of the patient during the aspiration event. **BOOP** = bronchiolitis obliterans with organizing pneumonia; **CVID** = common variable immunodeficiency.	

Aspiration pneumonia usually present several days after the aspiration event. Most patients have foul-smelling sputum and symptoms that progress over 1-2 weeks. Aspiration typically introduces microbes into the dependent portions of the lungs (m/c right lobe). Aspiration events that occur while the patient is upright usually affect the lower lobes, and those that occur when the patient is recumbent (eg, bed-bound) usually affect the superior portions of the lower lobes or posterior portions of the upper lobes. Therefore, recurrent aspiration pneumonia may occur in the same lobe or different lobes depending on the position of the patient during aspiration.
Although aspiration pneumonia was previously thought to frequently involve anaerobic bacteria, more recent data indicate that anaerobes are present in a small minority of cases. Therefore, empiric treatment is geared towards aerobic upper respiratory organisms; when no empyema or lung abscess are present, treatment of aspiration pneumonia is the same as for community-acquired pneumonia (eg, ceftriaxone plus azithromycin).

Atypical antipsychotic medications (eg, quetiapine) increase the risk of CAP in elderly patients. Although the exact mechanism is unclear, it may be due to anticholinergic and antihistamine effects of the drug, which cause oropharyngeal dryness and reduce the ability to form a food bolus, increasing the risk of aspiration.

The major cause of death in patients with advanced Parkinson disease is bacterial aspiration pneumonia. Therefore, swallow evaluation is required as the disease progresses; those with swallowing impairment can alter food consistency or eating position to reduce the risk of aspiration pneumonia.



Cryptogenic organizing pneumonia

(formerly called bronchiolitis obliterans organizing pneumonia (BOOP)) causes dry cough and systemic symptoms that last for months. Cross-sectional chest imaging usually demonstrates ground-glass infiltrates (typically bilateral). Noninfectious; responds to glucocorticoids.

Atypical pneumonia (indolent fever, malaise, and cough) is most commonly caused by mycoplasma pneumoniae and frequently results in the formation of cold agglutinins (not routinely used for diagnosis). However, M pneumoniae is less likely to cause focal findings on lung examination, can be accompanied by extrapulmonary (eg, GI) manifestations, and usually causes indolent rather than acute symptoms.

Influenza pneumonia (viral) symptoms commonly take 2 weeks to resolve.

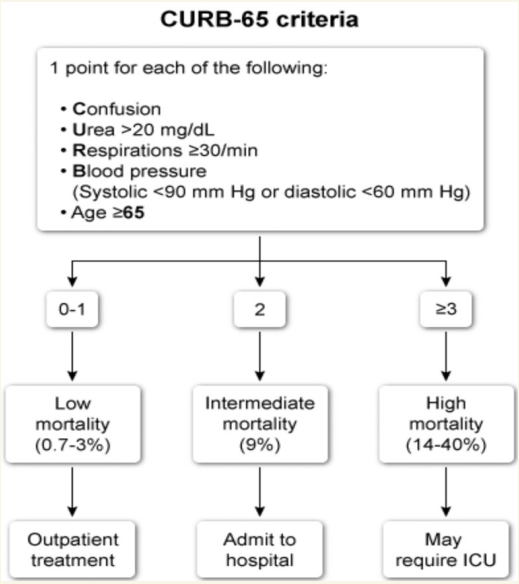
Patients with community-acquired pneumonia usually have a pulmonary infiltrate on initial chest x-ray. However, those who are immunosuppressed may have normal pulmonary imaging despite signs and symptoms that localize the infection to the lungs. These patients should undergo additional pulmonary imaging with high-resolution CT scan of the chest to identify pulmonary infiltrate. Immunosuppressed patients are susceptible to pneumonia due to typical organisms (eg, Streptococcus pneumoniae) as well as opportunistic organisms (eg, Pneumocystis jiroveci).

Pneumocystis pneumonia is a common opportunistic infection characterized by dyspnea, nonproductive cough, fever, and (usually) bilateral, diffuse, interstitial infiltrates on chest imaging. It is a common cause of dyspnea in patients with HIV/AIDS. However, it typically occurs in patients with CD4+ counts <200/mm3 and tends to be subacute in presentation. Imaging commonly shows a diffuse interstitial pattern.

Cytomegalovirus is a common opportunistic infection that may cause pneumonitis marked by dyspnea, nonproductive cough, low-grade fever, and (usually) patchy or diffuse ground-glass opacities on CT scan.

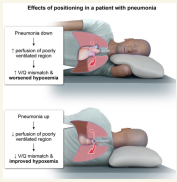
Histoplasma capsulatum is a common endemic mycosis in the temperate areas world-wide. Infections are usually subclinical in immunocompetent hosts; however, patients with high-dose exposure may have subacute pulmonary illness with bilateral infiltrates and hilar lymphadenopathy. Manifestations usually begin 2-4 weeks after exposure with subacute fever, chills, malaise, headache, myalgia, and dry cough. X-ray typically reveals mediastinal or hilar lymphadenopathy with focal, reticulonodular, or miliary infiltrates (depending on the degree of exposure). Diagnosis is usually made with Histoplasma antigen testing of the urine or blood. Some patients may require tissue diagnosis, which often reveals granulomas with narrow-based budding yeasts. Most cases resolve completely over weeks without intervention. For those with moderate/severe disease, oral itraconazole or IV liposomal amphotericin B can be administered.

For inpatients, sputum culture and blood culture should be sent to attempt to identify the organism and empiric treatment with a beta-lactam plus macrolide (eg, ceftriaxone + azithromycin) should be initiated. Although fluoroquinolones (eg, levofloxacin) that target respiratory tract organisms can also be used for CAP in the inpatient setting, this class of medication is generally avoided (when possible) in elderly patients due to increased risk of Clostridium difficile infection, tendon rupture, and aortic dissection.



Community-acquired pneumonia	
Setting	**Recommended therapy**
Outpatient	• Healthy patients ◦ Amoxicillin or doxycycline • Comorbid conditions (eg, diabetes, malignancy) ◦ Fluoroquinolone or beta-lactam + macrolide
Inpatient(non-ICU)	• Fluoroquinolone **OR** • Beta-lactam + macrolide
Inpatient(ICU)	• Beta-lactam + macrolide **OR** • Beta-lactam + fluoroquinolone

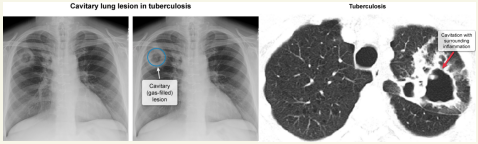
Alveolar consolidation in pneumonia causes hypoxemia due to ventilation-perfusion (V/Q) mismatch from localized intrapulmonary shunting. Positional changes that promote gravity-dependent blood distribution to the consolidated areas create a more profound V/Q mismatch and worsen the hypoxemia.
For this reason, patients with unilateral lung airspace diseas
(eg, pneumonia) often prefer to lie on the contralateral side (ie, trepopnea).



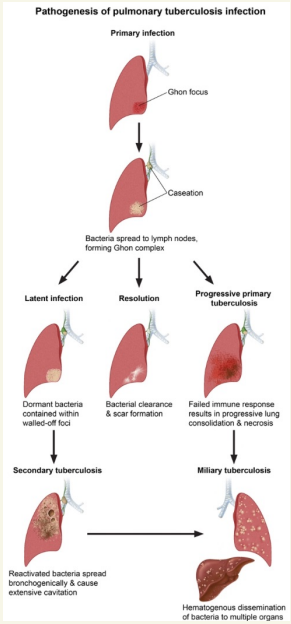
Lung abscess

Lung abscess is a localized collection of pus within parenchyma. Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [eg, alcohol overuse, epilepsy]) or bronchial obstruction (eg, cancer).
Air-fluid levels often seen on CXR; presence suggests cavitation. Due to anaerobes (eg, Bacteroides) or S aureus.
Treatment: antibiotics, drainage, or surgery.

TB



Primary pulmonary tuberculosis	
Risk factors	• Immunosuppression (eg, HIV) • Travel from endemic area • Exposure to infected household contact • Resident/employee of prison, homeless shelter, health care facility
Clinicalmanifestations	• Chronic cough • Prolonged fever • Weight loss, failure to thrive
Diagnosis	• Positive screening PPD or interferon-γ release assay • Chest x-ray: hilar adenopathy, effusion, consolidation, cavitation • Positive AFB smear & mycobacterial culture
Treatment	• Multidrug therapy: isoniazid, rifampin, pyrazinamide, ethambutol
AFB = acid-fast bacilli; **PPD** = purified protein derivative.	



Most patients first exposed to TB have asymptomatic primary infection because the organism is rapidly contained within granulomas and can become "latent" if the body fails to clear the bacteria; they are at risk of secondary (reactivation) TB later in life. In contrast, ~10% of adults first exposed to TB develop symptomatic primary disease ("progressive primary TB"); risk factors for primary progression include impaired immunity due to comorbid conditions (eg, diabetes mellitus, renal disease, HIV), advanced age, or immunosuppressive medications, particularly when treatment for common pulmonary diseases (eg, pneumonia) does not improve symptoms. Compression of the right middle lobe (multiple surrounding lymph nodes, relatively longer length) and pleural effusions may also occur.

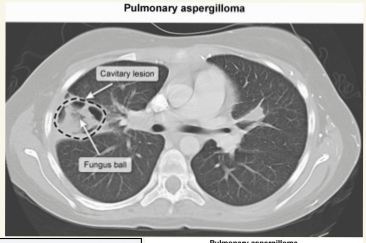
Reactivation of latent TB typically causes an apical cavitary lesion seen on the chest x-ray. Generally, patients report chronic low-grade fever as well as night sweats and weight loss; a cough productive of blood-tinged sputum is classic, but its absence does not exclude TB.

Most cases of active tuberculosis in the United States occur in foreign-born individuals who have recently emigrated from endemic areas (especially Mexico, the Philippines, China, Vietnam, India, Dominican Republic, and Haiti), with the highest rates for those arriving in the last 5 years.

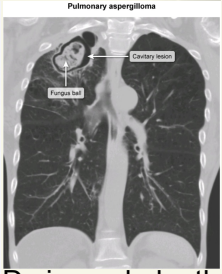
Reactivation TB can cause nodules or cavitary lesions in the lung apex that may be colonized by Aspergillus species, creating an aspergilloma.

Although autoimmune adrenalitis is the most common etiology of primary adrenal insufficiency (PAI), disseminated chronic infection (eg, tuberculosis, histoplasmosis) can also cause the disorder. PAI is a potential complication of miliary tuberculosis. Signs and symptoms of aldosterone deficiency (eg, hypovolemia, hyperkalemia) are present in PAI and can help differentiate PAI from secondary adrenal insufficiency. Antituberculous therapy rarely improves adrenal function, as the infection often causes irreversible destruction.

Aspergillosis



	Invasive aspergillosis	Chronic pulmonary aspergillosis*
Risk factors	• Immunocompromise (neutropenia, glucocorticoids, HIV)	• Lung disease/damage (cavitary tuberculosis)
Manifestations	• Triad of fever, chest pain, hemoptysis • Pulmonary nodules with halo sign • Positive cultures • Positive cell wall biomarkers (galactomannan, β-D-glucan)	• >3 months: weight loss (>90%), cough, hemoptysis, fatigue • Cavity lesion ± fungus ball • Positive *Aspergillus* IgG serology
Management	• Voriconazole ± caspofungin	• Resect aspergilloma (if possible) • Azole medication (voriconazole) • Embolization (if severe hemoptysis)
∗Simple aspergilloma (fungus ball in preexisting lung cavity) is a form of chronic pulmonary aspergillosis but is usually quiescent with occasional hemoptysis.		



Dx is made by the presence of all 3 of the following

Diagnostic testing includes serum biomarkers for cell wall components (eg, galactomannan assay) and sputum stain/culture. However, sensitivity is low; and bronchoscopy with bronchoalveolar lavage (BAL) and biopsy are required if noninvasive testing (eg, sputum stain/culture) is inconclusive. Patients are treated with 1-2 weeks of IV voriconazole + an echinocandin (eg, caspofungin) and then transitioned to prolonged therapy with oral voriconazole alone. The mortality rate is >50%.

Anaphylaxis

Triggers	• Food (eg, nuts, shellfish) • Medications (eg, β-lactam antibiotics) • Insect stings
Clinicalmanifestations	• Cardiovascular ◦ Vasodilation → hypotension & tissue edema ◦ Tachycardia • Respiratory ◦ Upper airway edema → stridor & hoarseness ◦ Bronchospasm → wheezing • Cutaneous ◦ Urticarial rash, pruritus, flushing • Gastrointestinal ◦ Nausea, vomiting, abdominal pain

Management of anaphylaxis	
Immediate management	Epinephrine (most important): ◦ IM preferred, may be repeated (eg, 3 doses) ◦ IV in severe/refractory cases IV crystalloid & Trendelenburg positioning for hypotension Albuterol for bronchospasm Early intubation for upper airway obstruction
Adjunct management	H_1/H_2 antihistamines Glucocorticoids Glucagon for patients on beta blockers (reversal) Hospital admission for severe initial presentation (eg, shock) or ongoing symptoms despite treatment

Diagnosing anaphylaxis may be challenging in patients with confounding conditions (eg, asthma), nonclassic presentations (eg, protracted symptoms), or ongoing physiologic shifts (eg, childbirth, dialysis).
Intramuscular (IM) epinephrine is the most important step in management of anaphylaxis. It can be repeated every 5-15-minutes (up to 3 doses) if symptoms persist. Epinephrine is not initially administered intravenously (IV) due to higher risk for dosing errors and cardiac complications (eg, arrhythmias).

Diagnostic criteria for anaphylaxis	
Anaphylaxis is likely if there is rapid symptom onset & any 1 of the following criteria:	
1	Skin/mucosa involvement (eg, hives, lip/tongue swelling) & either hypotension or respiratory distress
2	Involvement of ≥2 organ systems after exposure to a likely allergen • Skin/mucosa (eg, hives, lip/tongue swelling) • Respiratory (eg, wheezing, stridor, dyspnea) • Cardiovascular (eg, hypotension, tachycardia, syncope) • Gastrointestinal (eg, abdominal pain, vomiting, diarrhea)
3	Hypotension after exposure to a known allergen

Study SIADH in Endocrinology, page 9

SIADH

Pulmonary pathology (e.g., small cell lung cancer) may lead to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which is characterized by hypotonic hyponatremia in a euvolemic patient. Infusion of normal saline may worsen hyponatremia in patients with SIADH. So, fluid restriction is the initial treatment of choice in asymptomatic or mildly symptomatic patients.

Myasthenic Crisis

Precipitatingfactors	• Infection or surgery • Pregnancy or childbirth • Tapering of immunosuppressive drugs • Medications (eg, aminoglycosides, beta blockers)
Signs/symptoms	• ↑ Generalized & oropharyngeal weakness • Respiratory insufficiency/dyspnea
Treatment	• Intubation for deteriorating respiratory status • Plasmapheresis or IVIG as well as corticosteroids

Pyridostigmine (acetylcholinesterase inhibitor) is sometimes used to treat mild myasthenia gravis exacerbations, but it is not effective for severe crises with respiratory impairment. Due to the potential for increased secretions (increased cholinergic activity), it is typically discontinued in patients with impending respiratory failure.

Study sarcoidosis in Nephrology, page 21 & Cardiology, page 13

Sarcoidosis



It typically occurs in young adults, is 3-4 times more common in African Americans, and affects more women than men. It is frequently detected incidentally on chest x-ray, and bilateral hilar adenopathy is the first manifestation of disease in 50% of patients. Additionally, there are reticular opacities in the upper zone and increased ACE and Ca2+ levels. Bronchoscopy with transbronchial biopsy is often performed to obtain tissue diagnosis. If there is evidence of systemic involvement, more accessible sites such as peripheral lymph nodes or cutaneous lesions can be biopsied. Patients with incidental bilateral hilar adenopathy are typically monitored without biopsy unless symptoms develop.

Diseases associated with erythema nodosum (EN) include streptococcal infection, sarcoidosis, tuberculosis (TB), endemic fungal disease (eg, histoplasmosis), inflammatory bowel disease (IBD), and Behçet disease.
Even in the absence of respiratory symptoms, chest x-ray should be performed in patients with EN to assess for findings consistent with sarcoidosis.

Goodpasture Syndrome

Anti–glomerular basement membrane disease (previously Goodpasture syndrome) affects the lungs (causing cough, dyspnea, and hemoptysis) and kidneys (causing nephritic range proteinuria, acute renal failure, and dysmorphic red cells/red cell casts on urinalysis). Systemic symptoms are uncommon. Diagnosis is made by renal biopsy showing linear IgG antibodies along the glomerular basement membrane. The underlying cause is formation of antibodies to the alpha-3 chain of type IV collagen, a protein expressed most strongly in the glomerular and alveolar basement membranes.

Study Granulomatosis with Polyangitis in Rheumatology, page 15

Wegener granulomatosis

Necrotizing pulmonary vasculitis occurs in granulomatosis with polyangiitis [GPA] (formerly Wegener granulomatosis). It commonly includes the following:

- Upper respiratory tract (most common site of involvement):

Chronic rhinosinusitis, nasal ulcers, saddle nose deformity, hearing loss

- Lower respiratory tract:

Tracheal narrowing with ulceration (highly characteristic of GPA), lung nodules with cavitation, fibrotic interstitial lung disease, alveolar opacities and hemorrhage

- Kidneys:

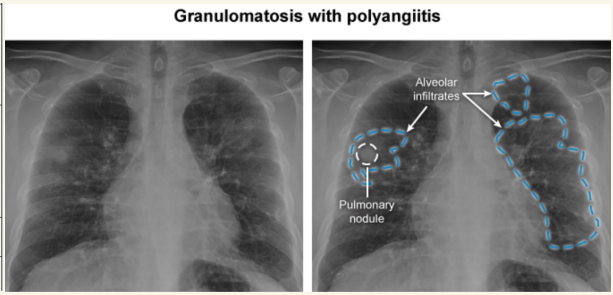
Elevated creatinine (85% of cases)

Patients also commonly have fever, weight loss, and anemia of chronic disease.

Pulmonary nodules and alveolar consolidation are typical findings on chest x-ray. Diagnosis of GPA is made with antineutrophil cytoplasmic antibody (ANCA) testing and definitively with tissue biopsy showing capillaritis or granulomatous inflammation.

Clinical manifestations	• Upper respiratory: sinusitis/otitis, saddle nose • Lower respiratory: lung nodules/cavitation, interstitial lung disease, diffuse alveolar hemorrhage • Renal: rapidly progressive GN • Skin: livedo reticularis, nonhealing ulcers
Diagnosis	• ANCA: PR3 (~70%), MPO (~20%) • Biopsy: ◦ Skin (leukocytoclastic vasculitis) ◦ Kidney (pauci-immune GN) ◦ Lung (granulomatous vasculitis)
Management	• Corticosteroids & immunomodulators (eg, cyclophosphamide)

ANCA = antineutrophil cytoplasmic antibody; **GN** = glomerulonephritis; **MPO** = myeloperoxidase; **PR3** = proteinase-3.



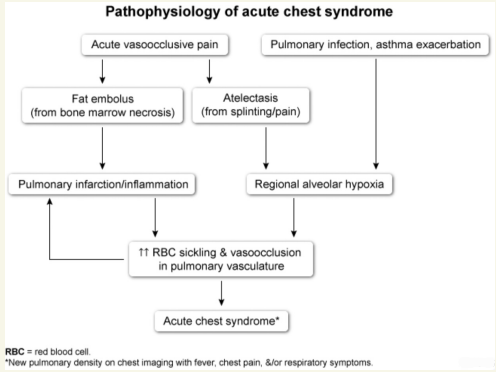
Acute Chest Syndrome

Acute chest syndrome (ACS) is a potentially fatal vasoocclusive complication of sickle cell disease that presents with a new pulmonary infiltrate in addition to fever, hypoxia, or respiratory symptoms. Management includes antibiotics (eg, ceftriaxone and azithromycin) because pneumonia is clinically indistinguishable from ACS and may be the underlying trigger. ACS is most common in children but can occur at any age, with the highest mortality rate in adults.

Splinting from pain and/or opioid therapy (eg, constricted pupils) can lead to hypoventilation and atelectasis.

Thrombocytopenia is often seen with fat embolism.

Pathogenesis	• Vasoocclusion of pulmonary vasculature • Most commonly triggered by fat embolus (usually adults) or infection (usually children)
Diagnostic criteria	• New pulmonary infiltrate on chest x-ray PLUS ≥1 of the following: ◦ Increased work of breathing, cough, tachypnea, or wheezing ◦ Temperature >38.5 C (101.3 F) ◦ Hypoxemia ◦ Chest pain
Initial treatment	• Ceftriaxone & azithromycin • Intravenous fluids • Pain control



Initial treatment of ACS includes intravenous fluids because dehydration can exacerbate sickling, and analgesics (eg, opioids, nonsteroidal anti-inflammatory drugs) for pain control.
Because pneumonia cannot be differentiated from ACS, prompt antibiotic therapy is also required. Empiric coverage for CAP includes ceftriaxone and azithromycin, which target typical (eg, Streptococcus pneumoniae, Haemophilus influenzae) and atypical (eg, Mycoplasma, Chlamydia) bacteria, respectively.



Step 2

& Relevant Clinical Step 1

Gastroenterology

تَذكَّر:

إنَّ الطِّبَّ وسِيلةٌ.. لا غايَةٌ!

Contact & Updates:

Ehab Alroud

Oropharyngeal Candidiasis

Patients with Sjögren syndrome have immune-mediated destruction of the exocrine glands of the eyes and mouth. Most patients struggle with mouth dryness, which leads to difficulty forming a food bolus. Lack of salivary function also dramatically increases the risk for dental caries and chronic atrophic candidiasis.

In contrast to pseudomembranous oropharyngeal candidiasis, which is marked by fluffy white exudates, patients with chronic atrophic candidiasis typically have diffuse or patchy erythema with no white exudate; the hard palate is primarily affected, but lesions can occur on the gums or buccal mucosa. Common symptoms include a painful, burning sensation and sensitivity to acidic or spicy foods.

The diagnosis can be confirmed using potassium hydroxide (KOH) preparation of an oral scraping, which shows budding yeasts with or without hyphae. Treatment with 7-10 days of topical or systemic antifungal therapy is required to eliminate the infection, but recurrences are common, particularly after antibiotic or glucocorticoid administration.

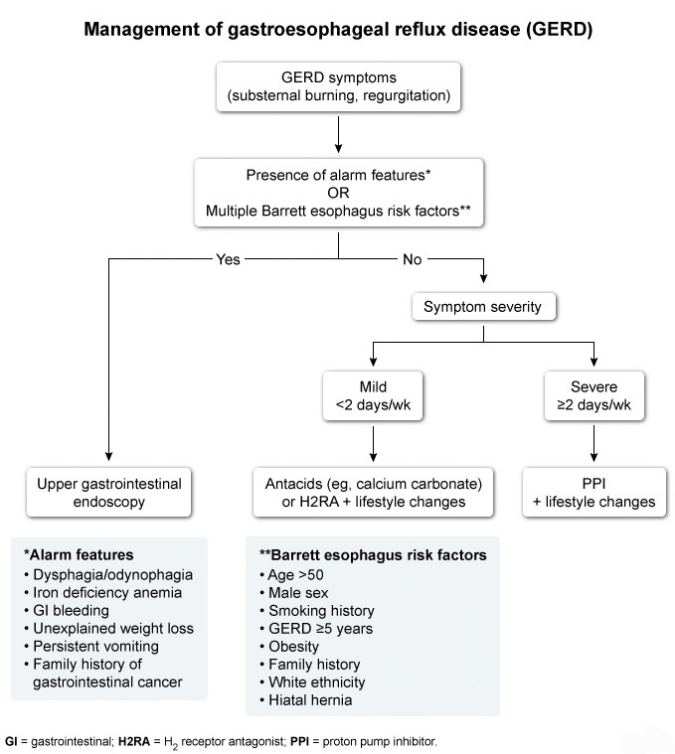
Esophagitis

Inflammation of esophageal mucosa. Presents with odynophagia and/or dysphagia. Types:

- Reflux (erosive) esophagitis—most common type. 2° to GERD.
- Eosinophilic esophagitis—chronic, immune-mediated, eosinophil-predominant. Associated with atopic disorders (eg, asthma). Esophageal rings and linear furrows on endoscopy.
- Infectious esophagitis—Candida (most common; white pseudomembranes), HSV-1 (punched-out ulcers), CMV (linear ulcers). Associated with immunosuppression.
- Corrosive esophagitis—2° to caustic ingestion.
- Medication-induced esophagitis—

Medication-induced esophagitis	
Drug class	Drug
Antibiotics	Tetracyclines
Anti-inflammatory agents	Aspirin & many nonsteroidal anti-inflammatory drugs
Bisphosphonates	Alendronate, risedronate
Others	Potassium chloride, iron

GERD



Transient decreases in LES tone. Commonly presents as heartburn, regurgitation, dysphagia. May also present as chronic cough, hoarseness (laryngopharyngeal reflux). Associated with asthma.

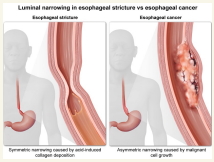
Complications include: erosive esophagitis, strictures, and Barrett esophagus (specialized intestinal metaplasia that increases the risk for esophageal adenocarcinoma). Therefore, patients with GERD & IDA should undergo upper gastrointestinal endoscopy, even if fecal occult blood testing is negative (given its low sensitivity for detecting upper GI bleeding).

Esophageal Cancer

Typically presents with progressive dysphagia (first solids, then liquids) and weight loss. Aggressive course due to lack of serosa in esophageal wall, allowing rapid extension. Poor prognosis due to advanced disease at presentation.

CANCER	PART OF ESOPHAGUS AFFECTED	RISK FACTORS	PREVALENCE
Squamous cell carcinoma	Upper 2/3	Alcohol, hot liquids, caustic strictures, smoking, achalasia, nitrosamine-rich foods	More common worldwide
Adenocarcinoma	Lower 1/3	Chronic GERD, Barrett esophagus, obesity, tobacco smoking	More common in America

Esophageal stricture



Esophageal stricture is a complication of chronic gastroesophageal reflux disease (GERD) and is caused by reparative collagen deposition in response to acid damage. At onset, patients have progressive dysphagia to solids but not liquids. Endoscopic findings include concentric, symmetric narrowing of the distal esophagus.

Plummer-Vinson syndrome: Triad of dysphagia, IDA, and esophageal webs. It may be also associated with glossitis. Additionally, it increases the risk of esophageal SCC.

Mallory-Weiss syndrome: Partial thickness, longitudinal lacerations of gastroesophageal junction, confined to mucosa/ submucosa, due to severe vomiting. It is often presents with hematemesis +/– abdominal/back pain, and usually found in patients with alcohol use disorder, or bulimia nervosa.

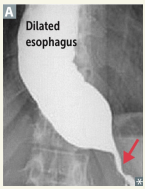
Diffuse Esophageal Spasm



Distal esophageal spasm is known to be precipitated by emotional stress.

Pathophysiology	• Uncoordinated, simultaneouscontractions of esophageal body
Symptoms	• Intermittent **chest pain** • **Dysphagia** for solids & liquids
Diagnosis	• Manometry: Intermittent peristalsis,multiple **simultaneous contractions** • Esophagram: "**Corkscrew**" pattern
Treatment	• Calcium channel blockers • Alternates: Nitrates or tricyclics

Achalasia



Failure of LES to relax due to degeneration of inhibitory neurons (containing NO and VIP) in the myenteric (Auerbach) plexus of esophageal wall.

1° idiopathic. 2° from Chagas disease (T cruzi infection) or extraesophageal malignancies (mass effect or paraneoplastic). Chagas disease can cause achalasia.

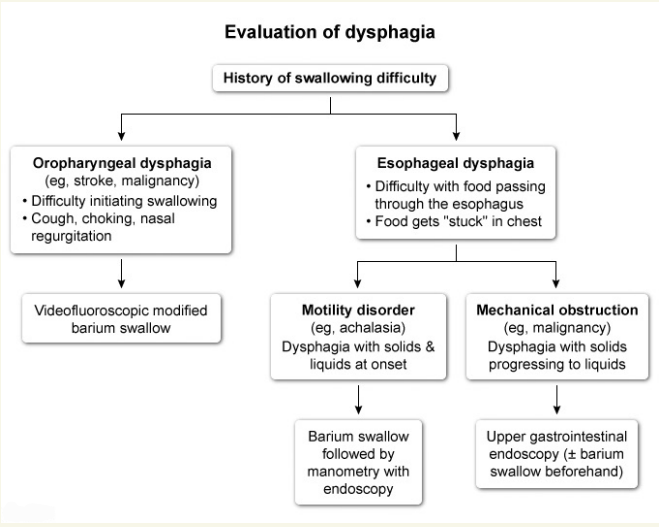
Presents with progressive dysphagia to solids and liquids (vs obstruction—primarily solids). Associated with risk of esophageal cancer.

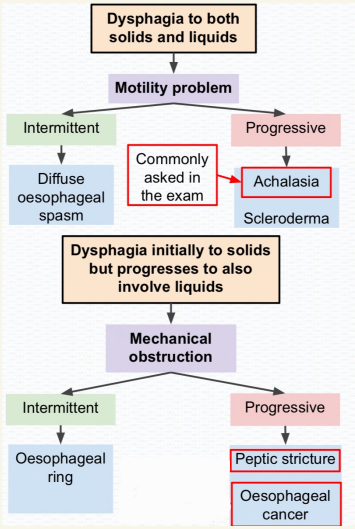
Manometry findings include uncoordinated or absent peristalsis with increase LES resting pressure.

Barium swallow shows dilated esophagus with area of distal stenosis (“bird’s beak”).

Treatment: surgery, endoscopic procedures (eg, botulinum toxin injection).
Myotomy is a recommended treatment for idiopathic achalasia for patients at low surgical risk. In contrast, calcium channel blocker therapy is much less effective and is considered for patients who want to avoid invasive procedures. These treatments should be considered only after malignancy is excluded and achalasia is confirmed with manometry.

Pseudoachalasia results from a malignancy near the lower esophageal sphincter (eg, esophageal cancer) and can mimic idiopathic achalasia in clinical presentation and barium swallow study findings. Therefore, patients with suspected achalasia should undergo upper gastrointestinal endoscopy to rule out malignancy.





Gastric Cancer

Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoid (rare). It has an early aggressive local spread with liver/ node metastases, most commonly to Virchow node (left supraclavicular node).
Often presents late, with WEAPON (**W**eight loss, **E**arly satiety, **A**bdominal Pain, **O**bstruction, and in some cases acanthosis **N**igricans or Leser-Trélat sign).

It has two main types:

- Intestinal—associated with H pylori, dietary nitrosamines (smoked foods common in East Asian countries), tobacco smoking, achlorhydria, chronic gastritis.
Commonly on lesser curvature; looks like ulcer with raised margins.

- Diffuse—not associated with H pylori; most cases due to E-cadherin mutation; (signet ring cells seen [mucin-filled cells with peripheral nuclei]); and stomach wall grossly thickened and leathery (linitis plastica).

Gastritis

Acute erosive gastropathy is characterized by the development of hemorrhagic lesions after ischemia or the exposure of gastric mucosa to various injurious agents (eg, alcohol, cocaine, aspirin). Patients typically present with acute abdominal pain and hematemesis.

Chronic gastritis is characterised by mucosal inflammation, often leading to atrophy (hypochlorhydria hypergastrinemia) and intestinal metaplasia (risk of gastric cancers), caused by H pylori (most common), leading to peptic ulcer disease (PUD) & MALT lymphoma. Additionally, it could be autoimmune due to autoantibodies (T-cell induced) to the H+/K+-ATPase on parietal cells and to intrinsic factor, leading to pernicious anemia.

Stress ulceration is common in patients in the intensive care unit and can cause occult or gross gastrointestinal bleeding. Risk factors include shock, sepsis, coagulopathy, mechanical ventilation, traumatic spinal cord/brain injury, burns, and high-dose corticosteroids.

Dyspepsia	
Symptoms	• Epigastric pain or burning • Postprandial fullness, early satiety, bloating • ≥1 months
Etiology	• Functional/idiopathic (75%) • Malignancy (eg, gastric, esophageal) • Peptic ulcer (eg, *Helicobacter pylori* infection, NSAIDs) • Drug-induced (eg, NSAIDs, bisphosphonate)
Work-up	• Low malignancy risk (eg, age <60 & no alarm symptoms*) ◦ Testing & treatment for *H pylori* • High malignancy risk (eg, age >60 or alarm symptoms) ▫ Gastroenterology referral/upper endoscopy
Treatment	• Treatment of underlying cause • Trial of proton pump inhibitor if no cause found
*GI bleeding, weight loss, iron deficiency anemia, lymphadenopathy, dysphagia, odynophagia, persistent vomiting, palpable mass, family history of upper GI cancer.	

PUD



Peptic Ulcer Disease

	Gastric ulcer	Duodenal ulcer
PAIN	Can be greater with meals—weight loss	Decreases with meals—weight gain
H PYLORI INFECTION	~ 70%	~ 90%
MECHANISM	↓ mucosal protection against gastric acid	↓ mucosal protection or ↑ gastric acid secretion
OTHER CAUSES	NSAIDs	Zollinger-Ellison syndrome
RISK OF CARCINOMA	↑ Biopsy margins to rule out malignancy	Generally benign Not routinely biopsied

Biopsy of the gastric antrum during endoscopy can confirm infection. In a patient without occult bleeding, noninvasive diagnostic testing, including stool antigen studies & urea breath testing, can be employed. Serology cannot distinguish between active & cleared infection and is not preferred.

Perforated viscus is primarily a clinical diagnosis; however, confirmation can often be made quickly via demonstration of subdiaphragmatic free air

NSAID avoidance and oral proton pump inhibitors are part of uncomplicated PUD management. In contrast, this patient has signs (eg, fever, peritonitis) concerning for complicated PUD (eg, perforation) and should remain NPO while awaiting radiologic confirmation of the diagnosis and/or definitive management.

endoscopy is contraindicated if acute gastrointestinal perforation is suspected because air insufflation and instrumentation may worsen the perforation.

Management of DU due to H pylori requires the following:

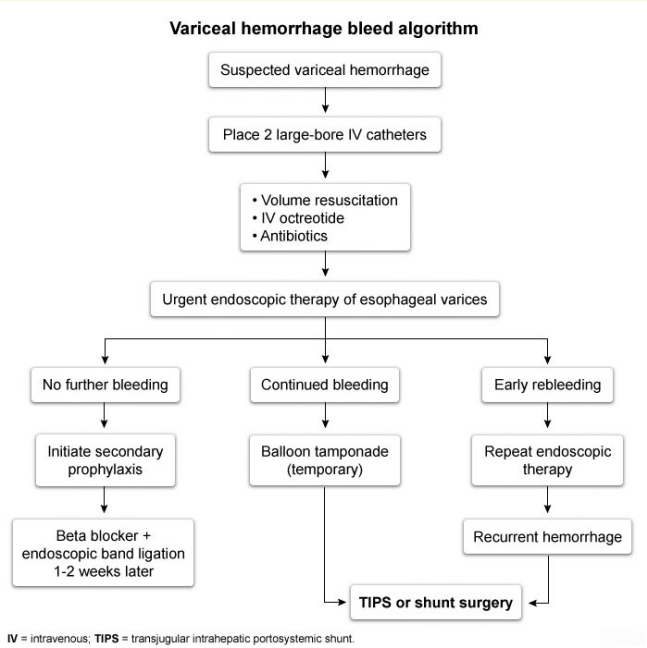
- Antisecretory therapy, preferably a proton pump inhibitor (PPI) (eg, omeprazole, pantoprazole), and
- Antibiotic eradication (eg, amoxicillin plus clarithromycin)

Compared to antisecretory therapy with antibiotic eradication, antisecretory therapy alone leads to reduced healing rates and a higher risk of recurrent ulcer in patients with H pylori-associated DU. Antisecretory therapy without antibiotics would be recommended for DU attributable to causes other than H pylori.

Unlike cobalamin deficiency, folate deficiency is associated with normal methylmalonic acid levels and no neurologic manifestations. Unlike cobalamin (vitamin B12), body stores of folate are minimal, and deficiency occurs quickly if dietary intake wanes. This is rare in developed countries due to the fortification of flour with folic acid; however, patients with severe alcohol use and poor nutrition may become deficient in as little as 5-6 weeks.

Upper GI bleeding

Patients with upper (but not lower) GI bleeding often have an elevated blood urea nitrogen (BUN) and elevated BUN/creatinine ratio. Possible causes include increased urea production from intestinal breakdown of hemoglobin and increased urea reabsorption in the proximal tubule due to associated hypovolemia.



Patients with upper gastrointestinal bleeding who have a depressed level of consciousness and ongoing hematemesis should be intubated to protect the airway as a part of initial stabilization and resuscitation. Prompt endoscopic treatment with ligation or sclerotherapy should then be performed to stop the bleeding.

In general, stable patients without significant comorbid conditions should receive PRBC transfusion for hemoglobin <7 g/dL. A higher threshold of hemoglobin <9 g/dL can be considered for patients with acute coronary syndrome.

Nonselective beta blockers (eg, nadolol, propranolol, carvedilol) are used in patients with esophageal varices to prevent variceal growth and risk of bleeding (ie, primary prophylaxis). These medications reduce portal pressure largely by promoting splanchnic vasoconstriction and decreasing cardiac output.

Octreotide (a somatostatin analogue) helps treat actively bleeding varices by decreasing portal pressure via inhibition of vasodilator release (which promotes splanchnic vasoconstriction). However, this effect on portal pressure is only transient (ie, hours) due to tachyphylaxis, making octreotide ineffective for long-term prevention of variceal bleeding.

Although endoscopic sclerotherapy (ie, injection of a scar-inducing solution) can treat actively bleeding varices, it is not recommended for nonbleeding varices because the risks (eg, transmural wall injury) outweigh the benefits for primary prophylaxis.

Acute Liver Failure

Acute liver failure	
Etiology	• Viral hepatitis (eg, HSV; CMV; hepatitis A, B, D, E) • Drug toxicity (eg, acetaminophen overdose, idiosyncratic) • Ischemia (eg, shock liver, Budd-Chiari syndrome) • Autoimmune hepatitis • Wilson disease • Malignant infiltration
Clinical presentation	• Generalized symptoms (eg, fatigue, lethargy, anorexia, nausea) • Right upper quadrant abdominal pain • Pruritus & jaundice due to hyperbilirubinemia • Renal insufficiency • Thrombocytopenia • Hypoglycemia
Diagnostic requirements	• Severe acute liver injury (ALT & AST often >1,000 U/L) • Signs of hepatic encephalopathy (eg, confusion, asterixis) • Synthetic liver dysfunction (INR ≥1.5)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; HSV = herpes simplex virus; INR = international normalized ratio.

Acute liver failure is defined as acute onset of severe liver injury with encephalopathy and impaired synthetic function (defined as INR ≥1.5) in a patient without cirrhosis or underlying liver disease. Drug toxicity and acute viral hepatitis are the most common causes. In the presence of HBV, acute superinfection with hepatitis D virus carries a high risk of ALF development, particularly in intravenous drug users.

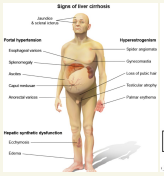
The presence of hepatic encephalopathy differentiates ALF from acute hepatitis, which has a much better prognosis than ALF.

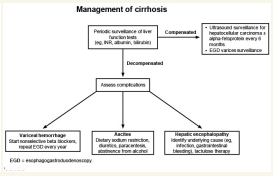
Approximately only half of patients with ALF will survive without liver transplant. Cerebral edema is a potential complication of ALF that may lead to coma and brain stem herniation, and is the most common cause of death.

In ALF due to acetaminophen toxicity, liver transplantation is firmly indicated in patients with grade III or IV hepatic encephalopathy, PT >100 seconds, and serum creatinine >3.4 mg/dL.

One-year survival following liver transplantation for ALF is approximately 80%.

Cirrhosis + Ascites





Overview of cirrhosis management	
Treat underlyingliver disease -_	• HCV, HBV: antiviral therapy • NASH: weight loss
Providepreventive care	• Avoid alcohol & hepatotoxic medications • Vaccinate for HAV & HBV (unless already immune)
Managecomplications	• Screen for esophageal varices (endoscopy) • Screen for HCC: ultrasound ± serum AFP every 6-12 months • Frequent clinical assessment for ascites and encephalopathy (prophylactic treatment not recommended)

Hepatic encephalopathy	
Precipitating factors	• Drugs (eg, sedatives, narcotics) • Hypovolemia (eg, diarrhea) • Electrolyte changes (eg, hypokalemia) • ↑ Nitrogen load (eg, GI bleeding) • Infection (eg, pneumonia, UTI, SBP) • Portosystemic shunting (eg, TIPS)
Clinical presentation	• Sleep pattern changes • Altered mental status • Ataxia • Asterixis
Treatment	• Correct precipitating causes (eg, fluids, antibiotics) • ↓ Blood ammonia concentration (eg, lactulose, rifaximin)

Management includes sodium restriction as well as spironolactone and furosemide, which improve both ascitic fluid retention and peripheral edema. These medications are usually used concurrently to increase the efficacy of natriuresis and prevent electrolyte disturbances. Alcohol abstinence is also important since cessation improves portal hypertension and decreases ascites. Large-volume paracentesis or transjugular intrahepatic portosystemic shunt may be required for refractory ascites.

Patients with cirrhosis have low mean arterial pressure due to splanchnic vasodilation and are dependent on the renin-angiotensin-aldosterone system to help normalize blood pressure and renal perfusion. ACE inhibitors (eg, lisinopril) and angiotensin receptor blockers blunt this critical response and promote organ hypoperfusion in this group. These medications should be avoided in patients with cirrhosis

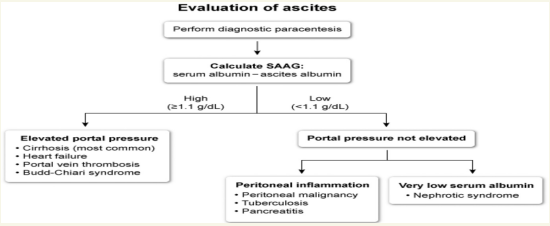
Hepatic hydrothorax generally results in transudative pleural effusions and is thought to occur due to small defects in the diaphragm. These defects permit peritoneal fluid to pass into the pleural space, which occurs much more commonly on the right side due to the less muscular hemidiaphragm. Patients have dyspnea, cough, pleuritic chest pain, and hypoxemia. Diagnosis involves documentation of the effusion (eg, chest x-ray) and testing to exclude other causes (eg, thoracentesis, echocardiogram).

SBP

Common and potentially fatal bacterial infection in patients with cirrhosis and ascites. Often asymptomatic.

Spontaneous bacterial peritonitis	
Clinical presentation	• Temperature ≥37.8 C (100 F) • Abdominal pain/tenderness • Altered mental status (abnormal connect-the-numbers test) • Hypotension, hypothermia, paralytic ileus with severe infection
Diagnosis from ascitic fluid	• PMNs ≥250/mm3 • Positive culture, often gram-negative organisms (eg, Escherichia coli, Klebsiella) • Protein <1 g/dL • SAAG ≥1.1 g/dL
Treatment	• Empiric antibiotics - third-generation cephalosporins (eg, cefotaxime) • Fluoroquinolones for SBP prophylaxis
PMN = polymorphonuclear leukocytes; SAAG = serum-ascites albumin gradient; SBP = spontaneous bacterial peritonitis.	

Lymphocyte predominance indicates malignancy or tuberculosis; neutrophil predominance (ie, ≥250/mm3) suggests spontaneous bacterial peritonitis.



Ascitic fluid characteristics	
Gross appearance	• Typically straw-colored & clear • Bloody: suggests trauma or malignancy • Cloudy: suggests infection • Milky: suggests lymphatic disruption (chylous)
Serum-to-ascitesalbumin gradient (SAAG)	◦ ≥1.1 g/dL indicates portal HTN ◦ Causes include cirrhosis, heart failure ◦ <1.1 g/dL indicates no portal HTN ◦ Causes include malignancy, TB, nephrotic syndrome
Total protein	• <2.5 g/dL is consistent with cirrhosis or nephrotic syndrome
Cell count	• ≥250 neutrophils/mm3 is diagnostic of SBP

Autoimmune Hepatitis

ALT & AST > 1000 U/L

Chronic inflammatory liver disease. More common in females. May be asymptomatic or present with fatigue, nausea, pruritus. Often ⊕ for anti-smooth muscle or anti-liver/kidney microsomal-1 antibodies. Labs: ALT and AST. Histology: portal and periportal lymphoplasmacytic infiltrate.

* large gamma gap (total protein − albumin = >4 g/dL).

* Transaminases are generally >1,000 U/L and would be expected to normalize after 3 months.

* First-line treatment includes oral glucocorticoids.

* Sarcoidosis is a multisystemic, inflammatory granulomatous disease. Asymptomatic liver involvement (eg, abnormal LFTs, hepatomegaly) is common (~65%).

Ischemic Hepatits

ALT & AST > 1000 U/L

Ischemic hepatic injury occurs in the setting of severe hypotension (e.g., in ICU) and manifests as acute, massive increases (>1000 U/L) in the transaminases with milder associated increases in the total bilirubin and alkaline phosphatase. In patients who survive the inciting condition (eg, hypotension), liver enzymes typically return to normal within a few weeks (self-limited).

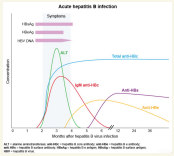
Tylenol-induced Hepatitis

ALT & AST > 1000 U/L

Paracetamol/ Acetaminophen (APAP, which is metabolised to a toxic metabolite called NAPQI, inactivated by glutathione) overdose of single acute ingestion of >75 mg/kg (over 1 hr or less) or a staggered overdose (multiple ingestion over more than 1 hr) can lead to ALF.
N-acetyl cysteine (NAC) is the antidote (activated charcoal can also used to prevent APAP absorption if presented within the first hour).

Viral Hepatitis

ALT & AST > 1000 U/L



There can be a time lag (weeks to months) between the disappearance of HBsAg and the appearance of anti-HBs, which is termed the window period. IgM anti-HBc may be the only detectable marker for acute hepatitis B infection during this period. As such, HBsAg and anti-HBc are the most appropriate diagnostic tests for acute hepatitis B infection as these are both elevated during initial infection and anti-HBc will remain elevated during the window period.

Chronic hepatitis B infection is defined by the presence of HBsAg in the serum for >6 months.

Although chronic HCV infection is often asymptomatic and may cause only mild elevations in aminotransferases, some infected individuals (~20%) develop cirrhosis. Laboratory findings suggestive of cirrhosis include thrombocytopenia, hypoalbuminemia, and coagulopathy (eg, elevated PT/INR). Liver biopsy showing extensive fibrosis and regenerative nodules can confirm the diagnosis if necessary.

	HBsAg	HBeAg	IgM anti-HBc	IgG anti-HBc	Anti-HBs	Anti-HBe	HBV DNA
Acute HBV							
Early phase	+	+	+				+++
Window phase			+				+
Recovery phase				+	+	+	Likely +
Chronic HBV carrier	+			+			
Acute flare of chronic HBV	+	Likely +	+	+			+
Vaccinated for HBV					+		
Immune due to natural HBV infection				+	+		

HAV has fecal-oral transmission, and outbreaks have been linked to contaminated water or food, as well as to overcrowded homeless shelters. Unvaccinated individuals are at increased risk, as are day care workers, homeless shelter residents, international travelers, and men who have sex with men.

Alcoholic Hepatitis

Clinical presentation	•Jaundice, anorexia, fever •Right upper quadrant &/or epigastric pain •Abdominal distension due to ascites •Proximal muscle weakness from muscle wasting if malnourished •Possible hepatic encephalopathy
Laboratory & imaging studies	•Elevated AST & ALT, usually <300 U/L •AST/ALT ratio ≥2 •Elevated GGT, bilirubin &/or INR , Ferritin •Leukocytosis, predominantly neutrophils •Decreased albumin if malnourished •Abdominal imaging may show fatty liver

Alcohol cessation significantly reduces liver inflammation, fibrosis, and portal pressure.

Nonalcoholic Fatty Liver Disease

Definition	• Hepatic steatosis on imaging or biopsy • Exclusion of other etiologies (eg, alcohol, hepatitis C,glucocorticoids)
Clinicalfeatures	• Mostly asymptomatic • Metabolic syndrome • AST/ALT ratio <1 • Hyperechoic texture on ultrasound examination
Treatment	• Weight loss (eg, diet modification, exercise) • Consider bariatric surgery if BMI ≥35 kg/m^2
Prognosis	• Hepatic fibrosis associated with increased riskfor cirrhosis & liver-related death

Nonalcoholic fatty liver disease (NAFLD) is associated with metabolic syndrome (obesity, insulin resistance, HTN, hypertriglyceridemia (fatty infiltration of hepatocytes, leading to cellular “ballooning” and eventual necrosis). Steatosis present without evidence of significant inflammation or fibrosis. May persist or even regress over time.

Nonalcoholic steatohepatitis (NASH) is associated with lobular inflammation and hepatocyte ballooning, and fibrosis. May progress to cirrhosis and HCC.

Management focuses on weight loss of 5%-10% of body weight, which can reduce hepatic fat content and reverse inflammatory damage and fibrosis.

Hereditary Hemochromatosis

Clinical manifestations	• Hyperpigmentation • Arthropathy • Hepatomegaly, cirrhosis, hepatocellular carcinoma • Diabetes mellitus • Hypopituitarism, secondary hypogonadism • Cardiomyopathy
Diagnosis	• Elevated liver transaminases • Elevated serum ferritin, transferrin saturation • HFE genetic mutations
Management	• Therapeutic phlebotomy (urgent if ferritin >1,000 ng/mL)

Arthropathy of hereditary hemochromatosis	
Clinical features	• Onset at age <40 • Chronic pain & bony swelling • Most common at 2nd & 3rd MCP joints • Occasional acute flare
X-ray signs	• Joint space narrowing • Chondrocalcinosis • Hook-shaped osteophytes at metacarpal heads
Management	• Oral analgesics (eg, acetaminophen, NSAIDs) • Therapeutic phlebotomy (to prevent other complications)

HH presents after age 40 when total body iron > 20 g; iron loss through menstruation slows progression in females.
Classic triad of cirrhosis, diabetes mellitus, skin pigmentation (“bronze diabetes”).

Patients with extreme hyperferritinemia (serum ferritin >1000 ng/mL) must not wait for genetic testing results before receiving urgent phlebotomy because they are at exceptionally high risk for immediate and irreversible end-organ damage (eg, cardiomyopathy, cirrhosis, arthritis, DM).

Wilson Disease

Wilson disease is characterized by the combination of liver disease and neuropsychiatric symptoms that present in patients age 5-35.
Liver dysfunction ranges from asymptomatic liver function abnormalities to cirrhosis.

Pathogenesis	• Autosomal recessive mutation of *ATP7B* → hepatic copper accumulation → leak from damaged hepatocytes → deposits in tissues (eg, basal ganglia, cornea)
Clinicalfindings	• Hepatic (acute liver failure, chronic hepatitis, cirrhosis) • Neurologic (parkinsonism, gait disturbance, dysarthria) • Psychiatric (depression, personality changes, psychosis)
Diagnosis	• ↓ Ceruloplasmin & ↑ urinary copper excretion • Kayser-Fleischer rings on slit-lamp examination • ↑ Copper content on liver biopsy
Treatment	• Chelators (eg, D-penicillamine, trientine) • Zinc (interferes with copper absorption)

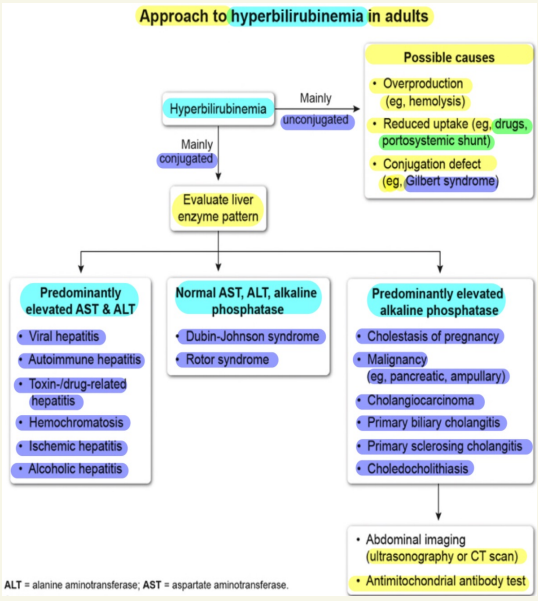


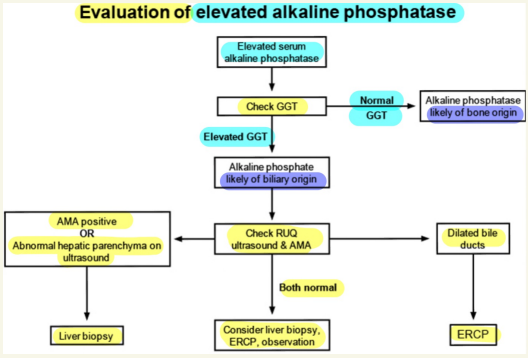
Alpha-1-Antitrypsin Deficiency

Alpha-1-antitrypsin deficiency (AATD) can result in obstructive lung disease (emphysema), liver dysfunction (eg, cirrhosis), and skin disease. It has a co-dominant trait.
Patients who smoke are at very high risk of early onset emphysema, but AATD often presents in young patients with liver damage and dyspnea without a history of tobacco smoking.

Gilbert Syndrome

Epidemiology	• Most common inherited disorder of bilirubin metabolism
Pathogenesis	• ↓ Hepatic UDP glucuronosyltransferase activity → ↓ conjugation of bilirubin
Clinical findings	• Recurrent episodes of mild jaundice • Provoked by stress (eg, febrile illness, fasting, dehydration, vigorous exercise, menstruation, surgery)
Diagnosis	• ↑ Unconjugated bilirubin (ie, indirect hyperbilirubinemia) • Normal CBC, blood smear, reticulocyte count • Normal AST, ALT, alkaline phosphatase
Treatment	• Benign; no treatment required

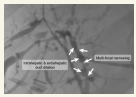




Acute Cholangitis

Etiology	• Ascending infection due to biliary obstruction
Clinicalpresentation	• Fever, jaundice, RUQ pain (Charcot triad) • ± Hypotension, AMS (Reynolds pentad)
Diagnosis	• Cholestatic liver function abnormalities ○ ↑ Direct bilirubin, alkaline phosphatase ○ Mildly ↑ aminotransferases • Biliary dilation on abdominal ultrasonography or CT scan
Treatment	• Antibiotic coverage of enteric bacteria • Biliary drainage by ERCP within 24–48 hr

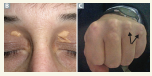
(PSC)



Clinical features	• Asymptomatic initially; fatigue & pruritus with progressive disease • Associated with IBD, particularly ulcerative colitis (٩٥٪)
Laboratory & imaging results	• Cholestasis (↑ ALP, GGT, bilirubin) intrahepatic & extrahepatic • Multifocal strictures/dilation of bile ducts on MRCP • Liver biopsy: onion-skin pattern fibrous obliteration
Complications	• Cholangitis, cholangiocarcinoma, colon cancer • Fat-soluble vitamin deficiencies, Osteoporosis

For Primary Sclerosing Cholangitis (PSC), MRCP is the imaging modality of choice due to its rapid, noninvasive nature; however, ERCP can be performed in patients who cannot undergo MRI (eg, those with metal implants).

PBC



Primary biliary cholangitis (PBC): Autoimmune reaction (lymphocytic infiltrate +/– granulomas — destruction of lobular (intahepatic) bile ducts. Classically in middle-aged females. Antimitochondrial antibody (AMA) ⊕, IgM. It is associated with other autoimmune conditions. A right upper quadrant ultrasound distinguishes intrahepatic (no biliary tract dilation) from extrahepatic (biliary tract dilation; eg, due to gallstones).

Pathogenesis	• Autoimmune intrahepatic bile duct destruction
Clinical features	• Women age 30–60 • Fatigue & pruritus → jaundice, hepatomegaly, cirrhosis • Xanthomas & xanthelasmas
Laboratory findings	• Cholestatic liver injury (↑↑ ALP, bilirubin) • Less prominent AST, ALT elevation • Antimitochondrial antibody • Severe hypercholesterolemia
Treatment	• Ursodeoxycholic acid (delays progression) • Liver transplant for advanced disease
Complications	• Fat-soluble vitamin malabsorption (A, D, E, K) • Metabolic bone disease (osteoporosis, osteomalacia) • Hepatocellular carcinoma

This hyperlipidemia is characterized by elevation of HDL out of proportion to LDL and does not appear to significantly increase the risk for atherosclerosis.

Despite its name, PBC is not associated with ascending cholangitis, which is a possible complication of extrahepatic biliary obstruction (eg, common bile duct stone) and typically presents acutely with Charcot triad (eg, fever, jaundice, right upper quadrant pain). Ascending cholangitis is associated with PSC.

Acute Pancreatitis

Acute pancreatitis	
Etiology	• Chronic alcohol use (~40%) • Gallstones (~40%) • Hypertriglyceridemia • Drugs (eg, azathioprine, valproic acid, thiazides) • Infection (eg, CMV, Legionella, Aspergillus) • Iatrogenic (post-ERCP, ischemic/ atheroembolic)
Clinical presentation	Diagnosis (requires 2 of the following) • Acute epigastric pain radiating to the back • Amylase or lipase >3× normal limit • Abnormalities on imaging consistent with pancreatitis Other findings • ALT level >150 U/L suggests biliary pancreatitis • Severe disease: fever, tachypnea, hypoxemia, hypotension

Most patients with acute pancreatitis have mild disease and recover with conservative management (eg, fluids, bowel rest, pain medication) in 3-5 days. However, nearly 15%-20% of patients can develop severe acute pancreatitis, defined as pancreatitis with failure of at least 1 organ. Clinical markers associated with increased risk for severe pancreatitis include age >75, alcoholism, obesity, C-reactive protein >150 mg/dL at 48 hours, and increased blood urea nitrogen (BUN)/ creatinine in the first 48 hours. Abdominal imaging (computed tomography scan or magnetic resonance cholangiopancreatography) is indicated for suspected severe pancreatitis to look for pancreatic necrosis and extrapancreatic inflammation, which also indicate severe acute pancreatitis. Severe pancreatitis causes local release of activated pancreatic enzymes that enter the vascular system and increase vascular permeability within and around the pancreas.

Idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune disease, Scorpion sting, Hypercalcemia/ Hypertriglyceridemia (> 1000 mg/dL), ERCP, Drugs

Complications: pancreatic pseudocyst (lined by granulation tissue, not epithelium), abscess, necrosis, hemorrhage, infection, organ failure (ALI/ ARDS, shock, renal failure), hypocalcemia (precipitation of Ca2+ soaps).

Analgesics	• Acetaminophen • Nonsteroidal anti-inflammatory drugs • Mesalamine, sulfasalazine • Opiates
Antibiotics	• Isoniazid • Tetracyclines • Metronidazole • Trimethoprim-sulfamethoxazole
Antiepileptics	• Valproic acid • Carbamazepine
Antihypertensives	• Thiazides, furosemide • Enalapril, losartan
Antivirals	• Lamivudine • Didanosine
Immunosuppressants	• Azathioprine, mercaptopurine • Corticosteroids
Others	• Asparaginase • Estrogens

Chronic Pancreatitis + Pancreatic Cancer

Overview of chronic pancreatitis	
Etiology	• Alcohol use • Cystic fibrosis (common in children) • Ductal obstruction (eg, malignancy, stones) • Autoimmune
Clinical presentation	• Chronic epigastric pain with intermittent pain-free intervals • Malabsorption: steatorrhea, weight loss • Diabetes mellitus
Laboratory results/ imaging	• Amylase/lipase can be normal & nondiagnostic • CT scan or MRCP can show calcifications, dilated ducts & enlarged pancreas
Treatment	• Pain management • Alcohol & smoking cessation • Frequent, small meals • Pancreatic enzyme supplements



CA 19-9 levels should not be used to diagnose suspected pancreatic cancer (due to limited sensitivity and specificity). Abdominal CT scan is usually the first step.

Pancreatic adenocarcinoma	
Risk factors	• Smoking • Hereditary pancreatitis • Nonhereditary chronic pancreatitis • Obesity & lack of physical activity
Clinicalpresentation	• Systemic symptoms (eg, weight loss, anorexia) (>85%) • Abdominal pain/back pain (80%) • Jaundice (56%) • Recent-onset atypical diabetes mellitus • Unexplained migratory superficial thrombophlebitis • Hepatomegaly & ascites with metastasis
Laboratorystudies	• Cholestasis (↑ alkaline phosphatase & direct bilirubin) • ↑ CA-19-9 (not as a screening test) • Abdominal ultrasonography (if jaundiced) or CT scan (if no jaundice)

Celiac disease



Also called gluten-sensitive enteropathy, celiac sprue. Autoimmune-mediated intolerance of gliadin (gluten protein found in wheat, barley, rye). Associated with HLA-DQ2, HLA-DQ8, northern European descent.
Primarily affects distal duodenum and/or proximal jejunum malabsorption and steatorrhea.
Treatment: gluten-free diet.
Associated with dermatitis herpetiformis, decrease bone density, iron deficiency anemia, moderately increase risk of malignancy (eg, T-cell lymphoma).
d-xylose test (absorbed in the proximal small bowel) : abnormal.
Serology: ⊕ IgA anti-tissue transglutaminase (IgA tTG), anti-endomysial, and anti-deaminated gliadin peptide antibodies, may be absent if there is concurrent selective IgA deficiency.
Histology: Loss of villi, mucosal atrophy, crypt hyperplasia, intraepithelial lymphocytosis.

Clinical manifestations of celiac disease	
Gastrointestinal	• Diarrhea, ± steatorrhea, weight loss • Abdominal pain • Flatulence/bloating • Late manifestations: ulcerative jejunitis, enteropathy-associated T-cell lymphoma
Mucocutaneous	• Dermatitis herpetiformis • Atrophic glossitis
Endocrine	• Vitamin D deficiency • Secondary hyperparathyroidism
Bone disorders	• Osteomalacia/osteoporosis (adults) • Rickets (children)
Hematologic	• Iron deficiency anemia
Neuropsychiatric	• Peripheral neuropathy • Depression/anxiety

Peripheral neuropathy, seen in up to 50% of patients, and other neuropsychiatric manifestations may be due to autoantibody production, rather than nutritional deficiency, because they often precede symptoms of malabsorption. Although atrophic glossitis may be caused by vitamin deficiencies, it might be due to autoantibodies, given that it manifests early in the disease course.

A false-positive D-xylose test (ie, low urinary D-xylose level despite normal mucosal absorption) can be seen in the following:

- Delayed gastric emptying
- Impaired glomerular filtration
- Small intestinal bacterial overgrowth (SIBO), characterized by alterations in small intestinal flora (due to abnormal intestinal anatomy or motility), leading to bacterial fermentation of the D-xylose before it can be absorbed. SIBO is treated with rifaximin

Whipple disease

Whipple disease is a rare multi-systemic illness. It is an infectious disease caused by the bacillus Tropheryma whippelii. It is most commonly seen in white men in the fourth-to-sixth decades of life, and often presents with weight loss. Gastrointestinal symptoms include abdominal pain, diarrhea, and malabsorption with distension, flatulence, and steatorrhea. Extraintestinal manifestations include migratory polyarthropathy, chronic cough, and myocardial or valvular involvement leading to congestive failure or valvular regurgitation. Later stages of the disease may be characterized by dementia and other central nervous system findings, such as supranuclear ophthalmoplegia and myoclonus. Intermittent low-grade fever, pigmentation, and lymphadenopathy may also be occasionally seen.
PAS-positive material in the lamina propria of the small intestine is a classical biopsy finding.

Lactose Intolerance

- Positive hydrogen breath test
- No steatorrhea
- Low stool pH
- Positive stool test for reducing substances
- Increased stool osmotic gap

Inflammatory diarrhea	
Etiologies	• Inflammatory bowel disease (eg, Crohn disease, ulcerative colitis) • Invasive infections (eg, *Clostridioides difficile, Entamoeba histolytica*, CMV) • Ischemic colitis, radiation colitis
Clinical characteristics	• Bloody stool (occult or gross) • Peripheral leukocytosis & reactive thrombocytosis • ± Anemia of chronic disease • Inflammatory markers (eg, CRP, ESR, fecal calprotectin or lactoferrin)

* The osmotic gap is calculated as 290 - [2 (stool Na + stool K)].

It is >75 mOsm/kg in all forms of osmotic diarrhea (vs. secretory diarrhea (e.g., Cholera)).

Giardiasis

Risk factors	• Contaminated food or water • Fecal incontinence & crowding (eg, day care, nursing home) • Immunodeficiency (eg, CVID, IgA deficiency, CF, HIV)
Pathogenesis	• Villous blunting, disruption of epithelial tight junctions, loss of brush border enzymes → malabsorption
Clinical features	• Subacute (<4 weeks) or chronic (months) • Loose, oily, nonbloody stools • Bloating, flatulence • Weight loss, decreased linear velocity (children), vitamin deficiencies
Diagnosis	• Stool antigen or PCR testing (↑ sensitivity) • Stool microscopy (↓ sensitivity)
Treatment	• First-line: tinidazole or nitazoxanide • Alternate: metronidazole (Flagyl) • Pregnancy (first trimester): paromomycin • Refractory/recurrent symptoms: evaluation for immunodeficiency

Chronic diarrhea due to organic causes should be suspected when there are nocturnal symptoms, systemic findings, or rectal bleeding.

Norovirus can cause chronic diarrhea in immunocompromised patients (eg, HIV, solid-organ transplant), but symptoms are typically brief (eg, 1-2 days) and self-limited in immunocompetent individuals.

C. difficile colitis

Risk factors	• Recent antibiotic use or hospitalization • Advanced age (>65) • Gastric acid suppression (eg, PPI, H_2 blocker) • Underlying inflammatory bowel disease • Chemotherapy
Clinicalpresentation	• Profuse watery diarrhea • Leukocytosis (~15,000/mm^3) • Fulminant colitis or toxic megacolon
Diagnosis	• Stool PCR for *C difficile* genes* • Stool EIA for *C difficile* toxin & glutamate dehydrogenase antigen
Infectioncontrol	• Hand hygiene with soap & water • Contact isolation • Sporicidal disinfectants (eg, bleach)

Laxative-induced Diarrhea



Laxative abuse is characterized by frequent, watery, nocturnal diarrhea. The diagnosis is suggested by a positive laxative screen or colonoscopy with characteristic findings of melanosis coli (dark brown discoloration with pale patches of lymph follicles).

Helpful tests in evaluating factitious diarrhea include:

- Stool osmolality: Stool osmolality is in equilibrium with plasma osmolality and typically remains constant (eg, 290 mOsm/kg) in organic gastrointestinal disease. Hypoosmolality suggests addition of water or other dilute fluid; hyperosmolality suggests addition of a concentrated fluid (eg, urine).
- Stool electrolytes: Elevated stool magnesium or phosphate levels suggest overuse of saline osmotic (ie, magnesium- or phosphate-containing) laxatives.
- Stool osmotic gap: Osmotic laxatives (eg, lactulose, polyethylene glycol) cause a high osmotic gap diarrhea, whereas senna and bisacodyl produce a low osmotic gap secretory diarrhea.

Chemotherapy-related Diarrhea

Chemotherapy-related diarrhea often presents with voluminous, watery, brown stool that persists despite periods of fasting (eg, nocturnal diarrhea). Evaluation includes complete blood count, serum chemistry, and stool studies (eg, Clostridioides difficile, fecal occult blood) to rule out other etiologies. First-line therapy is oral hydration and antidiarrheal medications (eg, loperamide).

Carcinoid

Features of carcinoid syndrome	
Clinical manifestations	• Skin: flushing, telangiectasias, cyanosis • Gastrointestinal: diarrhea, cramping • Cardiac: valvular lesions (right > left side) • Pulmonary: bronchospasm • Miscellaneous: niacin (vitamin B3) deficiency (dermatitis, diarrhea, dementia)
Diagnosis	• Elevated 24-hr urinary excretion of 5-HIAA • CT scan/MRI of abdomen & pelvis to localize tumor • OctreoScan to detect metastases • Echocardiogram (if symptoms of carcinoid heart disease are present)
Treatment	• Octreotide for symptomatic patients & prior to surgery/ anesthesia • Surgery for liver metastases

Carcinoids are well-differentiated neuroendocrine tumors found most commonly in the distal small intestine, proximal colon, and lung, with a strong propensity for metastasis to liver. These tumors can secrete several products including histamine, serotonin, and vasoactive intestinal peptide (VIP) that are metabolized in the liver. In patients with liver metastasis, these hormones are released directly into the systemic circulation, leading to carcinoid syndrome.

Angiodysplasia



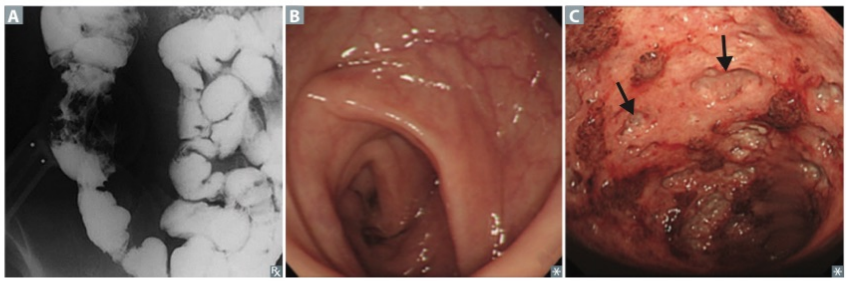
Its clinical presentation is episodic painless gastrointestinal (GI) bleeding suggests angiodysplasia. Angiodysplasia is characterized by dilated submucosal veins and arteriovenous malformations (AVM), and has an increased incidence after age 60. It may occur anywhere in the GI tract but is most common in the right colon. Angiodysplasia is more frequently diagnosed in patients with advanced renal disease and von Willebrand (vW) disease, possibly due to the bleeding tendency associated with these disorders. Angiodysplasia may also be more common in patients with aortic stenosis (AS), possibly due to acquired vW factor deficiency (from disruption of the vW multimers as they traverse the turbulent valve space induced by AS). Angiodysplastic bleeding has been reported to remit following aortic valve replacement.

Diagnosis of angiodysplasia is usually made on endoscopic evaluation (eg, upper GI endoscopy, colonoscopy). However, it is not uncommon for angiodysplasia to be missed on colonoscopy due to poor bowel preparation or location behind a haustral fold. Asymptomatic patients do not require treatment. Patients with anemia or gross or occult bleeding can be treated endoscopically, usually with cautery.

IBD (Crohns & Ulcerative Colitis) & Microscopic Colitis

Inflammatory bowel diseases

	Crohn disease	Ulcerative colitis
LOCATION	Any portion of the GI tract, usually the terminal ileum and colon. Skip lesions, rectal sparing.	Colitis = colon inflammation. Continuous colonic lesions, always with rectal involvement.
GROSS MORPHOLOGY	Transmural inflammation → fistulas. Cobblestone mucosa, creeping fat, bowel wall thickening ("string sign" on small bowel follow-through A), linear ulcers, fissures.	Mucosal and submucosal inflammation only. Friable mucosa with superficial and/or deep ulcerations (compare normal B with diseased C). Loss of haustra → "lead pipe" appearance on imaging.
MICROSCOPIC MORPHOLOGY	Noncaseating granulomas, lymphoid aggregates.	Crypt abscesses/ulcers, bleeding, no granulomas.
COMPLICATIONS	Malabsorption/malnutrition, colorectal cancer (↑ risk with pancolitis).	
	Fistulas (eg, enterovesical fistulae, which can cause recurrent UTI and pneumaturia), phlegmon/abscess, strictures (causing obstruction), perianal disease.	Fulminant colitis, toxic megacolon, perforation.
INTESTINAL MANIFESTATION	Diarrhea that may or may not be bloody.	Bloody diarrhea (usually painful).
EXTRAINTESTINAL MANIFESTATIONS	Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis).	
	Kidney stones (usually calcium oxalate), gallstones. May be ⊕ for anti-*Saccharomyces cerevisiae* antibodies (ASCA).	1° sclerosing cholangitis. Associated with MPO-ANCA/p-ANCA.
TREATMENT	Glucocorticoids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), biologics (eg, infliximab, adalimumab).	5-aminosalicylic acid preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy.
DISEASE ACTIVITY	Fecal calprotectin used to monitor activity and distinguish from noninflammatory diseases (irritable bowel).	



Microscopic colitis Inflammatory disease of colon that causes chronic watery diarrhea. Most common in older females. Colonic mucosa appears normal on endoscopy. Histology shows lymphocytic infiltrate in lamina propria with intraepithelial lymphocytosis or thickened subepithelial collagen band.

Colon Cancer

Patients with abdominal pain, microcytic anemia, positive fecal occult blood, and hepatomegaly with a hard edge on liver palpation have typical features of gastrointestinal malignancy, likely colon cancer, metastatic to the liver

About 30% of patients with C septicum bacteremia have colon cancer; therefore, colonoscopy is required for those with no history of the tumor. Bacteremia with group D streptococci, particularly Streptococcus bovis, is also strongly associated with colon cancer and should prompt screening colonoscopy.

Risk factors for colon cancer	
Lifestyle factors	• Frequent consumption of red/processed meat • Tobacco, alcohol use
Medical/ family history	• Personal/family history of adenomatous polyps or colon cancer • Inherited colon cancer syndromes (eg, familial adenomatous polyposis, Lynch syndrome) • Ulcerative colitis • Diabetes/obesity • Prior abdominopelvic radiation
Protective factors	• High-fiber diet • Aspirin/NSAID use

Colon cancer screening	
Patients ataverage risk	◦ Start at age 45: ◦ Colonoscopy every 10 years ◦ gFOBT or FIT every year ◦ FIT-DNA every 1-3 years ◦ CT colonography every 5 years • Flexible sigmoidoscopy every 5 years (or every 10 years with annual FIT)
Patients with FDR with CRC or high-risk adenomatous polyp*	• Colonoscopy at age 40 (or 10 years prior to age of diagnosis in FDR, whichever comes first) • Repeat every 5 years (every 10 years if FDR diagnosed at age >60)
Patients with ulcerative colitis	• Start screening 8-10 years after diagnosis • Colonoscopy every 1-3 years

*Adenomatous polyp ≥10 mm, high-grade dysplasia, villous elements (for example).

CRC = colorectal cancer; FDR = first-degree relative; FIT = fecal immunochemical test; FIT-DNA = multitarget stool DNA test; gFOBT = guaiac-based fecal occult blood test.

Patients with familial adenomatous polyposis (FAP) have a significantly increased risk of colorectal cancer. Frequent screening with colonoscopy is started in childhood, and elective total proctocolectomy is considered in the late teens or early twenties. Urgent total proctocolectomy is performed no matter the patient's age in those with CRC or adenomas with high-grade dysplasia; other indications for colectomy include severe symptoms related to colonic neoplasia (eg, hemorrhage) and a significant increase in polyp number during the screening interval.

For individuals with a history of abdominopelvic radiation treatment, colon CA screening should commence at an earlier age (eg, age 30-40) than that recommended for average-risk patients.

Colorectal cancer is the most common source of liver metastasis and should be suspected when unexplained IDA accompanies multiple hepatic masses on imaging. Colonoscopy should be performed to confirm the primary cancer and the source of occult blood loss.

Common hereditary cancer syndromes	
Syndrome	**Associated neoplasms**
Lynch syndrome	• Colorectal cancer • Endometrial cancer • Ovarian cancer
Familial adenomatous polyposis	• Colorectal cancer • Desmoids & osteomas • Brain tumors
von Hippel-Lindau syndrome	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma
Multiple endocrine neoplasia type 1	• Parathyroid adenomas • Pituitary adenomas • Pancreatic adenomas
Multiple endocrine neoplasia type 2	• Medullary thyroid cancer • Pheochromocytoma • Parathyroid hyperplasia (type 2A)
BRCA1* & *BRCA2	• Breast cancer • Ovarian cancer

The most common cause of iron deficiency anemia in the elderly is GI blood loss. The next step in evaluation would be colonoscopy and endoscopy. A single negative occult blood test does not exclude the possibility of GI bleeding.

Minimal rectal bleeding usually is due to hemorrhoids or other benign conditions. In patients with no clinical features (eg, blood mixed with stool, fever, weight loss, change in bowel habits or stool caliber) suggesting a serious issue and no other indications for colonoscopy (eg, age ≥45), initial evaluation with anoscopy is appropriate.

Fecal Impaction



Fecal impaction is common in older patients with impaired mobility, chronic constipation, or decreased sensation of stool in the rectal vault. Obstruction of fecal flow in the rectum can cause backup of stool; passage of liquid stool around the impaction can lead to incontinence. Initial management includes manual disimpaction and enemas to clear the rectal vault.

Gonococcal Proctitis

Transmission	• Receptive anal intercourse • Direct spread from the vagina
Manifestations	• Mucopurulent anal discharge, occasional rectal bleeding • Tenesmus, constipation • Pruritus, rectal pain, rectal fullness
Diagnosis	• Nucleic acid amplification test of rectal swab
Treatment	• Ceftriaxone + doxycycline (to cover Chlamydia)

Proctalgia Fugax

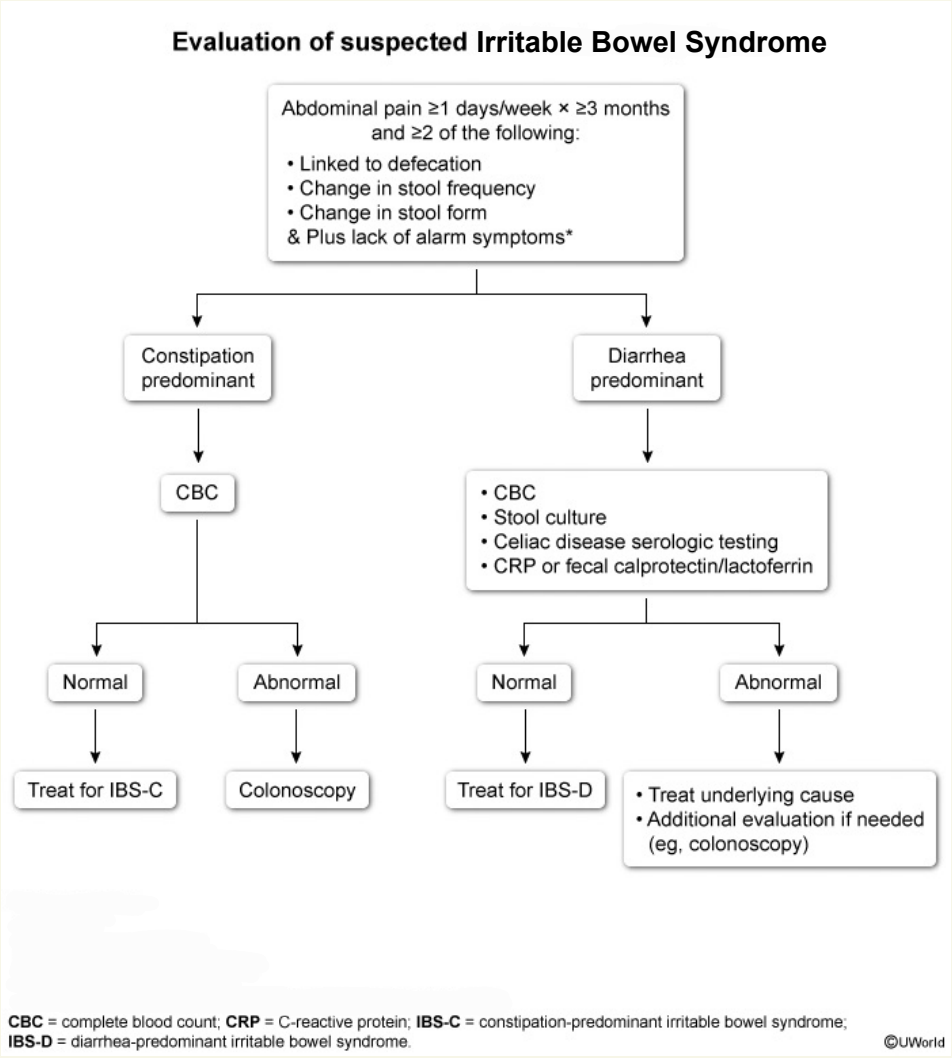
Pathophysiology	- Spastic contraction of the anal sphincter - Pudendal nerve compression
Risk factors	- Female sex - Other functional pathologies (eg, irritable bowel syndrome) - Psychosocial stress, anxiety
Manifestations	- Recurrent rectal pain unrelated to defecation - Episodes lasting seconds to minutes (≤30 min) - No pain between episodes
Evaluation	- Normal physical examination (eg, rectal, pelvic, prostate) - No laboratory abnormalities
Management	- Reassurance - Nitroglycerin cream ± biofeedback therapy for refractory symptoms

Gastroparesis

Causes	• Diabetes mellitus (autonomic neuropathy) • Medications (eg, opioids, anticholinergic drugs) • Traumatic/postsurgical injury (ie, vagus nerve injury) • Neurologic (eg, multiple sclerosis, spinal cord injury) • Idiopathic/postviral
Clinical features	• Nausea & vomiting, epigastric abdominal pain • Early satiety, bloating, weight loss • Labile glucose (diabetes mellitus) • Epigastric distension & succussion splash
Diagnosis	• Exclude obstruction: upper endoscopy ± CT/MR enterography • Assess motility: nuclear gastric emptying study
Treatment	• Frequent small meals (low fat, soluble fiber only) • Promotility drugs (eg, metoclopramide, erythromycin) • Gastric electrical stimulation &/or jejunal feeding tube (refractory symptoms)

Common secondary causes of constipation	
Lifestyle	• Low-fiber diet, dehydration, inactivity
Functional	• Irritable bowel syndrome, depression
Medications	• Opioids, iron supplements, anticholinergics*, CCBs
Metabolic	• Hypothyroidism, diabetes mellitus, hypercalcemia
Obstruction	• Colon cancer, inflammatory/ischemic/surgical stricture
Neurologic	• Spinal cord injury, multiple sclerosis, Parkinson disease
*Anticholinergic medication classes: antipsychotics, antidepressants, antihistamines, antispasmodics.	

IBS



Alarm features	• Older age of onset (≥50) • Gastrointestinal bleeding • Nocturnal diarrhea (ie, fasting state) • Worsening pain • Unintended weight loss • Iron deficiency anemia • Elevated C-reactive protein • Positive fecal lactoferrin or calprotectin • Family history of early colon cancer or IBD

Eating disorders (Anorexia Nervosa, Bulimia Nervosa, Binge-eating disorder)

Eating disorders		
Diagnosis	**Clinical features**	**Treatment**
Anorexia nervosa	**BMI <18.5 kg/m^2** Intense fear of weight gain Distorted views of body weight & shape	Cognitive-behavioral therapy Nutritional rehabilitation **Olanzapine** if no response to above
Bulimia nervosa	Recurrent episodes of binge eating Binge eating & **inappropriate compensatory behavior** to prevent weight gain Excess worrying about body shape & weight	Cognitive-behavioral therapy Nutritional rehabilitation **SSRI (fluoxetine)**, often in combination with above
Binge-eating disorder	Recurrent episodes of binge eating **No inappropriate compensatory behaviors** Lack of control during eating	Cognitive-behavioral therapy Behavioral weight loss therapy SSRI Lisdexamfetamine

Anorexia nervosa	
Clinical features	• BMI <18.5 kg/m2 • Fear of weight gain, distorted body image
Medical complications	• Osteoporosis • Amenorrhea • Lanugo, hair loss, dry skin • Gastroparesis, constipation • Enlarged parotid glands (if binge/purge type) • Hypotension, hypothermia, bradycardia • Cardiac atrophy, arrhythmias

Other Related Topics

Pellagra



Pellagra ("rough skin" in Italian vernacular) is due to niacin (vitamin B3) deficiency and is characterized by the "3 Ds": dermatitis, diarrhea, and dementia:

- Dermatitis is primarily on sun-exposed areas of the body and is characterized by rough, hyperpigmented, scaly skin.
- Diarrhea is often associated with abdominal pain, nausea, and loss of appetite.
- Dementia is due to neuronal degeneration in the brain and spinal cord and can lead to memory loss, affective symptoms (eg, depressed mood in this patient), and psychosis.

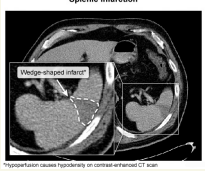
Niacin is present in a broad variety of foods and can be synthesized endogenously from tryptophan. In developing countries, niacin deficiency is seen in populations that subsist primarily on corn products (niacin in corn occurs in a bound, unabsorbable form). In developed countries, it is primarily seen in patients with impaired nutritional intake (eg, heavy alcohol use, chronic illness). Pellagra can also be seen occasionally in those with carcinoid syndrome (due to depletion of tryptophan) or Hartnup disease (congenital disorder of tryptophan absorption). Prolonged isoniazid therapy without concomitant use of pyridoxine (vitamin B6), which is needed for niacin synthesis, can interfere with metabolism of tryptophan and occasionally lead to pellagra.

Shingles

patient with burning, localized pain and regional hyperesthesia/allodynia, in the context of recent cancer treatment, has common features of herpes zoster (shingles). Pain from shingles may precede the onset of the classic vesicular rash by several days, during which the diagnosis may not be obvious. The possibility of shingles should be considered in patients with regional pain who have no conclusive evidence of disease in the local internal organs.

Shingles may occur at any age, but it is most common after age 50 and the risk increases with age. It is frequently triggered by severe physical stress (such as cancer treatment) or immunosuppressed states, but many cases are spontaneous.

Splenic Infarction



Acute left upper quadrant pain and CT evidence of a wedge-shaped splenic deficit indicate splenic infarction. Most cases arise due to an acute interruption in arterial blood flow through the splenic artery or its subbranches in the setting of 1 of the following:

- Thrombosis due to a hypercoagulable state (eg, cancer, systemic lupus erythematosus [SLE], antiphospholipid antibody syndrome [APLAS])
- Embolism due to atrial fibrillation, endocarditis, or atheroma
- Hemoglobinopathy (eg, sickle cell disease)

Patient young age, long-standing joint pain, and thrombocytopenia raise suspicion for possible SLE. In patients with SLE, possible etiologies of splenic infarction include splenic artery thrombosis or embolism from nonbacterial thrombotic endocarditis. Therefore, in addition to antinuclear antibody testing (as part of the workup for SLE), the patient should also undergo antiphospholipid antibody testing (to evaluate for APLAS) as well as echocardiography (to examine the heart valves for vegetations). Mitral regurgitation murmur (holosystolic radiating to apex) may indicate that nonbacterial thrombotic endocarditis is the cause of her infarction.

Most patients with splenic infarction have acute pain and tenderness in the left upper quadrant; fever, nausea, splenomegaly, and leukocytosis also frequently occur. The diagnosis is typically made with abdominal CT scan.

Chronic Mesenteric Ischemia

Etiology	• Atherosclerosis (smoking, dyslipidemia)
Clinical features	• Crampy, postprandial epigastric pain • Food aversion & weight loss
Diagnosis	• Signs of malnutrition, abdominal bruit • CT angiography (preferred), Doppler ultrasonography
Management	• Risk reduction (eg, tobacco reduction), nutritional support • Endovascular or open surgical revascularization

The anginal pain frequently starts within the first hour of eating and slowly resolves over the next 2 hours; it is most likely related to shunting of blood away from the small intestine to meet the increased demand of the stomach. In patients with atherosclerosis, the celiac or the superior mesenteric arteries may be narrowed and unable to dilate appropriately to maintain adequate blood flow to the intestines.



Step 2

& Relevant Clinical Step 1

Hemato-Oncology

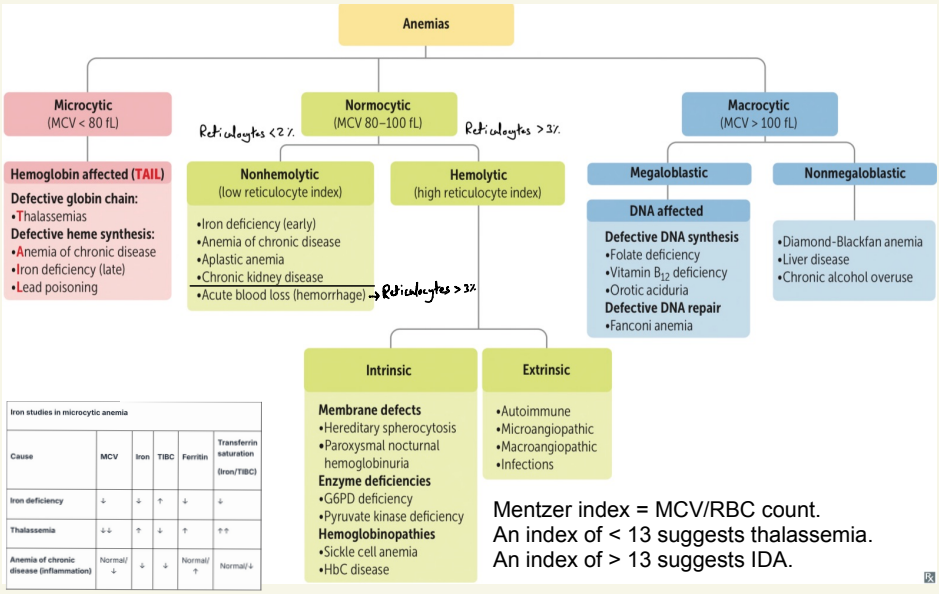
تَذكَّر:

إنَّ الطِّبَّ وسِيلةٌ.. لا غايَةٌ!

Contact & Updates:

Ehab Alroud

Anemias



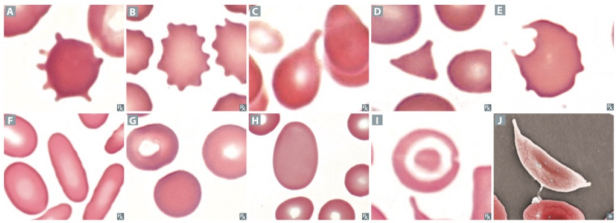
Iron studies in microcytic anemia

Cause	MCV	Iron	TIBC	Ferritin	Transferrin saturation (Iron/TIBC)
Iron deficiency	↓	↓	↑	↓	↓
Thalassemia	↓↓	↑	↓	↑	↑↑
Anemia of chronic disease (inflammation)	Normal/↓	↓	↓	Normal/↑	Normal/↓

Mentzer index = MCV/RBC count.
An index of < 13 suggests thalassemia.
An index of > 13 suggests IDA.

RBC morphology

TYPE	ASSOCIATED PATHOLOGY	NOTES
Acanthocytes A ("spur cells")	Liver disease, abetalipoproteinemia, vitamin E deficiency	Projections of varying size at irregular intervals (acanthocytes are asymmetric)
Echinocytes B ("burr cells")	Liver disease, ESRD, pyruvate kinase deficiency	Smaller and more uniform projections than acanthocytes (echinocytes are even)
Dacrocytes C ("teardrop cells")	Bone marrow infiltration (eg, myelofibrosis)	RBC "sheds a tear" because it's mechanically squeezed out of its home in the bone marrow
Schistocytes D ("helmet" cells)	Microangiopathic hemolytic anemia (eg, DIC, TTP/HUS, HELLP syndrome), mechanical hemolysis (eg, heart valve prosthesis)	Fragmented RBCs
Degmacytes E ("bite cells")	G6PD deficiency	Due to removal of Heinz bodies by splenic macrophages (they "deg" them out of/bite them off of RBCs)
Elliptocytes F	Hereditary elliptocytosis	Caused by mutation in genes encoding RBC membrane proteins (eg, spectrin)
Spherocytes G	Hereditary spherocytosis, autoimmune hemolytic anemia	Small, spherical cells without central pallor ↓ surface area-to-volume ratio
Macro-ovalocytes H	Megaloblastic anemia (also hypersegmented PMNs)	
Target cells I	HbC disease, Asplenia, Liver disease, Thalassemia	"HALT," said the hunter to his target ↑ surface area-to-volume ratio
Sickle cells J	Sickle cell anemia	Sickling occurs with low O_2 conditions (eg, high altitude, acidosis), high HbS concentration (ie, dehydration)



Microcytic, hypochromic anemias — MCV < 80 fL.

Iron deficiency

↓ iron due to chronic bleeding (eg, GI loss, heavy menstrual bleeding), malnutrition, absorption disorders, GI surgery (eg, gastrectomy), or ↑ demand (eg, pregnancy) → ↓ final step in heme synthesis.

Labs: ↓ iron, ↑ TIBC, ↓ ferritin, ↑ free erythrocyte protoporphyrin, ↑ RDW, ↓ RI. Microcytosis and hypochromasia (↑ central pallor) A.

Symptoms: fatigue, conjunctival pallor B, restless leg syndrome, pica (persistent craving and compulsive eating of nonfood substances), spoon nails (koilonychia).

May manifest as glossitis, cheilosis, Plummer-Vinson syndrome (triad of iron deficiency anemia, esophageal webs, and dysphagia).

α-thalassemia

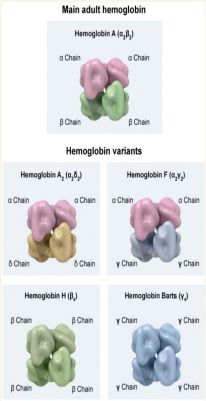
α-globin gene deletions on chromosome 16 → ↓ α-globin synthesis. May have *cis* deletion (deletions occur on same chromosome) or *trans* deletion (deletions occur on separate chromosomes). Normal is αα/αα. Often ↑ RBC count, in contrast to iron deficiency anemia. ↑ prevalence in people of Asian and African descent. Target cells C on peripheral smear.

# OF α-GLOBIN GENES DELETED[a]	DISEASE	CLINICAL OUTCOME
1	α-thalassemia minima	No anemia (silent carrier)
2 (Cis)	α-thalassemia minor	Mild microcytic, hypochromic anemia
2 (Trans)	α-thalassemia minor	Mild microcytic, hypochromic anemia
3	Hemoglobin H disease (HbH); excess β-globin forms β_4	Moderate to severe microcytic hypochromic anemia
4	Hemoglobin Barts disease; no α-globin, excess γ-globin forms γ_4	Hydrops fetalis; incompatible with life

* Recent NSAIDs use —> PUD/ gastritis —> chronic blood loss —> IDA

Hemoglobinopathy traits are inherited in an autosomal recessive manner. Therefore, if the mother is identified as a carrier, the father is also tested; and if both parents are carriers, genetic counseling (regarding implications for the offspring) and fetal testing (eg, chorionic villus sampling) are offered.

	Disorder (genotype)	Hb electrophoresis	Anemia severity
Alpha thalassemia	Silent carrier (α α / α -)	Normal	Asymptomatic
	Trait (α α / - - **OR** α - / α -)	Normal	Mild symptoms
	Hb H disease (α - / - -)	5%-30% Hb H (adults)	Chronic hemolysis
	Major (fetal hydrops) (- - / - -)	• Hb Barts, Hb Portland & Hb H present • Absent Hb A, Hb F & Hb A2	Fatal in utero
Beta thalassemia	Trait (β / β^0)	Increased Hb A2	Mild
	Intermediate (β^+ / β^+, others)	Increased Hb F	Moderate
	Major (β^0 / β^0)	Absent Hb A, only Hb A2 & Hb F present	Severe



Hemoglobin A2 levels are increased in patients with beta thalassemia trait.

Hemoglobin F levels are increased in patients with sickle cell anemia, beta thalassemia, congenital aplastic anemia, and hereditary persistence of fetal hemoglobin.

β-thalassemia

Point mutation in splice sites or Kozak consensus sequence (promoter) on chromosome 11 → ↓ β-globin synthesis (β^+) or absent β-globin synthesis (β^0). ↑ prevalence in people of Mediterranean descent.

# OF β-GLOBIN GENES MUTATED[a]	DISEASE	CLINICAL OUTCOME
1	β-thalassemia minor	Mild microcytic anemia. ↑ HbA_2.
2 (β^+/β^+ or β^+/β^0)	β-thalassemia intermedia	Variable anemia, ranging from mild/ asymptomatic to severe/transfusion-dependent.
2	β-thalassemia major (Cooley anemia)	Severe microcytic anemia with target cells and ↑ anisopoikilocytosis requiring blood transfusions (↑ risk of 2° hemochromatosis), marrow expansion ("crew cut" on skull x-ray) → skeletal deformities, extramedullary hematopoiesis → HSM. ↑ risk of parvovirus B19-induced aplastic crisis. ↑ HbF and HbA_2, becomes symptomatic after 6 months when HbF declines (HbF is protective). Chronic hemolysis → pigmented gallstones.
1 (β^+/HbS or β^0/HbS)	Sickle cell β-thalassemia	Mild to moderate sickle cell disease depending on whether there is ↓ (β^+/HbS) or absent (β^0/HbS) β-globin synthesis.

Lead poisoning

Lead inhibits ferrochelatase and ALA dehydratase → ↓ heme synthesis and ↑ RBC protoporphyrin. Also inhibits rRNA degradation → RBCs retain aggregates of rRNA (basophilic stippling).

Symptoms of LLEEAAD poisoning:

- Lead Lines on gingivae (Burton lines) and on metaphyses of long bones D on x-ray.
- Encephalopathy and Erythrocyte basophilic stippling.
- Abdominal colic and sideroblastic Anemia.
- Drops—wrist and foot drop.

Treatment: chelation with succimer, EDTA, dimercaprol.

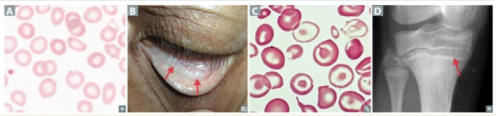
Exposure risk ↑ in old houses (built before 1978) with chipped paint (children) and workplace (adults).

Sideroblastic anemia

Causes: genetic (eg, X-linked defect in ALA synthase gene), acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead poisoning, vitamin B_6 deficiency, copper deficiency, drugs [eg, isoniazid, linezolid]).

Lab findings: ↑ iron, normal/↓ TIBC, ↑ ferritin. Ringed sideroblasts (with iron-laden, Prussian blue–stained mitochondria) seen in bone marrow. Peripheral blood smear: basophilic stippling of RBCs. Some acquired variants may be normocytic or macrocytic.

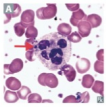
Treatment: pyridoxine (B_6, cofactor for ALA synthase).



Parameter	Iron deficiencyanemia	α-Thalassemiaminor	β-Thalassemiaminor
MCV	↓	↓	↓
RDW	↑	Normal	Normal
RBCs	↓	Normal/↑	Normal/↑
Peripheralsmear	Microcytosis,hypochromia	Target cells	Target cells
Serum ironstudies	↓ Iron & ferritin↑ TIBC	Normal/↑ iron & ferritin(RBC turnover)	Normal/↑ iron & ferritin(RBC turnover)
Response to ironsupplementation	↑ Hemoglobin	No improvement	No improvement
Hemoglobinelectrophoresis	Normal	Normal	↑ Hemoglobin A_2

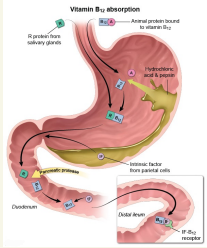
Iron depletion and thalassemia are the most 2 common causes of microcytic anemia. Differentiation requires iron studies, but empiric iron supplementation is sometimes prescribed. Lack of improvement in hemoglobin levels within 4 weeks makes iron deficiency unlikely. The disproportionately elevated RBC count (eg, normal or high rather than low) and decreased MCV help distinguish thalassemia minor from IDA, which does not typically cause microcytosis until hemoglobin is <10 g/dL. So, significant microcytosis in the setting of mild anemia and a normal (rather than low) erythrocyte count suggests thalassemia.

Macrocytic anemias MCV > 100 fL.

	DESCRIPTION	FINDINGS
Megaloblastic anemia 	Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation of cytoplasm. Causes: vitamin B_{12} deficiency, folate deficiency, medications (eg, hydroxyurea, phenytoin, methotrexate, sulfa drugs).	RBC macrocytosis, hypersegmented neutrophils (arrow in A), glossitis.
Folate deficiency	Causes: malnutrition (eg, chronic alcohol overuse), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), ↑ requirement (eg, hemolytic anemia, pregnancy).	↑ homocysteine, normal methylmalonic acid. **No neurologic symptoms** (vs B_{12} deficiency).
Vitamin B_{12} (cobalamin) deficiency	Causes: pernicious anemia, malabsorption (eg, Crohn disease), pancreatic insufficiency, gastrectomy, insufficient intake (eg, veganism), *Diphyllobothrium latum* (fish tapeworm).	↑ homocysteine, ↑ methylmalonic acid. **Neurologic symptoms:** reversible dementia, subacute combined degeneration (due to involvement of B_{12} in fatty acid pathways and myelin synthesis): spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction. Folate supplementation in vitamin B_{12} deficiency can correct the anemia, but worsens neurologic symptoms. Historically diagnosed with the Schilling test, a test that determines if the cause is dietary insufficiency vs malabsorption. Anemia 2° to insufficient intake may take several years to develop due to liver's ability to store B_{12} (vs folate deficiency, which takes weeks to months).
Orotic aciduria	Inability to convert orotic acid to UMP (de novo pyrimidine synthesis pathway) because of defect in UMP synthase. Autosomal recessive. Presents in children as failure to thrive, developmental delay, and megaloblastic anemia refractory to folate and B_{12}. No hyperammonemia (vs ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia).	Orotic acid in urine. Treatment: uridine monophosphate or uridine triacetate to bypass mutated enzyme.
Nonmegaloblastic anemia	Macrocytic anemia in which DNA synthesis is normal. Causes: chronic alcohol overuse, liver disease.	RBC macrocytosis without hypersegmented neutrophils.
Diamond-Blackfan anemia	A congenital form of pure red cell aplasia (vs Fanconi anemia, which causes pancytopenia). Rapid-onset anemia within 1st year of life due to intrinsic defect in erythroid progenitor cells.	↑ % HbF (but ↓ total Hb). Short stature, craniofacial abnormalities, and upper extremity malformations (triphalangeal thumbs) in up to 50% of cases.

Common causes of macrocytic anemia

- Folate deficiency
- Vitamin B_{12} deficiency
- Myelodysplastic syndromes
- Acute myeloid leukemias
- Drug-induced (eg, hydroxyurea, zidovudine,chemotherapy agents)
- Liver disease
- Alcohol use disorder
- Hypothyroidism



Megaloblastic anemia: typically associated with MCV >110 µm3, low reticulocyte count, macroovalocyte RBCs, hypersegmented neutrophils (mean lobe count >5), anisocytosis, and poikilocytosis.

Although patients with heavy alcohol use can develop vitamin B12 deficiency, nutritional folate deficiency arises far more quickly (due to smaller total body stores). In addition, vitamin B12 deficiency is rare in patients with alcohol use disorder who do not have chronic pancreatitis; most cases of vitamin B12 deficiency arise in older individuals with disorders of the stomach (eg, pernicious anemia, atrophic gastritis) or small intestine that impair absorption, but total body stores are generally sufficient for >1 year (total stores are 2-5 mg and daily requirement is ~2 μg/day).

Folate is an essential dietary nutrient found in leafy vegetables and fortified grains; because it has relatively limited total body stores, consumption of an unbalanced or nutrient-poor diet (as is common in those with alcohol use disorder) frequently results in folate deficiency within 5-10 weeks. Alcohol also directly hastens folate deficiency by reducing folate absorption in the small intestine, impairing uptake/storage in the liver, and increasing urinary excretion.

Folate supplementation is often given to patients with heavy alcohol use; cobalamin supplementation is not routinely administered because, in these patients, cobalamin deficiency is rare in the absence of chronic pancreatitis. Because both folate and cobalamin are cofactors in the conversion of homocysteine to methionine, folate supplementation can improve the anemia of cobalamin deficiency. However, because cobalamin is used in other processes as well, neurologic deficits can be precipitated or worsened when folic acid is given without cobalamin supplementation. Therefore, it is important to consider cobalamin deficiency prior to starting folic acid replacement.

Thiamine deficiency is common in alcoholics, however it is not associated with megaloblastic anemia; rather it is associated with Wernicke encephalopathy.

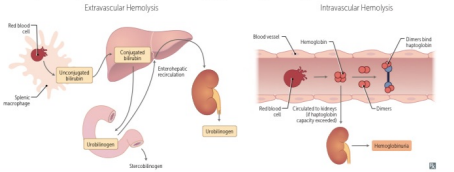
Phenytoin commonly causes megaloblastic anemia and gingival hyperplasia due to impaired folic acid absorption in the jejunum. Supplementation with folic acid prevents these adverse effects. Calcium and vitamin D supplementation are also usually given to counter alterations in bone mineral metabolism that impair bone density.

Pernicious anemia, associated with auto-antibodies against intrinsic factor, is the most common cause of vitamin B12 deficiency. It occurs most often in older adults with other autoimmune conditions. Manifestations include megaloblastic anemia, atrophic glossitis (smooth, shiny tongue due to impaired replication of tongue epithelial cells), and/or neurologic abnormalities (eg, paresthesia, subacute combined degeneration).

Hypothyroidism typically causes anemia via decreased red blood cell mass with a normocytic MCV or in association with pernicious anemia (ie, macrocytic MCV).

Normocytic, normochromic anemias

Normocytic, normochromic anemias are classified as nonhemolytic or hemolytic. The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic vs extrinsic to the RBC) and by the location of hemolysis (intravascular vs extravascular). Hemolysis can lead to ↑ in LDH, reticulocytes, unconjugated bilirubin, pigmented gallstones, and urobilinogen in urine.



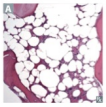
Intravascular hemolysis

Findings: ↓ haptoglobin, ↑ schistocytes on blood smear. Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. Notable causes are mechanical hemolysis (eg, prosthetic valve), paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias.

Extravascular hemolysis

Mechanism: macrophages in spleen clear RBCs. Findings: splenomegaly, spherocytes in peripheral smear (most commonly due to hereditary spherocytosis and autoimmune hemolytic anemia), no hemoglobinuria/hemosiderinuria. Can present with urobilinogen in urine.

Nonhemolytic, normocytic anemias

	DESCRIPTION	FINDINGS
Anemia of chronic disease	Inflammation (eg, ↑ IL-6) → ↑ hepcidin (released by liver, binds ferroportin on intestinal mucosal cells and macrophages, thus inhibiting iron transport) → ↓ release of iron from macrophages and ↓ iron absorption from gut. Associated with conditions such as chronic infections, neoplastic disorders, chronic kidney disease, and autoimmune diseases (eg, SLE, rheumatoid arthritis).	↓ iron, ↓ TIBC, ↑ ferritin. Normocytic, but can become microcytic. Treatment: address underlying cause of inflammation, judicious use of blood transfusion, consider erythropoiesis-stimulating agents such as EPO (eg, in chronic kidney disease).
Aplastic anemia 	Failure or destruction of hematopoietic stem cells. Causes (reducing volume from inside diaphysis): • Radiation • Viral agents (eg, EBV, HIV, hepatitis viruses) • Fanconi anemia (autosomal recessive DNA repair defect → bone marrow failure); normocytosis or macrocytosis on CBC. Common associated findings include short stature, café-au-lait spots, thumb/radial defects, predisposition to malignancy. • Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis • Drugs (eg, benzene, chloramphenicol, alkylating agents, antimetabolites)	↓ reticulocyte count, ↑ EPO. Pancytopenia characterized by anemia, leukopenia, and thrombocytopenia (vs aplastic crisis, which causes anemia only). Normal cell morphology, but hypocellular bone marrow with fatty infiltration A. Symptoms: fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection. Treatment: withdrawal of offending agent, immunosuppressive regimens (eg, antithymocyte globulin, cyclosporine), bone marrow allograft, RBC/platelet transfusion, bone marrow stimulation (eg, GM-CSF).

* Treating the underlying inflammatory disorder will often improve the anemia (e.g., MTX for RA).

* Osteoarthritis does not involve a significant release of inflammatory cytokines and would not cause anemia of chronic disease.

* Colon cancer is a common cause of chronic anemia in older individuals who have not undergone screening colonoscopy. Reticulocytosis would be unusual (it is more common with acute, rather than chronic, blood loss anemia).

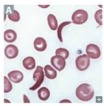
Anemia of chronic kidney disease is due to erythropoietin deficiency; treatment is with erythropoiesis-stimulating agents (ESAs) (eg, erythropoietin, darbepoetin). Goal hemoglobin is typically 10-11.5 g/dL. In concurrent iron deficiency, which is the most common cause of inadequate response to ESAs in patients on dialysis, iron stores can be rapidly depleted during hematopoiesis after ESA administration, especially in chronically ill patients whose iron stores may already be low. Iron stores should therefore be evaluated prior to starting ESAs and frequently thereafter. The treatment of choice for iron deficiency in patients on dialysis is intravenous iron.
Darbepoetin is an ESA with a longer half-life than erythropoietin and can be dosed less frequently; however, they both have the same effects on hematopoiesis.

Up to 30% of patients receiving an ESA for CKD-induced anemia develop new or worsening hypertension, which typically occurs 2-8 weeks after treatment initiation. Hypertension is generally mild but can be severe. The mechanism by which ESAs cause hypertension appears to be independent of increased blood volume and likely involves systemic vasoconstriction caused by:

- Activation of erythropoietin receptors on vascular smooth muscle cells
- Heightened sensitivity of alpha receptors
- Depletion of endothelium-derived nitric oxide

The risk of ESA-induced hypertension is increased by large doses and a rapidly rising Hb soon after ESA administration. Following acute treatment of hypertension, subsequent ESA doses should be decreased with a goal of slowly increasing Hb.

Intrinsic hemolytic anemias

	DESCRIPTION	FINDINGS
Hereditary spherocytosis	Primarily autosomal dominant. Due to defect in proteins interacting with RBC membrane skeleton and plasma membrane (eg, ankyrin, band 3, protein 4.2, spectrin). Small, round RBCs with no central pallor. ↓ surface area/dehydration → ↑ MCHC → premature removal by spleen (extravascular hemolysis).	Splenomegaly, pigmented gallstones, aplastic crisis (parvovirus B19 infection). Labs: ↓ mean fluorescence of RBCs in eosin 5-maleimide (EMA) binding test, ↑ fragility in osmotic fragility test (RBC hemolysis with exposure to hypotonic solution). Normal to ↓ MCV with abundance of RBCs. Treatment: splenectomy.
Paroxysmal nocturnal hemoglobinuria (PNH)	Hematopoietic stem cell mutation → ↑ complement-mediated intravascular hemolysis, especially at night. Acquired *PIGA* mutation → impaired GPI anchor synthesis for decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59), which protect RBC membrane from complement.	Triad: Coombs ⊖ hemolytic anemia (mainly intravascular), pancytopenia, venous thrombosis (eg, Budd-Chiari syndrome). Pink/red urine in morning. Associated with aplastic anemia, acute leukemias. Labs: CD55/59 ⊖ RBCs on flow cytometry. Treatment: eculizumab (targets terminal complement protein C5).
G6PD deficiency	X-linked recessive. G6PD defect → ↓ NADPH → ↓ reduced glutathione → ↑ RBC susceptibility to oxidative stress (eg, sulfa drugs, antimalarials, fava beans) → hemolysis. Causes extravascular and intravascular hemolysis.	Back pain, hemoglobinuria a few days after oxidant stress. Labs: ↓ G6PD activity (may be falsely normal during acute hemolysis), blood smear shows RBCs with Heinz bodies and bite cells. "Stress makes me eat bites of fava beans with Heinz ketchup."
Pyruvate kinase deficiency	Autosomal recessive. Pyruvate kinase defect → ↓ ATP → rigid RBCs → extravascular hemolysis. Increases levels of 2,3-BPG → ↓ hemoglobin affinity for O_2.	Hemolytic anemia in a newborn. Labs: blood smear shows burr cells.
Sickle cell anemia 	Point mutation in β-globin gene → single amino acid substitution (glutamic acid → valine) alters hydrophobic region on β-globin chain → aggregation of hemoglobin. Causes extravascular and intravascular hemolysis. Pathogenesis: low O_2, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) → vaso-occlusive disease. Newborns are initially asymptomatic because of ↑ HbF and ↓ HbS. Heterozygotes (sickle cell trait) have resistance to malaria. Sickle cells are crescent-shaped RBCs A. "Crew cut" on skull x-ray due to marrow expansion from ↑ erythropoiesis (also seen in thalassemias).	Complications: ▪ Aplastic crisis (transient arrest of erythropoiesis due to parvovirus B19). ▪ Autosplenectomy (Howell-Jolly bodies) → ↑ risk of infection by encapsulated organisms (eg, *Salmonella* osteomyelitis). ▪ Splenic infarct/sequestration crisis. ▪ Painful vaso-occlusive crises: dactylitis (painful swelling of hands/feet), priapism, acute chest syndrome (respiratory distress, new pulmonary infiltrates on CXR, common cause of death), avascular necrosis, stroke. ▪ Sickling in renal medulla (↓ Po_2) → renal papillary necrosis → hematuria (also seen in sickle cell trait). Hb electrophoresis: ↓↓ HbA, ↑ HbF, ↑↑ HbS. Treatment: hydroxyurea (↑ HbF), hydration.
HbC disease	Glutamic acid–to-lysine (lysine) mutation in β-globin. Causes extravascular hemolysis.	HbSC (1 of each mutant gene) milder than HbSS. Blood smear in homozygotes: hemoglobin crystals inside RBCs, target cells.

Splenic infarction usually occurs in the setting of splenic artery (or subbranch) occlusion due to hypercoagulable states, embolic disease, or hemoglobinopathy (eg, sickle cell disease or trait). Sickle hemoglobin mutations are often linked to Sub-Saharan Africa but are also common in other regions that have a high burden of malaria, including Central/South America, the Caribbean, the Middle East, the Mediterranean, and India. Most patients with sickle cell trait (eg, one altered beta-hemoglobin chain) are asymptomatic and considered benign carriers; however, certain stressors, such as flying at high altitude or dehydration due to alcohol consumption, can sometimes lead to intravascular hemolysis, tissue ischemia (eg, splenic infarction), and/or vasoocclusive pain. Hemoglobin electrophoresis is diagnostic.

Hereditary spherocytosis	
Epidemiology	• Usually autosomal dominant
Clinical presentation	• Hemolytic anemia • Jaundice • Splenomegaly
Laboratory findings	• ↑ MCHC • Negative Coombs test • Spherocytes on peripheral smear • ↑ Osmotic fragility on acidified glycerol lysis test • Abnormal eosin-5-maleimide binding test
Treatment	• Folic acid supplementation • Blood transfusion • Splenectomy

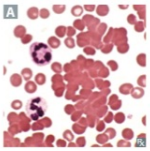
* Hereditary spherocytosis is associated with elevated MCHC (>36% Hb/cell) due to the increased (Hb:cell membrane ratio). It most commonly occurs in Northern Europeans.

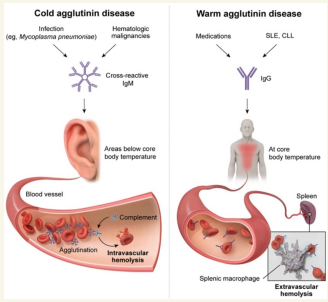
* Classic symptoms of acute cholecystitis (fever, right upper quadrant pain, positive Murphy sign, leukocytosis) due to pigment gallstones.

* G6PD deficiency causes hemolytic anemia due to oxidative stress (infection, fava beans, sulfa drugs (Dapsone is classically linked with G6PD exacerbations)). Treated by remove the responsible condition with supportive care. G6PD activity testing can be normal (low sensitivity) in acute hemolytic episodes because older erythrocytes (lowest G6PD activity) have been hemolyzed and young erythrocytes/reticulocytes (higher G6PD activity) are disproportionally elevated. So, repeat testing should be done at 3 months to confirm the diagnosis in those whose initial test was negative.

Patients with asplenia are at risk for fulminant infection with encapsulated bacteria (eg, Streptococcus pneumoniae, Haemophilus influenzae) due to deficits in antibody response and antibody-mediated phagocytosis/complement activation.

Extrinsic hemolytic anemias

	DESCRIPTION	FINDINGS
Autoimmune hemolytic anemia  (AIHA)	A normocytic anemia that is usually idiopathic and Coombs ⊕. Two types: ▪ **Warm** AIHA–chronic anemia in which primarily **IgG** causes extravascular hemolysis. Seen in SLE and CLL and with certain drugs (eg, β-lactams, α-methyldopa). "**Warm** weather is **G**ood." ▪ Cold AIHA–acute anemia in which primarily **IgM** + complement cause RBC agglutination and extravascular hemolysis upon exposure to cold → painful, blue fingers and toes. Seen in CLL, *Mycoplasma pneumoniae* infections, infectious **m**ononucleosis.	Spherocytes and agglutinated RBCs A on peripheral blood smear. Warm AIHA treatment: steroids, rituximab, splenectomy (if refractory). Cold AIHA treatment: cold avoidance, rituximab.
Drug-induced hemolytic anemia	Most commonly due to antibody-mediated immune destruction of RBCs or oxidant injury via free radical damage (may be exacerbated in G6PD deficiency). Common causes include antibiotics (eg, penicillins, cephalosporins), NSAIDs, immunotherapy, chemotherapy.	Spherocytes suggest immune hemolysis. Bite cells suggest oxidative hemolysis. Can cause both extravascular and intravascular hemolysis.
Microangiopathic hemolytic anemia (MAHA)	RBCs are damaged when passing through obstructed or narrowed vessels. Causes intravascular hemolysis. Seen in DIC, TTP/HUS, SLE, HELLP syndrome, hypertensive emergency.	**Schisto**cytes (eg, "helmet cells") are seen on peripheral blood smear due to mechanical destruction (***schisto*** = to split) of RBCs.
Macroangiopathic hemolytic anemia	Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction of RBCs.	Schistocytes on peripheral blood smear.
Hemolytic anemia due to infection	↑ destruction of RBCs (eg, malaria, *Babesia*).	



Autoimmune hemolytic anemia (AIHA)		
	Warm agglutinin AIHA	**Cold agglutinin AIHA**
Etiology	Drugs (eg, penicillin) Viral infections Autoimmune (eg, SLE) Immunodeficiency states Lymphoproliferative (eg, CLL)	Infections (eg, *Mycoplasma pneumoniae* infection & infectious mononucleosis) Lymphoproliferative diseases
Clinical presentation	Asymptomatic to life-threatening anemia Direct Coombs positive with anti-IgG, anti-C3, or both	Symptoms of anemia Livedo reticularis & acral cyanosis with cold exposure that disappear with warming Direct Coombs positive with anti-C3 or anti-IgM, but usually not IgG
Treatment	Corticosteroids Splenectomy for refractory disease	Avoidance of cold temperatures Rituximab ± fludarabine
Complications	Venous thromboembolism Lymphoproliferative disorders	Ischemia & peripheral gangrene Lymphoproliferative disorders

Penicillins (eg, amoxicillin) and cephalosporins are common triggers of drug-induced hemolytic anemia because these medications bind to the surface of erythrocytes, creating a hapten for IgG attachment. IgG-coated erythrocytes are then partially or wholly phagocytized by splenic macrophages, leading to extravascular hemolysis. Complement-mediated intravascular hemolysis may also occur. They may occur within 2-4 days of medication exposure. Treated by:

- Discontinue offending drug
- Transfusion (if severe)
- ± Glucocorticoids, IVIG

Scleroderma renal crisis (SRC) can occur in up to 20% of patients with diffuse cutaneous systemic sclerosis (SSc). It usually occurs within the first 5 years of SSc diagnosis, and typically presents with acute renal failure (without previous kidney disease) and malignant hypertension (eg, headache, blurry vision, nausea). Urinalysis may show mild proteinuria. Peripheral blood smear can show microangiopathic hemolytic anemia with fragmented red blood cells (eg, schistocytes) and thrombocytopenia.

A mechanical or severely calcified aortic valve can cause hemolytic anemia due to erythrocyte shearing. Patients also frequently have mildly low platelets due to concurrent mechanical platelet injury. Hepatosplenomegaly can develop as the fragmented erythrocytes are cleared in the macrophages and monocytes within the liver and spleen. An echocardiogram should be performed to assess the valvular function. Damaged erythrocytes that are not lysed in the intravascular space are generally destroyed by splenic macrophages, leading to concurrent extravascular hemolysis.

Causes of hemolysis	
Intravascularhemolysis	• Microangiopathic hemolytic anemia (eg, disseminated intravascular coagulation) • Transfusion reactions • Infections (eg, clostridial sepsis) • Paroxysmal nocturnal hemoglobinuria • Intravenous Rho(D) immunoglobulin infusion
Extravascularhemolysis	• Intrinsic RBC enzyme deficiencies (eg, G6PD) • Hemoglobinopathies (eg, sickle cell, thalassemia) • Membrane defects (eg, hereditary spherocytosis) • Hypersplenism, intravenous immunoglobulin infusion • Warm- or cold-agglutinin autoimmune hemolytic anemia (most cases) • Infections (eg, *Bartonella*, malaria)

In extravascular hemolysis, the RBCs are predominantly destroyed by phagocytes in the reticuloendothelial system (eg, lymph nodes, spleen). As a result, there is less hemoglobin release than in intravascular hemolysis, so laboratory results usually show normal to slightly low haptoglobin, slightly elevated LDH (vs. intravascular hemolysis, in which show significantly elevated LDH).

Pancytopenia

Causes of pancytopenia	
Bone marrow aplasia	• Aplastic anemia • Infection (eg, parvovirus, HIV, viral hepatitis) • Nutritional deficiency (eg, vitamin B_{12}/folate) • Medications (eg, hydroxyurea)
Bone marrow infiltration	• Cancer (eg, hematologic, metastatic) • Myelofibrosis • Infection (eg, tuberculosis, fungal infection)
Mature blood cell destruction	• Intravascular (eg, DIC, TTP) • Extravascular (eg, hypersplenism)

Leukopenias

CELL TYPE	CELL COUNT	CAUSES
Neutropenia	Absolute neutrophil count < 1500 cells/mm^3 Severe infections typical when < 500 cells/mm^3	Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, autoimmunity (eg, SLE), radiation, congenital
Lymphopenia	Absolute lymphocyte count < 1500 cells/mm^3 (< 3000 cells/mm^3 in children)	HIV, DiGeorge syndrome, SCID, SLE, glucocorticoids[a], radiation, sepsis, postoperative
Eosinopenia	Absolute eosinophil count < 30 cells/mm^3	Cushing syndrome, glucocorticoids[a]

[a]Glucocorticoids cause neutrophilia, despite causing eosinopenia and lymphopenia. Glucocorticoids ↓ activation of neutrophil adhesion molecules, impairing migration out of the vasculature to sites of inflammation. In contrast, glucocorticoids sequester eosinophils in lymph nodes and cause apoptosis of lymphocytes.

Severe thrombocytopenia: (platelet count <50,000/mm3). Platelet transfusions are typically given for a platelet count <10,000/mm3 (increased risk of spontaneous hemorrhage) or for a platelet count <50,000/mm3 with active bleeding.

Red blood cell transfusions are considered for life-threatening bleeding or a Hb level <7 g/dL (and possibly higher [<9 g/dl] in patients with coronary artery disease [CAD]).

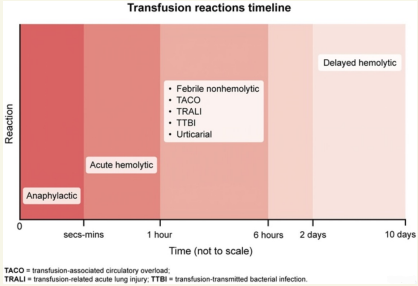
Drug-induced neutropenia	
Common triggers	• Methimazole, propylthiouracil • Trimethoprim-sulfamethoxazole • Clozapine • Sulfasalazine
Mechanism	• Immune mediated: drug or metabolite binds to neutrophils & triggers a cell-mediated or humoral response • Bone marrow toxicity: drug or metabolite directly or indirectly damages granulocyte precursors
Manifestations	• Usually within 3 months of drug exposure • Oropharyngeal ulceration ± fever • Other cell lines unaffected
Management	• Discontinue inciting medication • Antibiotics in setting of treatable infection • Consider granulocyte colony-stimulating factor

Drug-induced neutropenia is typically severe (ANC <500/mm3), isolated to leukocytes (eg, no anemia or thrombocytopenia) due to by direct toxicity (dose-dependent) or immune-mediated destruction (not dose-dependent), and often manifests with oropharyngeal mucositis and fever.
The most important first step is discontinuation of the offending medication. Most cases resolve within 1-3 weeks.

Transfusions

COMPONENT	DOSAGE EFFECT	CLINICAL USE
Packed RBCs	↑ Hb and O_2 binding (carrying) capacity, ↑ hemoglobin ~1 g/dL per unit, ↑ hematocrit ~3% per unit	Acute blood loss, severe anemia
Platelets	↑ platelet count ~30,000/microL per unit (↑ ~5000/mm^3/unit)	Stop significant bleeding (thrombocytopenia, qualitative platelet defects)
Fresh frozen plasma/ prothrombin complex concentrate	↑ coagulation factor levels; FFP contains all coagulation factors and plasma proteins; PCC generally contains factors II, VII, IX, and X, as well as protein C and S	Cirrhosis, immediate anticoagulation reversal
Cryoprecipitate	Contains fibrinogen, factor VIII, factor XIII, vWF, and fibronectin	Coagulation factor deficiencies involving fibrinogen and factor VIII
Albumin	↑ intravascular volume and oncotic pressure	Post-paracentesis, therapeutic plasmapheresis

Blood transfusion risks include infection transmission (low), transfusion reactions, transfusion-associated circulatory overload (TACO; volume overload → pulmonary edema, hypertension), transfusion-related acute lung injury (TRALI; hypoxia and inflammation → noncardiogenic pulmonary edema, hypotension), iron overload (may lead to 2° hemochromatosis), hypocalcemia (citrate is a Ca^{2+} chelator), and hyperkalemia (RBCs may lyse in old blood units).



Transfusion reactions associated with hypotension

Reaction	Onset*	Cause	Clinical features
Anaphylaxis	Seconds to minutes	Recipient anti-IgA antibodies	• Shock, angioedema/urticaria & respiratory distress
Transfusion-related acute lung injury	Minutes to hours	Donor antileukocyte antibodies	• Respiratory distress & noncardiogenic pulmonary edema • Bilateral pulmonary infiltrates
Acute hemolysis	Minutes to hours	ABO incompatibility	• Fever, flank pain, hemoglobinuria & DIC
Bacterial sepsis	Minutes to hours	Bacterial contamination of donor product	• Fever, chills, septic shock & DIC

*Time after transfusion initiation.

Delayed hemolytic transfusion reaction	
Pathogenesis	• Anamnestic antibody response: antibody production against minor RBC antigen to which patient was previously* exposed
Clinicalfindings	• Onset >24 hr to a month after transfusion • Often asymptomatic • Fatigue, dyspnea, tachycardia • Jaundice • Low-grade fever
Laboratoryfindings	• Hemolytic anemia ◦ ↑ Indirect bilirubin, LDH, reticulocyte count ◦ ↓ Hemoglobin, haptoglobin • New positive direct antiglobulin (Coombs) test
Management	• Supportive (eg, fluids)
Prevention	• Review transfusion history & prior antibody screens • Transfuse when necessary with extended-antigen cross-matched blood

*Prior transfusion (eg, sickle cell disease), pregnancy, or transplant.

Febrile nonhemolytic transfusion reaction (FNHTR) is the most common adverse reaction to transfusion, occurs within 1-6 hours of transfusion. During blood storage, leukocytes release cytokines that, when transfused, cause transient fevers, chills, and malaise. Management includes transfusion cessation (to exclude other serious reactions) and antipyretic administration.

Risk of recurrent FNHTR is high after a first episode, and prevention is best achieved by using leukoreduced blood products for future transfusions. Leukoreduction involves filtering out most of the leukocytes after blood collection but before blood storage, thereby minimizing cytokine production within the packed red blood cell product. It also reduces the risk of human leukocyte antigen alloimmunization and transmission of cytomegalovirus (which typically resides in leukocytes).

Patients with IgA deficiency are at higher risk of anaphylactic transfusion reaction because they may have anti-IgA antibodies that react with donor blood IgA and contribute to histamine release. Although IgA deficiency can present with recurrent sinopulmonary infections, it is often asymptomatic and may be diagnosed only after an anaphylactic transfusion reaction. Future transfusions should include IgA-deficient plasma and washed red blood cell products.
The first step in management of anaphylaxis is to immediately stop the transfusion and administer intramuscular epinephrine. Bronchodilators and antihistamines are typically also administered. In some cases, hemodynamic and respiratory support (eg, vasopressors, mechanical ventilation) may be required.

Transfusion-associated circulatory overload (TACO) is characterized by pulmonary edema due to volume overload. Patients have respiratory distress and hypoxia, but hypotension would not be expected (many patients are hypertensive).

Patients who have received the equivalent of more than one blood volume of blood transfusions or packed red blood cells over 24 hours (massive transfusions) may develop elevated plasma levels of citrate (a substance added to stored blood). Citrate chelates calcium and magnesium and may reduce their plasma levels, causing paresthesias.

Study Hereditary Hemochromatosis in Gastroenterology, page 14

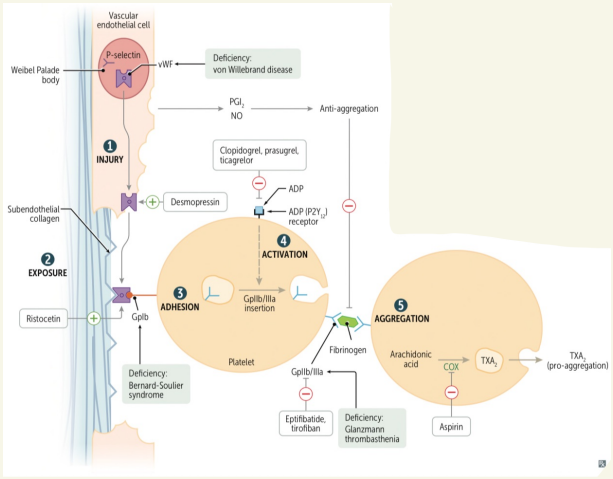
Hereditary Hemochromatosis (HH) patients are mostly diagnosed early in the disease due to elevated liver enzymes on routine laboratory studies. However, continued iron deposition can cause hepatic fibrosis and cirrhosis. with HH have an approximate 20-fold increased risk for hepatocellular cancer (HCC), accounting for 45% of deaths.

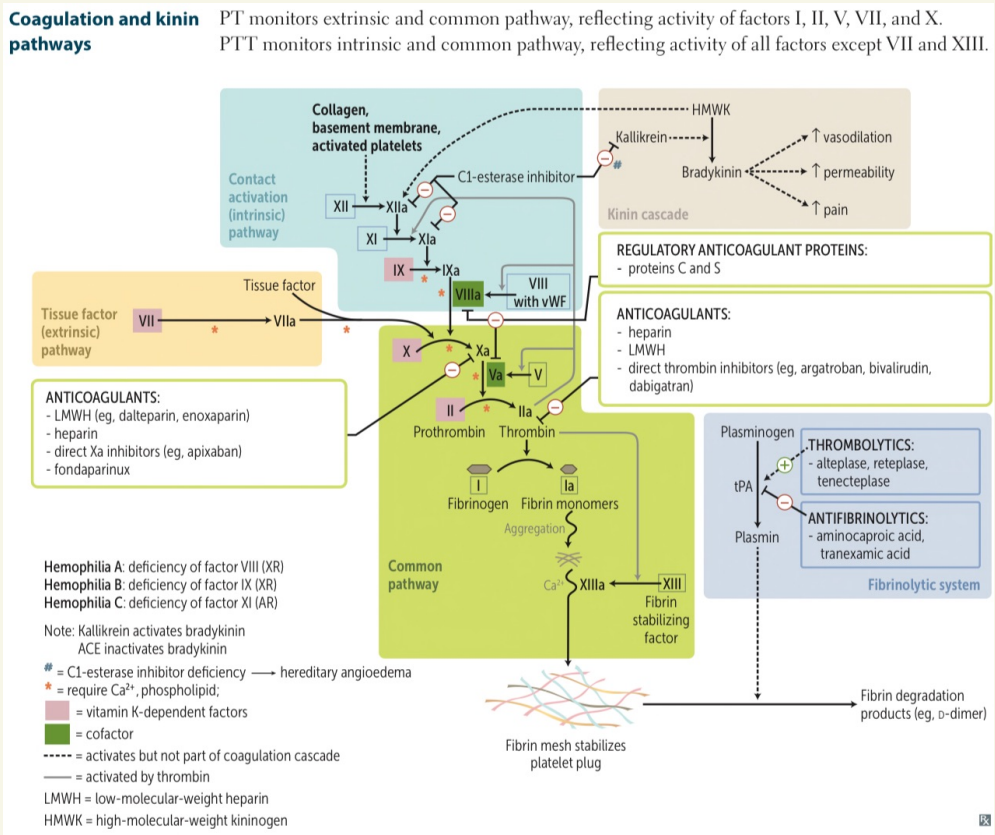
Clinical manifestations of hereditary hemochromatosis	
Skin	Hyperpigmentation (bronze diabetes)
Musculoskeletal	Arthralgia, arthropathy & chondrocalcinosis
Gastrointestinal	Elevated hepatic enzymes with hepatomegaly (early), cirrhosis (later) & increased risk of hepatocellular carcinoma
Endocrine	Diabetes mellitus, secondary hypogonadism & hypothyroidism
Cardiac	Restrictive or dilated cardiomyopathy & conduction abnormalities
Infections	Increased susceptibility to *Listeria*, *Vibrio vulnificus* & *Yersinia enterocolitica*

The initial evaluation of HH commonly shows elevated iron studies. Diagnosis can be confirmed by genetic analysis of HFE mutations. Serial phlebotomy to deplete excess iron stores can significantly reduce the risk for cirrhosis and HCC.

Fat embolism can be a complication of femoral or pelvic fracture and typically presents with respiratory distress and hypoxia. However, patients typically develop symptoms >24 hours after injury (vs. TRALI) and often also have altered consciousness and petechial rash.

1° & 2° Hemostasis





ITP & other Platelet disorders

All platelet disorders have increased bleeding time (BT), mucous membrane bleeding, and microhemorrhages (eg, petechiae, epistaxis). Platelet count (PC) is usually low, but may be normal in qualitative disorders.

DISORDER	PC	BT	NOTES
Bernard-Soulier syndrome	–/↓	↑	Autosomal recessive defect in adhesion. ↓ GpIb → ↓ platelet-to-vWF adhesion. Labs: ↓ platelet aggregation, Big platelets.
Glanzmann thrombasthenia	–	↑	Autosomal recessive defect in aggregation. ↓ GpIIb/IIIa (↓ integrin $\alpha_{IIb}\beta_3$) → ↓ platelet-to-platelet aggregation and defective platelet plug formation. Labs: blood smear shows no platelet clumping.
Immune thrombocytopenia	↓	↑	Destruction of platelets in spleen. Anti-GpIIb/IIIa antibodies → splenic macrophages phagocytose platelets. May be idiopathic or 2° to autoimmune disorders (eg, SLE), viral illness (eg, HIV, HCV), malignancy (eg, CLL), or drug reactions. Labs: ↑ megakaryocytes on bone marrow biopsy, ↓ platelet count. Treatment: glucocorticoids, IVIG, rituximab, TPO receptor agonists (eg, eltrombopag, romiplostim), or splenectomy for refractory ITP.
Uremic platelet dysfunction	–	↑	In patients with renal failure, uremic toxins accumulate and interfere with platelet adhesion.

Immune thrombocytopenic purpura	
Epidemiology	• Commonly acquired form of thrombocytopenia • Autoantibody formation • Often recent viral infection or comorbidity (eg, HIV, HCV, CLL)
Manifestations	• Frequently asymptomatic • Mucocutaneous bleeding (eg, menorrhagia, epistaxis) • Ecchymoses, petechiae, purpura • Severe hemorrhage is rare
Diagnosis	• Diagnosis of exclusion • Normal coagulation tests, platelet morphology (peripheral smear) • HIV, HCV testing (commonly induces ITP)
Treatment	• Observation if no bleeding & platelets >30,000/mm^3 • Corticosteroids if platelets <30,000/mm^3 • IVIG & platelet transfusion if hemorrhage

Although idiopathic thrombocytopenia (ITP) is a common cause of isolated thrombocytopenia (ie, normal hematocrit and leukocytes), it is a diagnosis of exclusion. HIV and hepatitis C are the most common secondary causes of ITP.

Hematologic abnormalities occur in > 50% of SLE patients and include:

- Anemia, resulting from immune destruction (AIHA), but also from coexisting renal disease or chronic inflammation.
- Leukopenia (eg, neutropenia), often immune-mediated and correlating with disease activity.
- Thrombocytopenia, most commonly due to ITP.

The presence of autoantibodies is the primary mechanism underlying the most common cytopenias in SLE. Thrombocytopenia is most often caused by antiplatelet antibodies, which trigger increased destruction of platelets via immunoglobulin binding in peripheral blood vessels and subsequent macrophage phagocytosis. “Peripheral” just means outside the bone marrow. So destruction in the spleen still counts as peripheral — as opposed to central causes, like decreased platelet production in the bone marrow.

TTP & HUS

	Thrombotic thrombocytopenic purpura	Hemolytic-uremic syndrome
EPIDEMIOLOGY	Typically females	Typically children
PATHOPHYSIOLOGY	Inhibition or deficiency of ADAMTS13 (a vWF metalloprotease) → ↓ degradation of vWF multimers → ↑ large vWF multimers → ↑ platelet adhesion and aggregation (microthrombi formation)	Predominately caused by Shiga toxin–producing *Escherichia coli* (STEC) infection (serotype O157:H7), which causes profound endothelial dysfunction.
PRESENTATION	Triad of thrombocytopenia (↓ platelets), microangiopathic hemolytic anemia (↓ Hb, schistocytes, ↑ LDH), acute kidney injury (↑ Cr)	
DIFFERENTIATING SYMPTOMS	Triad + fever + neurologic symptoms	Triad + bloody diarrhea
LABS	Normal PT and PTT helps distinguish TTP and HUS (coagulation pathway is not activated) from DIC (coagulation pathway is activated)	
TREATMENT	Plasma exchange, glucocorticoids, rituximab	Supportive care

Thrombotic microangiopathies are disorders overlap significantly in symptomatology.
May resemble DIC, but do not exhibit lab findings of a consumptive coagulopathy (PT, PTT, fibrinogen), as etiology does not involve widespread clotting factor activation.

Thrombotic Thrombocytopenic Purpura (TTP) is life threatening and must be treated with emergency plasma exchange (PEX), which removes the patient's plasma and replaces it with donor plasma. This replenishes ADAMTS13 and removes the autoantibodies. Without emergency PEX, mortality is approximately 90%. Patients with TTP frequently have acute (not chronic) anemia due to microangiopathic hemolysis. Most cases arise in middle age and are idiopathic; however, chronic infections (eg, HIV), malignancy, or certain medications can increase the risk for TTP. TTP must be treated urgently with plasma exchange. Patients should also receive high-dose glucocorticoids and rituximab to suppress autoantibody production by B cells. Caplacizumab (monoclonal antibody that blocks the vWF binding site for the ADAMTS13-autoantibody) is frequently added for severe disease.

DIC & vWF Disease

Mixed platelet and coagulation disorders

DISORDER	PC	BT	PT	PTT	NOTES
Von Willebrand Disease	—	↑	—	—/↑	Intrinsic pathway coagulation defect: ↓ quantity/function of vWF → ↑ PTT (vWF carries/protects factor VIII). Defect in platelet plug formation: ↓ vWF → defect in platelet-to-vWF adhesion. Most are autosomal dominant. Mild but most common inherited bleeding disorder. Commonly presents with menorrhagia or epistaxis. Treatment: vWF concentrates, desmopressin (releases vWF stored in endothelium).
Disseminated Intravascular Coagulation (DIC)	↓	↑	↑	↑	Widespread clotting factor activation → thromboembolic state with excessive clotting factor consumption → ↑ thromboses, ↑ hemorrhages (eg, blood oozing from puncture sites). May be acute (life-threatening) or chronic (if clotting factor production can compensate for consumption). Causes: heat Stroke, Snake bites, Sepsis (gram ⊖), Trauma, Obstetric complications, acute Pancreatitis, malignancy, nephrotic syndrome, transfusion (SSSTOP making new thrombi). Labs: schistocytes, ↑ fibrin degradation products (D-dimers), ↓ fibrinogen, ↓ factors V and VIII.

Because factor VIII degrades rapidly when not bound to vWF, patients with vWD generally have low factor VIII levels, which may prolong activated PTT.

Hemophilia & other Coagulation Disorders

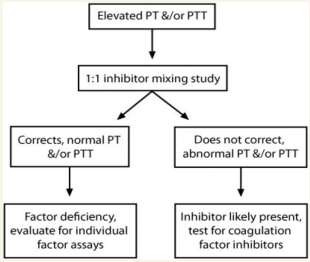
DISORDER	PT	PTT	MECHANISM AND COMMENTS
Hemophilia A, B, or C 	—	↑	Intrinsic pathway coagulation defect (↑ PTT). ▪ A: deficiency of factor VIII; X-linked recessive. Pronounce "hemophilia Ate (eight)." ▪ B: deficiency of factor IX; X-linked recessive. ▪ C: deficiency of factor XI; autosomal recessive. **Clinicalfeatures** • Delayed/prolonged bleeding after mild trauma ◦ Hemarthrosis, intramuscular hematomas ◦ Gastrointestinal or genitourinary tract bleeding ◦ Intracranial hemorrhage Treatment: desmopressin, factor VIII concentrate, emicizumab (A); factor IX concentrate (B); factor XI concentrate (C).
Vitamin K deficiency	↑	↑	General coagulation defect. Bleeding time normal. ↓ activity of factors II, VII, IX, X, protein C, protein S.

Study Hereditary Anti-Phospholipid Antibody Syndrome in Rheumatology, page 5

Anti-Phospholipid Antibody Syndrome (APAS)

Most patients with antiphospholipid antibodies are asymptomatic, but a minority develop antiphospholipid-antibody syndrome.
Patients with antiphospholipid antibodies (particularly LA) generally have prolonged PTT because antiphospholipid antibodies bind the phospholipids used in most testing assays and prevent them from inducing coagulation. This laboratory artifact will not be fixed in the mixing study by a 1:1 mixing with normal plasma (unlike coagulation factor deficiency). However, adding phospholipids to the testing assay will eventually overcome the presence of the inhibitor and normalize the PTT.

Diagnostic criteria for antiphospholipid-antibody syndrome **(1 clinical & 1 laboratory criterion must be met)**	
Clinical	**Vascular thrombosis** • Arterial or venous **Pregnancy morbidity** • ≥3 consecutive, unexplained fetal losses before 10th week • ≥1 unexplained fetal losses after 10th week • ≥1 premature births of normal neonates before 34th week due to preeclampsia, eclampsia, or placental insufficiency
Laboratory	• Lupus anticoagulant • Anticardiolipin antibody • Anti–beta-2 glycoprotein antibody I



Hereditary Thrombophilias

Antithrombin deficiency	Has no direct effect on the PT, PTT, or thrombin time but diminishes the increase in PTT following standard heparin dosing. Can also be acquired: renal failure/nephrotic syndrome → antithrombin loss in urine → ↓ inhibition of factors IIa and Xa.
Factor V Leiden	Production of mutant factor V (guanine → adenine DNA point mutation → Arg506Gln mutation near the cleavage site) that is resistant to degradation by activated protein C. Complications include DVT, cerebral vein thrombosis, recurrent pregnancy loss.
Protein C or S deficiency	↓ ability to inactivate factors Va and VIIIa. ↑ risk of warfarin-induced skin necrosis. Together, protein C Cancels, and protein S Stops, coagulation.
Prothrombin *G20210A* mutation	Point mutation in 3′ untranslated region → ↑ production of prothrombin → ↑ plasma levels and venous clots.

VTE

Modified Wells criteria for pretest probabilityof deep venous thrombosis	
Score 1 point for each feature present	• Previously documented DVT • Active cancer • Recent immobilization of the legs • Recently bedridden >3 days • Localized tenderness along vein distribution • Swollen leg • Calf swelling >3 cm compared to other leg • Pitting edema • Collateral superficial nonvaricose veins • Alternate diagnosis more likely (−2 points)
Total score for clinical probability	• 0 points = Low probability • 1 or 2 points = Moderate probability • ≥3 points = High probability

* In the absence of any clear provoking factors (eg, recent surgery, immobilization), patients with a first episode of venous thromboembolism (VTE) should be referred for age-appropriate cancer screening (eg, colonoscopy) to evaluate for malignancy as a potential risk factor for this disease.

Patients with clinical evidence of PE (eg, pleuritic chest pain, dyspnea, tachypnea, tachycardia) should be started on anticoagulation if there are no contraindications (eg, active bleeding) while undergoing diagnostic evaluation (eg, chest CT angiogram).
The deep veins of the lower extremities are the most frequent source of PE.
Lower extremity deep vein thrombosis (DVT) is divided into 2 categories:

- Proximal/thigh (eg, iliac, femoral, popliteal): These DVTs are the source of >90% of acute PEs, probably due to their large caliber and proximity to the lungs.
- Distal/calf: Although most DVTs occur in the calf vein, distal/calf DVTs are less likely than proximal/thigh DVTs to embolize to the lungs and cause PE and they are more likely to spontaneously resolve.

* Thrombi originating from the renal veins are most common in patients with nephrotic syndrome. The prevalence of PE in patients with nephrotic syndrome is 10%-30%.
* Thrombi originating in the right atrium are more common in patients with intracardiac devices (eg, pacemaker) and are less likely to occur spontaneously.

Spontaneous upper extremity DVT is generally uncommon (1%-4%) and even less likely to cause PE. Common risk factors for upper extremity DVT include prothrombotic state, indwelling catheter, and anatomical venous obstruction (eg, cervical rib, bony overgrowth after clavicular fracture).

Anti-coagulants

Heparin vs warfarin

	Heparin	Warfarin
ROUTE OF ADMINISTRATION	Parenteral (IV, SC)	Oral
SITE OF ACTION	Blood	Liver
ONSET OF ACTION	Rapid (seconds)	Slow, limited by half-lives of normal clotting factors
DURATION OF ACTION	Hours	Days
MONITORING	PTT (intrinsic pathway)	PT/INR (extrinsic pathway)
CROSSES PLACENTA	No	Yes (teratogenic)

Direct coagulation factor inhibitors

DRUG	
Bivalirudin, argatroban, dabigatran	IIa
Apixaban, edoxaban, rivaroxaban	Xa

Treatment of acute deep vein thrombosis/pulmonary embolism		
	Oral factor Xa inhibitors	Warfarin
Mechanismof action	Direct factor Xa inhibition	Vitamin K antagonism
Therapeutic onset	2-4 hr	5-7 days
Overlap needed?	No	Yes, overlap with UFHor LMWH for ~5 days
Laboratory monitoring	No	PT/INR

Oral direct factor Xa inhibitors have similar efficacy to warfarin in the treatment of acute venous thromboembolism (VTE) and do not increase the risk of bleeding complications. These drugs do not require laboratory monitoring or overlap therapy with heparin and are becoming preferred agents for the treatment of acute VTE.

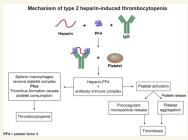
Anticoagulation failure (eg, recurrent or extending VTE while fully anticoagulated) or contraindication (eg, active bleeding, prosthetic valve, or dialysis) are indications for IVC filter placement.

Heparin “bridging”: heparin frequently used when starting warfarin. Heparin’s activation of antithrombin enables anticoagulation during initial, transient hypercoagulable state caused by warfarin. Initial heparin therapy reduces risk of recurrent VTE and skin/ tissue necrosis.

Heparin-induced thrombocytopenia (HIT):

- Type 1-HIT: (platelets > 100,000/mm3), transient, nonimmunologic drop in platelet count that typically occurs within the first 2 days of heparin administration. Not clinically significant.
- Type 2-HIT: should be suspected in patients receiving heparin who have thrombocytopenia, thrombosis (arterial or venous), or a >50% drop in the platelet count from baseline 5-10 days after the initiation of treatment, but it may occur earlier (sometimes <1 day) in patients previously exposed (e.g., patient with end-stage renal disease likely receives heparin with hemodialysis).

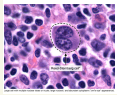
LMWH (e.g., anoxaparin, dalteparin) which acts mainly on factor Xa (not both II & X as unfractionated HEP does), has less risk. However, fonadparinux (anti-factor Xa) is safe and can be used instead.



Lymphomas

Lymphoma: discrete tumor mass arising from lymph nodes (vs Leukemia which is a lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood) with variable clinical presentation (eg, arising in atypical sites, leukemic presentation).

Hodgkin vs non-Hodgkin lymphoma



Hodgkin	Non-Hodgkin
Both may have constitutional ("B") signs/symptoms: low-grade fever, night sweats, weight loss.	
Localized, single group of nodes with contiguous spread (stage is strongest predictor of prognosis). Better prognosis.	Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread. Worse prognosis.
Characterized by Reed-Sternberg cells.	Majority involve B cells; rarely of T-cell lineage.
Bimodal distribution: young adults, > 55 years.	Can occur in children and adults.
Associated with EBV.	May be associated with autoimmune diseases and viral infections (eg, HIV, EBV, HTLV).

Hodgkin lymphoma	
Epidemiology	• Bimodal peak incidence: age 15-35 & >60 • Association with EBV in immunosuppression
Manifestations	• Painless lymphadenopathy • Mediastinal mass • B symptoms (ie, fever, sweats, weight loss) • Pruritus
Diagnosis	• Lymph node biopsy • Reed-Sternberg cells on histology

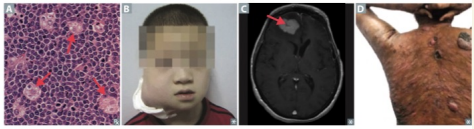
Hodgkin lymphoma often presents with painless peripheral lymphadenopathy (LAD) in the cervical and/or supraclavicular chains. Significant mediastinal LAD occurs in ~50% of cases and may lead to cough, SOB, or chest pain. Most patients have long-standing B symptoms (eg, fever, night sweats, weight loss) and pruritus (a paraneoplastic process classically associated with HL and likely due to cytokine and interleukin release). Laboratory evaluation often reveals normocytic anemia, eosinophilia (tumor cells secrete cytokines that generate eosinophils), lymphopenia(Massive lymphocytosis is unlikely), and elevated LDH (associated with high tumor burden).

Heterophile antibody testing can diagnose infectious mononucleosis (typically affects young adults), which often causes the classic triad of fever, tonsillar pharyngitis, and peripheral LAD (primarily in the cervical chain). LAD tends to be tender, splenomegaly is common, leukocytosis is generally mild (12,000-18,000/mm3), and cytopenias are rare. However, almost all cases resolve within a month.

Antinuclear antibodies (ANA) are elevated in systemic lupus erythematosus (SLE), which can cause fatigue, fever, and painless peripheral LAD in the cervical, axillary, or inguinal chains. However, supraclavicular LAD is quite uncommon and strongly suggests malignancy. In addition, SLE patients should have diagnostic features of SLE (eg, malar rash, arthralgia, serositis).

Non-Hodgkin lymphoma

TYPE	OCCURS IN	GENETICS	COMMENTS
Neoplasms of mature B cells			
Burkitt lymphoma	Adolescents or young adults "Burkid" lymphoma (more common in kids)	t(8;14)—translocation of c-*myc* (8) and heavy-chain Ig (14)	"Starry sky" appearance (StarBurst), sheets of lymphocytes with interspersed "tingible body" macrophages (arrows in A). Associated with EBV. Jaw lesion B in endemic form in Africa; pelvis or abdomen in sporadic form.
Diffuse large B-cell lymphoma	Usually older adults, but 20% in children	Mutations in *BCL-2*, *BCL-6*	Most common type of non-Hodgkin lymphoma in adults.
Follicular lymphoma	Adults	t(14;18)—translocation of heavy-chain Ig (14) and *BCL-2* (18)	Indolent course with painless "waxing and waning" lymphadenopathy. Bcl-2 normally inhibits apoptosis.
Mantle cell lymphoma	Adult males >> adult females	t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14), CD5+	Very aggressive, patients typically present with late-stage disease.
Marginal zone lymphoma	Adults	t(11;18)	Associated with chronic inflammation (eg, Sjögren syndrome, chronic gastritis [MALT lymphoma; may regress with *H pylori* eradication]).
Primary central nervous system lymphoma	Adults	EBV related; associated with HIV/AIDS	Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. CNS mass (often single, ring-enhancing lesion on MRI) in immunocompromised patients C, needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests.
Neoplasms of mature T cells			
Adult T-cell lymphoma	Adults	Caused by HTLV (associated with IV drug use)	Adults present with cutaneous lesions; common in Japan (T-cell in Tokyo), West Africa, and the Caribbean. Lytic bone lesions, hypercalcemia.
Cutaneous T-cell lymphoma	Adults		Heterogenous group of T-cell neoplasms affecting the skin ± blood, lymph nodes, or viscera. Most common subtype is mycosis fungoides D characterized by erythematous patches favoring sun-protected areas that progress to plaques, then eventually tumors.



* Malignancy is the most common cause of SVC syndrome. Lung cancer (particularly small cell lung cancer) and non-Hodgkin lymphoma (NHL) are often implicated. Other possible causes include fibrosing mediastinitis (secondary to histoplasmosis or TB infection) or thrombosis secondary to indwelling central venous devices. When the history and physical examination are suggestive (smoking history, weight loss, and other signs and symptoms including: dyspnea, venous congestion, and swelling of the head, neck and arms) chest x-ray is warranted. Abnormalities on chest x-ray warrant follow-up with chest CT and histology to determine the tumor type and to guide therapy.

* Patients with chronic autoimmune diseases are at increased risk for lymphoproliferative disorders such as NHL due to chronic B-cell stimulation, immune dysregulation, and use of immunosuppressive agents.

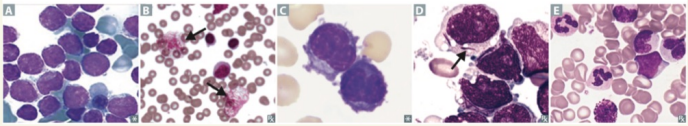
Patients with HIV are at a dramatically elevated risk of malignancy due to immune dysregulation and impaired cytokine signaling. This limits the ability of patrolling cytotoxic T-cells to induce apoptosis in cells that have accumulated genomic mutations. It also promotes reactivation of latent oncogenic viruses, which can cause AIDS-defining malignancies such as invasive cervical carcinoma (human papillomavirus), Kaposi sarcoma (human herpesvirus 8), CNS system lymphoma (Epstein-Barr virus [EBV]), and NHL.

Approximately 10% of patients with AIDS develop NHL; nearly all cases in this population are linked to the reactivation of EBV and the subsequent production of oncogenic viral proteins. Major manifestations include diffuse LAD, which may involve the epitrochlear, supraclavicular, and mediastinal (enlarged cardiac silhouette) lymph nodes. B symptoms (eg, night sweats, fevers, weight loss) are generally present. Diagnosis is usually made by excisional lymph node biopsy.

EBV is also associated with development of Hodgkin lymphoma, which can develop in patients with HIV, although NHL is more common in this population (possibly reflecting the immune interaction between Reed-Sternberg cells and nonmalignant inflammatory cells needed for the development of Hodgkin lymphoma).

Leukemias

TYPE	NOTES
Lymphoid neoplasms	
Acute lymphoblastic leukemia/lymphoma (ALL)	Most frequently occurs in children; less common in adults (worse prognosis). T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome. Peripheral blood and bone marrow have ↑↑↑ lymphoblasts A. TdT+ (marker of pre-T and pre-B cells), CD10+ (marker of pre-B cells). Most responsive to therapy. May spread to CNS and testes. t(12;21) → better prognosis; t(9;22) (Philadelphia chromosome) → worse prognosis.
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL)	Age > 60 years. Most common adult leukemia. CD20+, CD23+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells B in peripheral blood smear; autoimmune hemolytic anemia. CLL = Crushed Little Lymphocytes (smudge cells). Richter transformation—CLL/SLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).
Hairy cell leukemia	Adult males. Mature B-cell tumor. Cells have filamentous, hairlike projections (fuzzy appearing on LM C). Peripheral lymphadenopathy is uncommon. Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly and pancytopenia. Stains TRAP (Tartrate-Resistant Acid Phosphatase) ⊕ (TRAPped in a hairy situation). TRAP stain largely replaced with flow cytometry. Associated with *BRAF* mutations. Treatment: purine analogs (cladribine, pentostatin).
Myeloid neoplasms	
Acute myelogenous leukemia (AML)	Median onset 65 years. Auer rods D; myeloperoxidase ⊕ cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ↑↑↑ circulating myeloblasts on peripheral smear. May present with leukostasis (capillary occlusion by malignant, nondistensible cells → organ damage). Risk factors: prior exposure to alkylating chemotherapy, radiation, benzene, myeloproliferative disorders, Down syndrome (typically acute megakaryoblastic leukemia [formerly M7 AML]). APL: t(15;17), responds to all-*trans* retinoic acid (vitamin A) and arsenic trioxide, which induce differentiation of promyelocytes; DIC is a common presentation.
Chronic myelogenous leukemia (CML)	Peak incidence: 45–85 years; median age: 64 years. Defined by the Philadelphia chromosome (t[9;22], *BCR-ABL*) and myeloid stem cell proliferation. Presents with dysregulated production of mature and maturing granulocytes (eg, neutrophils, metamyelocytes, myelocytes, basophils E) and splenomegaly. May accelerate and transform to AML or ALL ("blast crisis"). Responds to BCR-ABL tyrosine kinase inhibitors (eg, imatinib).



Leukemia: unregulated growth and differentiation of WBCs in bone marrow —> marrow failure —> pancytopenia (anemia, infections, hemorrhage). Usually presents with increased circulating WBCs (malignant leukocytes in blood), although some cases present with normal/ decreased WBCs. Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

Chronic lymphocytic leukemia	
Clinical features	• Lymphadenopathy (cervical, supraclavicular, axillary) • Hepatosplenomegaly • Mild thrombocytopenia & anemia • Often asymptomatic
Diagnosis	• Severe lymphocytosis & smudge cells • Flow cytometry • Lymph node & bone marrow biopsy not generally needed
Prognosis	• Median survival 10 years • Worse prognosis with: ◦ Multiple chain lymphadenopathy ◦ Hepatosplenomegaly ◦ Anemia & thrombocytopenia
Complications	• Infection • Autoimmune hemolytic anemia • Secondary malignancies (eg, Richter syndrome)

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the United States.
Dramatic lymphocytosis is the classic hallmark of CLL. In an elderly patient, severe lymphocytosis combined with hepatosplenomegaly (abdominal fullness), lymphadenopathy, and bicytopenia (anemia, thrombocytopenia) strongly suggests underlying CLL. It is diagnosed by flow cytometry (clonality of mature B cells).

Hairy cell leukemia	
Features	• **Clonal B-cell neoplasm** • Middle-age/older adults • *BRAF* mutation
Manifestations	• **Pancytopenia** due to bone marrow fibrosis ◦ Granulocytopenia (infections) ◦ Anemia (fatigue, weakness) ◦ Thrombocytopenia (bleeding, bruising) • **Splenomegaly** (early satiety) • Hepatomegaly/lymphadenopathy rare
Diagnosis	• Peripheral smear – **"hairy" leukocyte cells** • **Bone marrow biopsy** with flow cytometry
Treatment	• Chemotherapy (for moderate/severe) • Life expectancy is often near-normal

Acute myeloid leukemia	
Background	• Most common adult acute leukemia • Median age 65
Manifestations	• **Fatigue** is common (other B symptoms unusual) • Often presents with **symptoms from cytopenias**: ◦ Fatigue, weakness (anemia) ◦ Bleeding, bruising (thrombocytopenia) ◦ Infection (granulocytopenia) • Hepatosplenomegaly/lymphadenopathy rare • Disseminated intravascular coagulation (if APML)
Laboratory	• Cytopenias (leukocytes may be ↑, normal or ↓) • Elevated lactate dehydrogenase • Peripheral smear - usually **myeloblasts** with **Auer rods**
Diagnosis	• **Bone marrow biopsy** - usually hypercellular with myeloid blasts

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and is typically associated with fatigue and symptoms related to >1 cytopenias.
Acute promyelocytic leukemia (APML) is a unique form of AML that often presents with life-threatening coagulopathy due to disseminated intravascular coagulation.

	Leukemoid reaction	CML
Leukocyte count	>50,000/mm^3 (>50 × 10^9)	Elevated(often >100,000/mm^3 [>100 × 10^9])
Cause	Severe infection	*BCR-ABL* fusion
LAP score	High	Low
Neutrophil precursors	More mature(metamyelocytes (bands) > myelocytes (promyelocytes))	Less mature(metamyelocytes < myelocytes)
Absolute basophilia	Not present	Present
LAP = leukocyte alkaline phosphatase.		

Severe infections can cause leukomoid reaction (LR) due to the mobilization of mature and immature leukocytes from the bone marrow. Given the severity of the infection, it may take >24 hours for clinical improvement with antibiotics

Chromosomal translocations

TRANSLOCATION	ASSOCIATED DISORDER	NOTES
t(8;14)	Burkitt (Burk-8) lymphoma (c-*myc* activation)	The Ig heavy chain genes on chromosome 14 are constitutively expressed. When other genes (eg, *c-myc* and *BCL-2*) are translocated next to this heavy chain gene region, they are overexpressed.
t(11;14)	Mantle cell lymphoma (cyclin D1 activation)	
t(11;18)	Marginal zone lymphoma	
t(14;18)	Follicular lymphoma (*BCL-2* activation)	
t(15;17)	APL (formerly M3 type of AML)	
t(9;22) (Philadelphia chromosome)	CML (*BCR-ABL* hybrid), ALL (less common); Philadelphia CreaML cheese	

PV & other Myeloproliferative Neoplasms

Polycythemia vera	
Manifestations	• ↑ Blood viscosity ◦ **Hypertension** ◦ **Erythromelalgia** (burning cyanosis in hands/feet) ◦ Transient visual disturbances • ↑ RBC turnover (gouty arthritis) • **Aquagenic pruritus** • Bleeding 
Examination	• Facial plethora (ruddy cyanosis) • Splenomegaly
Laboratory findings	• **Elevated hemoglobin** • Leukocytosis & thrombocytosis • **Low erythropoietin** level • ***JAK2* mutation** positive
Complications	• **Thrombosis** • Myelofibrosis & acute leukemia
Treatment	• **Phlebotomy** • Hydroxyurea (if ↑ risk of thrombus)

* Aquagenic pruritus (itching with warm water exposure) mostly suggests polycythemia Vera (PV).

* Most cases occur in patients age >60.

* Erythrocyte sedimentation rate (ESR) is increased in inflammatory or infectious states due to elevated circulating plasma proteins (usually fibrinogen). In PV, there is a higher relative concentration of erythrocytes to fibrinogen, which causes a low ESR.

Polycythemia

	PLASMA VOLUME	RBC MASS	O_2 SATURATION	EPO LEVELS	ASSOCIATIONS
Relative	↓	–	–	–	Dehydration, burns.
Appropriate absolute	–	↑	↓	↑	Lung disease, congenital heart disease, high altitude, obstructive sleep apnea.
Inappropriate absolute	–	↑	–	↑	Exogenous EPO (athlete misuse, also called "blood doping"), androgen supplementation. Inappropriate EPO secretion: malignancy (eg, RCC, HCC).
Polycythemia vera	↑	↑↑	–	↓	EPO ↓ in PCV due to negative feedback suppressing renal EPO production.

Serial phlebotomy is the mainstay of treatment for PV; it creates a relative iron deficiency and reduces hematocrit levels to normal range. Bone marrow suppressive drugs (eg, hydroxyurea) may be added in patients at high risk of thrombosis (eg, previous thrombosis, advanced age).
Transient ocular blindness in PV is not an indication for anticoagulation as it is due to microvascular sludging (from severe erythrocytosis), not thromboembolism.

The terms polycythemia and erythrocytosis are often used interchangeably. Polycythemia is a laboratory finding of elevated RBC count and hematocrit. Relative polycythemia is generally due to reduced plasma volume, whereas absolute polycythemia (ie, erythrocytosis) is due to increased RBC mass and can be primary (eg, polycythemia vera) or secondary (eg, due to chronic hypoxia or erythropoietin-producing tumors).

The mechanism for erythrocytosis in androgen abuse remains unclear, but increases in hematocrit and hemoglobin are dose dependent.

Budd-Chiari Syndrome	
Etiology	• Hepatic venous outflow obstruction • Usually due to: ◦ Myeloproliferative disorder (eg, PV) ◦ Malignancy (eg, hepatocellular carcinoma) ◦ Oral contraception use/pregnancy
Manifestations	• Acute ◦ Jaundice, hepatic encephalopathy, variceal bleeding ◦ Prolonged INR/PTT; elevated transaminases • Subacute/chronic ◦ Vague, progressive abdominal pain ◦ Hepatomegaly, splenomegaly, ascites ◦ Mild/moderate elevation in bilirubin, transaminases
Diagnosis	• Abdominal Doppler ultrasonography: ↓ hepatic vein flow • Investigation for underlying disorders (eg, *JAK2* testing for PV)

Patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) can develop pulmonary arteriovenous malformations associated with hemoptysis and right-to-left shunt physiology (AVMs in the lungs can shunt blood from the right to the left side of the heart, causing chronic hypoxemia, digital clubbing, and a reactive polycythemia). This diagnosis must be entertained in a patient with recurrent nose bleeds and oral (lips) lesions.

In patients with OSA, recurrent collapse of the pharynx during sleep results in transient airway obstruction. This causes short periods (20-40 seconds) of apnea or hypopnea, which reduce blood oxygen levels. The kidneys respond to the hypoxemia by increasing erythropoietin, which stimulates the bone marrow to differentiate more red blood cells (RBCs). Therefore, it is quite common for patients with OSA to have elevated hematocrit levels (polycythemia). Not all patients have obvious respiratory symptoms (eg, snoring, gasping for air); the sequelae of OSA (eg, erectile dysfunction, arterial hypertension) may be what prompts the initial evaluation.

	RBCs	WBCs	PLATELETS	PHILADELPHIA CHROMOSOME	*JAK2* MUTATIONS
Polycythemia vera	↑	↑	↑	⊖	⊕
Essential thrombocythemia	–	–	↑	⊖	⊕ (30–50%)
Myelofibrosis	↓	Variable	Variable	⊖	⊕ (30–50%)
CML	↓	↑	↑	⊕	⊖



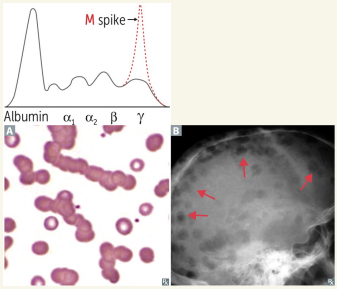
Essential thrombocythemia: Characterized by massive proliferation of megakaryocytes and platelets. Symptoms include bleeding and thrombosis. Blood smear shows markedly increased number of platelets, which may be large or otherwise abnormally formed. Erythromelalgia may occur.

Myelofibrosis: Atypical megakaryocyte hyperplasia —> increased TGF-β secretion —> increased fibroblast activity —> obliteration of bone marrow with fibrosis. Associated with massive splenomegaly and “teardrop” RBCs.

Plasma cell dyscrasias

Plasma cell dyscrasias are group of disorders characterized by proliferation of a single plasma cell clone, typically overproducing a monoclonal immunoglobulin (also called paraprotein). Seen in older adults.
Screening with serum protein electrophoresis (M spike represents overproduction of Monoclonal Ig), serum immunofixation, and serum free light chain assay.
Urine protein electrophoresis and immunofixation required to confirm urinary involvement (urine dipstick only detects albumin).
Diagnostic confirmation with bone marrow biopsy.

	Waldenström macroglobulinemia	Multiple myeloma
Major manifestations	• Hyperviscosity syndrome • Neuropathy • Bleeding • Hepatosplenomegaly • Lymphadenopathy	• Osteolytic lesions/fractures • Anemia • Hypercalcemia • Renal insufficiency
Monoclonal antibody	IgM	IgG, IgA, light chains
Peripheral smear	Rouleaux	Rouleaux
Bone marrow biopsy	>10% clonal B cells	>10% clonal plasma cells

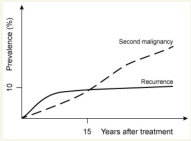


Multiple myeloma (MM) patients , at the time of diagnosis, approximately 25% of them will have hypercalcemia. Typically, this is a result of osteolytic bone destruction by the neoplastic plasma cells. Although hypercalcemia may be asymptomatic with a calcium level <12 mg/dL, fatigue, constipation, and depression are common. Neoplastic infiltration of the bone marrow alters and impairs the normal lymphocyte population, resulting in ineffective antibody production and hypogammaglobulinemia. Respiratory (eg, streptococcal pneumonia) and urinary tract infections are the most common infections seen in MM.

Waldenström macroglobulinemia (WM) characterised by:

- elevated serum IgM, which cause neuropathy, cryoglobulinemia, and hyperviscosity syndrome (headaches, dizziness, blurry vision, tinnitus, and large gamma gap (difference between total protein and albumin >4 g/dL), and tortious/ dilated/segmented (sausage-link) retinal changes on funduscopy).
- Neoplastic infiltration of tissue (hepatosplenomegaly, lymphadenopathy, cytopenias).

Chemotherapy & Radiotherapy & Bone Marrow Graft



Patients with Hodgkin lymphoma (HL) are generally treated with combination chemotherapy and radiation therapy, which cures >75% of cases. However, patients who undergo treatment for HL are at increased risk of death compared to an age-matched population due to the following:

1- HL relapse (or recurrence): The leading cause of death for the first 8-10 years after treatment is HL relapse. Relapses primarily occur in the first 2 years, but risk remains mildly elevated for life.

2- Second malignancy: The leading cause of death >8-10 years after treatment is second malignancy, and this risk increases with time:

- Radiotherapy: Breast and lung malignancies are most common due to their proximity to the mediastinum, which is often irradiated as part of HL treatment.
- Chemotherapy: Hematologic malignancy (eg, non-Hodgkin lymphoma) can also occur due to damage to hematologic stem cells from alkylating chemotherapy; milder chemotherapy regimens (eg, doxorubicin, bleomycin, vinblastine, and dacarbazine) are associated with less risk of second hematologic malignancy.

3- Cardiovascular disease: The leading cause of death not due to malignancy is cardiovascular disease. Most cardiovascular complications arise >10 years after treatment and are due to chemotherapy- or radiation-related damage to the heart muscle, valves, and vasculature.

Other common treatment-related complications include:

- pulmonary disease (eg, fibrosis, bronchiectasis) and hypothyroidism from chest radiation
- neuropathy from chemotherapy.

Patients who undergo treatment for HL typically receive intensive screening for HL relapse early after treatment and for malignancy and cardiovascular disease as time progresses (eg, >5 years after treatment). Modifiable risk factors for cancer (eg, quitting smoking) and heart disease (eg, control of hypertension and hyperlipidemia) should be addressed to lessen the risk of early death from these conditions.

* Induction therapy is an initial dose of treatment to rapidly kill tumor cells and send the patient into remission (<5% tumor burden). A typical example is induction chemotherapy for acute leukemia.

* Consolidation therapy is typically given after induction therapy with multidrug regimens to further reduce tumor burden. An example is multidrug therapy after induction therapy for acute leukemia.

* Neoadjuvant therapy is defined as treatment given before the standard therapy for a particular disease. For example, if the radiation therapy was given before the radical prostatectomy was done.

* Adjuvant therapy is defined as treatment given in addition to standard therapy. For example, if the radiation therapy was given at the same time as the radical prostatectomy.

* Maintenance therapy is usually given after induction and consolidation therapies (or initial standard therapy) to kill any residual tumor cells and keep the patient in remission. An example is daily antiandrogen therapy for prostate cancer.

* Salvage therapy is defined as treatment for a disease when standard therapy fails, such as radiation therapy for prostate-specific antigen recurrence after radical prostatectomy for prostate cancer.

* Serotonin (5HT) antagonists that block 5HT3 receptors are the drugs of choice for treating and preventing chemotherapy-induced nausea and vomiting.
Dopamine antagonists such as metoclopramide and prochlorperazine are useful second- or third-line agents for refractory vomiting. However, in the setting of recent chemotherapy, 5HT3 antagonists have a better side-effect profile and are more efficacious.

* Bisphosphonates (eg, zoledronic acid, pamidronate) are the drugs of choice for stabilizing bony metastatic lesions to prevent hypercalcemia of malignancy and pathologic fractures.

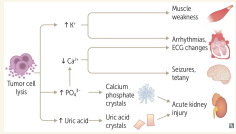
* Acute graft-versus-host disease (GVHD), which is common after bone marrow transplantation. Up to 50% of patients with BM transplantation from matched siblings develop the disease. The target organs for GVHD are the skin (maculopapular rash involving palms, soles, and face that may generalize is typical), intestine (blood-positive diarrhea), and liver (abnormal liver function tests and jaundice).
The basic pathophysiologic mechanism involved is recognition of host major and minor HLA-antigens by donor T-cells and consequent cell-mediated immune response.

* Graft rejection may occur in up to 20% of high-risk patients due to activation of the host T lymphocytes mediates the rejection of the graft, thereby resulting in the depression of myelopoiesis. Failure to generate blood cells manifests as severe neutropenia for several consecutive days and increased risk of infection.

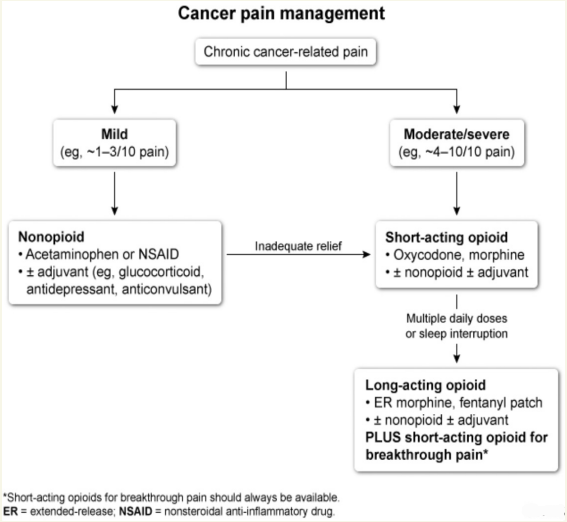
Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome	
Risk	• Tumors with high cell burden or rapid turnover • Combination chemotherapy/immunotherapy
Manifestations	• Severe electrolyte abnormalities ○ ↑ Phosphorus, potassium, uric acid ○ ↓ Calcium • Acute kidney injury • Cardiac arrhythmias • Seizures
Prophylaxis	• Intravenous fluids • Xanthine oxidase inhibitor* or rasburicase
Treatment	• Intravenous fluids + rasburicase • Continuous telemetry • Aggressive electrolyte monitoring & treatment
*Allopurinol or febuxostat.	

TLS is an ncologic emergency triggered by massive umor cell lysis, seen most often with lymphomas/leukemias. Usually caused by treatment initiation, but can occur spontaneously with fast-growing cancers. Renal injury can often be prevented with intravenous fluids to flush the kidneys and uric acid inhibitors to reduce serum uric acid levels.



Pain-Management



Once short-acting opioids have been started, if the patient's pain requires frequent dosing or if bedtime doses do not provide adequate relief through the night, conversion to long-acting opioids can improve convenience (eg, less frequent dosing) and help stabilize pain control. However, due to the risk of respiratory depression, patients not receiving opioids should generally not be started on long-acting opioids initially.

Radiation therapy can treat moderate to severe pain caused by bone metastases.



Nephrology

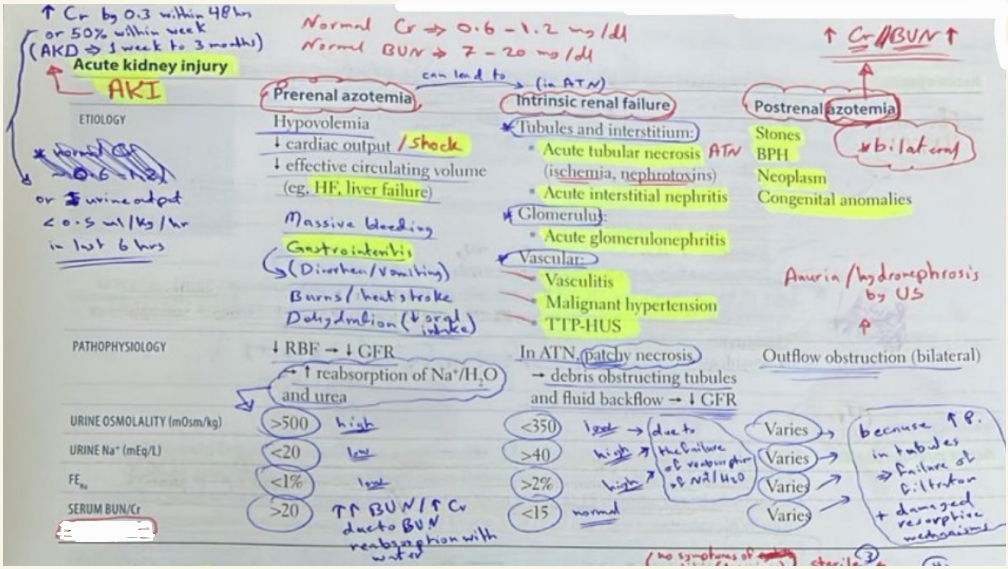
تَذكَّر:

إنَّ الطِّبَّ وسِيلةٌ.. لا غايَةٌ!

Contact & Updates:

Ehab Alroud

Acute Kidney Injury (AKI)



Renal ultrasound examination should be performed in all patients being evaluated for creatinine elevation or chronic kidney disease.

Most cases of renal failure result in hypocalcemia due to reduced renal phosphorus excretion; because phosphorous combines with calcium to form calcium phosphate salts, serum calcium levels usually decline. Patients who have acute renal failure and hypercalcemia often have an underlying malignancy that is driving calcium release. This is most often seen in the setting of multiple myeloma (MM), which classically presents with anemia, bone pain, hypercalcemia, and acute renal failure. MM-induced hypercalcemia is due to osteoclast activating factors and can cause AKI due to clogging of the renal tubules with calcium deposits or immunoglobulin light chains. Glassy light chain casts are often present, but the urinalysis may be bland if cast formation has not yet occurred. Urine dipstick typically demonstrates mild proteinuria (only detects albumin); however, a quantitative 24-hour protein assay will show elevated protein excretion (Bence-Jones proteinuria).

Acute Interstitial Nephritis (AIN)

Causes	• Medications (eg, antibiotics, NSAIDs, PPIs)* • Rheumatologic disease (eg, SLE, Sjögren syndrome, sarcoidosis) • Infections (eg, *Legionella*, tuberculosis, CMV)
Clinical features	• New medication exposure • Acute kidney injury • Arthralgias, malaise • Classic triad of fever, skin rash & eosinophilia rarely present**
Diagnosis	• Clinical presentation • Urinalysis: WBCs & WBC casts ± mild RBCs & proteinuria • Peripheral eosinophilia ± urine eosinophils • ± Renal biopsy: tubulointerstitial inflammation & edema
Management	• Discontinue offending drug or treat underlying condition • Systemic glucocorticoids • Supportive hemodialysis if needed
∗Medications account for ~75% of cases. ∗∗Classic triad is present in only ~10% of cases.	

Remember the causes of inflammation to your DRAINS:
- Diuretics
- Rifampin)
- Antibiotics (penicillins and cephalosporins)
- Proton pump Inhibitors
- NSAIDs
- Sulfa drugs

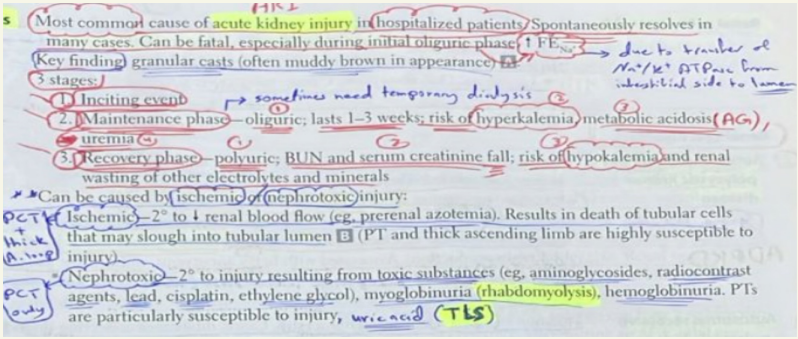
Patients with AIN are often asymptomatic. AIN involves antigen hypersensitivity that causes inflammation within the renal interstitium and tubules that leads to tubular accumulation of WBCs (ie, pyuria). Tubular damage may also lead to mild proteinuria and hematuria.
Glucocorticoids are used if the syndrome persists after drug discontinuation.

Renal Papillary Necrosis

Sloughing of necrotic renal papillae —> gross hematuria. May be triggered by recent infection or immune stimulus. Associated with: Sickle cell disease or trait, Acute pyelonephritis, Analgesics (eg, NSAIDs), and Diabetes mellitus.

Patients with sickle cell trait, a carrier mutation, do not typically have specific symptoms of sickle cell disease; however, sickling can occur in the setting of physiologic stress (eg, low oxygen tension, dehydration, acidosis), leading to renal papillary necrosis with hematuria and possibly flank pain. Increased renal medullary echogenicity seen on ultrasound

Acute Tubular Necrosis (ATN)



Accumulation to toxic levels typically occurs after >5-7 days of aminoglycoside use. Renal function usually returns to baseline within 3 weeks of drug cessation as PCT cells regenerate.

CA-AKI is a clinical diagnosis; kidney biopsy is typically not required. Consistent laboratory findings include a fractional excretion of sodium <1% (likely due to prerenal vasoconstriction) and muddy brown, granular casts on urine microscopy.

Metformin is typically held before administering contrast to patients at risk for CA-AKI. However, this is done in order to prevent metformin accumulation (eg, lactic acidosis) from reduced renal elimination. It does not reduce the risk for CA-AKI itself. Holding ACE inhibitors or angiotensin receptor blockers prior to arterial contrast administration has not been shown to reduce the risk for CA-AKI.
Systemic glucocorticoids are used to prevent an allergic reaction (eg, urticaria, bronchospasm) in patients with a known allergy to contrast media. However, glucocorticoids are not helpful in preventing CA-AKI.

Contrast-associated acute kidney injury	
Presentation	• Creatinine elevation 24–48 hr after *arterial* contrast administration • Gradual return to baseline within 3–7 days
Risk factors	• Chronic kidney disease (particularly diabetic nephropathy) • High contrast load • Hypovolemia • NSAID use
Pathophysiology	• Prerenal vasoconstriction • Direct tubular cytotoxicity
Diagnosis	• Clinical diagnosis (ie, biopsy usually not needed) • FeNa <1% & muddy brown, granular casts • Patchy necrosis of renal tubular cells on biopsy
Prevention	• Optimize renal perfusion (eg, 0.9% saline) • Hold NSAIDs • Use lowest volume of contrast agent possible

Clinical features of crystal-induced acute kidney injury	
Common etiologies	• Acyclovir • Sulfonamides • Methotrexate • Ethylene glycol • Protease inhibitors • Uric acid (tumor lysis syndrome)
Clinical presentation	• Usually asymptomatic • AKI ≤7 days of starting drug • UA: Hematuria, pyuria & crystals • Increased risk with volume depletion, CKD
Management	• Discontinuation of drug • Volume repletion • Loop diuretic

The kidneys rapidly excrete acyclovir into the urine, but the drug has low urine solubility. As a result, it easily precipitates (crystals) in renal tubules, causing intratubular obstruction and direct renal tubular toxicity.
A loop diuretic may be given concurrently with volume repletion to help flush the renal tubules. Preemptive administration of intravenous fluids while giving the drug can help prevent AKI.

Rhabdomyolysis

Etiology	Skeletal muscle lysis/necrosis due to: • Crush injury or prolonged immobilization • Intense muscle activity (eg, seizure, exertion) • Drug/medication toxicity (eg, statins)
Clinical features	• Muscle pain & weakness • Dark urine (myoglobinuria/pigmenturia) • + Blood on urinalysis & no RBCs on microscopy • ↑ Serum K & PO_4, ↓ serum Ca, ↑ AST > ALT • Acute kidney injury
Diagnosis	• Serum creatine kinase >1,000 U/L • Consistent clinical features
Management	• Aggressive intravenous fluid resuscitation • Sodium bicarbonate in some cases

Drug-induced rhabdomyolysis	
Major mechanism	**Examples**
Direct myotoxicity	Statins, fibrates Colchicine Ethanol Cocaine
Vasoconstrictive ischemia	Cocaine Amphetamines
Prolonged immobilization (compression ischemia)	Ethanol Opioids Benzodiazepines

Creatine phosphokinase is a marker of skeletal muscle damage, and serum elevation >1,000 U/L confirms the diagnosis in the appropriate clinical setting. An increase in serum creatinine is often delayed from presentation but can be profound over the ensuing days.

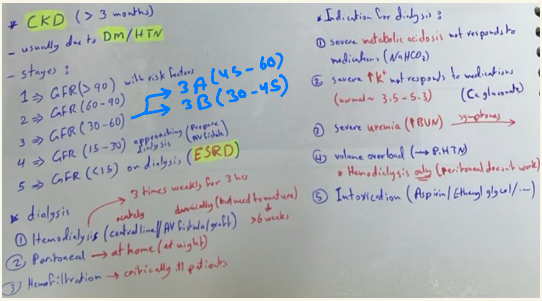
Discordance between urinalysis (rapid dipstick) and urine microscopy blood findings is useful in recognizing rhabdomyolysis. The blood component of urinalysis detects heme rather than actual RBCs. Therefore, myoglobinuria due to rhabdomyolysis leads to positive blood on urinalysis (due to the presence of heme from myoglobin degradation) in the absence of RBCs on urine microscopy; by contrast, true hematuria leads to positive blood on urinalysis and presence of RBCs on urine microscopy.

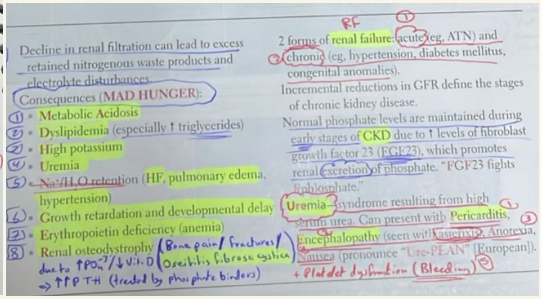
Alcohol binges can cause acute alcohol myopathy that predominantly affects the lower extremities, causing pain, weakness, and swelling.

Up to 50% of patients with rhabdomyolysis will develop acute kidney injury (AKI). During muscle cell lysis, intravascular fluid is shifted into the damaged muscle tissue, and heme-containing myoglobin is released into the bloodstream. The intravascular volume depletion causes an initial prerenal insult, which is followed by a subsequent insult from direct tubular toxicity of heme (pigment nephropathy).

Treatment of rhabdomyolysis involves aggressive volume resuscitation to replace intramuscular and intravascular fluid. Affected muscle groups must be monitored closely because the initial tissue damage and subsequent volume replacement create a risk for acute compartment syndrome

Chronic Kidney Disease (CKD)





Hypertensive nephrosclerosis develops in patients with chronically uncontrolled hypertension and is characterized by hyaline arteriolosclerosis and ischemic glomerulosclerosis. Clinical features include progressive, irreversible renal insufficiency with mild proteinuria and small, atrophic kidneys.

In patients with chronic kidney disease, platelet dysfunction is the most common cause of abnormal hemostasis (eg, easy bruising, nonpalpable purpura). PT and PTT are normal; platelet count is normal or mildly low.

In patients with an unknown baseline creatinine, renal ultrasonography can help establish the chronicity of injury; bilateral small kidneys on ultrasonography suggest chronic kidney disease (CKD).

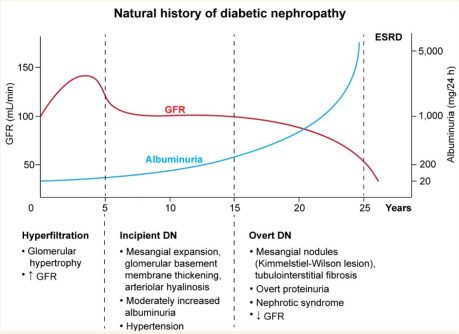
ACEi or ARBs are indicated for initial therapy in patients with renovascular hypertension (due to renal artery stenosis). Renal artery stenting or surgical revascularization is reserved for patients with resistant hypertension or recurrent flash pulmonary edema and/or refractory heart failure due to severe hypertension.

Cardiovascular risk factors in ESRD patients	
Traditional risk factors	• Hypertension, diabetes mellitus & dyslipidemia • Left ventricular hypertrophy • Advanced age & low physical activity
ESRD-specific risk factors	• Anemia of chronic kidney disease • Vascular calcifications (↑ phosphorus, ↑ calcium) • Oxidative stress related to uremia and dialysis

Cardiovascular disease (CVD) (eg, coronary artery disease, stroke) is the most common cause of death in patients with end-stage renal disease (ESRD), accounting for approximately 50% of deaths even in younger patients. Infection is the second most common cause of death in patients with ESRD, accounting for approximately 15%-20% of deaths. Dialysis catheter-related infections are common; mortality can be reduced with appropriate antibiotic treatment and replacement of infected catheters. Patients with ESRD are at increased risk for psychiatric conditions (prevalence of up to 70%), especially depression and anxiety.

Analgesic Nephropathy	
Pathophysiology	• Prolonged use of combination analgesics ◦ Acetaminophen: direct oxidative renal toxicity ◦ Aspirin/NSAIDs: depletion of glutathione impairs deactivation of reactive acetaminophen metabolites • Manifests as chronic interstitial nephritis ± papillary necrosis
Clinical presentation	• History of chronic pain (eg, headaches, lower back pain) • Often asymptomatic, may have malaise, fatigue, flank pain • Urinalysis: WBCs & WBC casts ± mild proteinuria • Hematuria & urine RBCs if papillary necrosis is present • Imaging: small kidneys ± papillary calcification & irregular contours

Although aspirin is a nonsteroidal anti-inflammatory drug, low-dose aspirin does not significantly affect renal blood flow and does not need to be held in patients with AKI. In patients with coronary artery disease, the benefits of continuing low-dose aspirin likely outweigh the risks.



Urine albumin/creatinine ratio (UACR) (ie, ratio of urine albumin [in milligrams] to urine creatinine [in grams]). UACR >30 mg/g suggests Diabetic Nephropathy (DN).

Metformin should be temporarily held in the setting of AKI and should not be given in patients with chronic kidney disease and an estimated glomerular filtration rate <30 mL/min.

* Advanced end-organ disease (eg, chronic kidney disease) is a common cause of unintentional weight loss in elderly patients. In the absence of signs, symptoms, or unexplained laboratory findings to suggest malignancy, watchful waiting and nutritional supplementation are appropriate in such patients.

Unintentional weight loss in elderly patients	
Definition	• >5% involuntary weight loss over 6-12 months
Causes	• Malignancy, depression • Chronic end-organ disease (eg, CKD, COPD) • Neurologic disease (eg, oropharyngeal dysphagia) • Social factors (eg, poverty, isolation) • Diminished smell & taste, poor dentition

Calcific uremic arteriolopathy (calciphylaxis)	
Pathophysiology	• Arteriolar & soft tissue calcification • Local tissue ischemia & necrosis
Risk factors	• End-stage renal disease • Hypercalcemia, hyperphosphatemia • Hyperparathyroidism • Oral anticoagulants (eg, warfarin)
Clinical manifestations	• Painful nodules & ulcers • Soft tissue calcification on imaging • Diagnosis requires skin biopsy: arteriolar calcification/occlusion, subintimal fibrosis
Management	• Analgesia & wound care • Treatment of risk factors (eg, high phosphorus, high calcium) • Optimization of dialysis

Renal Transplant

Renal artery stenosis (RAS) can occur in the renal allograft, typically within 2 years of transplant. Like other forms of RAS, suggestive findings include persistently elevated blood pressure, decline in renal function with the addition of ACE inhibitors, a lateralizing abdominal bruit, and recurrent flash pulmonary edema. The diagnosis is made with renal vascular imaging (eg, renal Doppler ultrasonography).

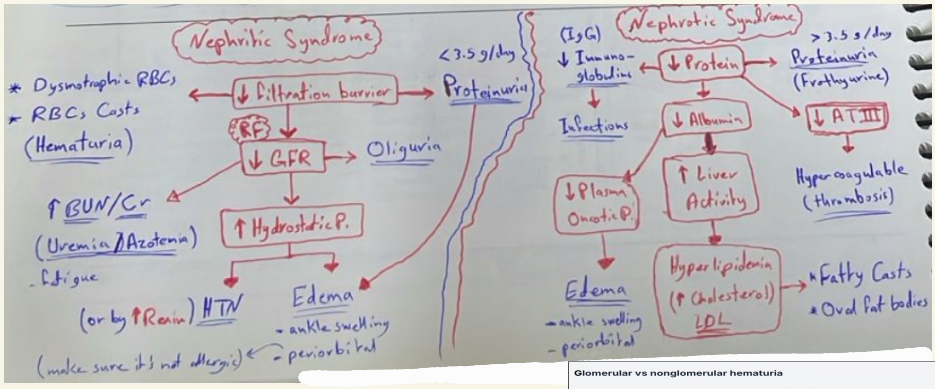
Management of transplant RAS usually includes angioplasty, possibly with stent placement.

Acute renal allograft rejection is predominantly T-cell mediated and usually occurs within the first 6 months following transplant. Affected patients typically experience an asymptomatic rise in serum creatinine, but they may have fever, decreased urine output, or graft tenderness, often accompanied by proteinuria.
The diagnosis is confirmed by renal biopsy showing lymphocytic infiltration of the intima, and treatment is with high-dose intravenous glucocorticoids, usually accompanied by increased dosing of the patient's maintenance immunosuppression regimen to help prevent further episodes.

Calcineurin inhibitors (eg, tacrolimus, cyclosporine) revolutionized organ transplant immunosuppression by providing relatively targeted inhibition of lymphocyte-mediated rejection (via inhibition of IL-2 production) with minimal hindrance of antimicrobial immunity. However, these drugs are not without adverse effects; they have vasoconstrictive properties that are responsible for much of their toxicity.

Acute CNIs toxicity is often triggered by impaired hepatic clearance of the drug and presents with hypertension and prerenal acute kidney injury. However, such adverse effects are more common with elevated plasma drug levels. Urine studies are usually unremarkable (bland), consistent with a prerenal etiology. The AKI is typically reversible with adjustment of CNI dosing and reduction in blood levels. Chronic CNIs renal toxicity can also occur. It likely results from both prolonged vasoconstrictive renal ischemia as well as possible direct tubular toxicity of the medication. It leads to a progressive, slow decline in renal function and is typically irreversible.

Nephritic & Nephrotic Syndromes



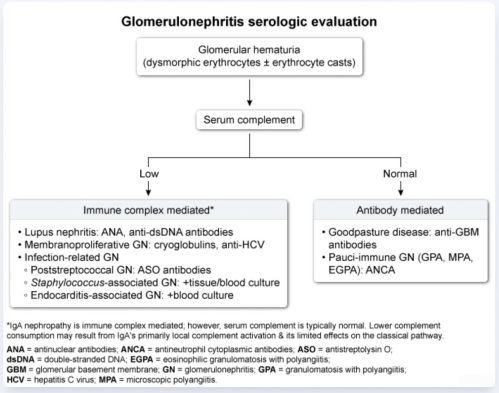
Urine dipstick for proteinuria (albumin)	
Trace	Between 15 and 30 mg/dL
1+	Between 30 and 100 mg/dL
2+	Between 100 and 300 mg/dL
3+	Between 300 and 1,000 mg/dL
4+	>1,000 mg/dL

	Nephritic	Nephrotic
Proteinuria	Mild	Significant (>3.5 g/day)
Serum albumin	Normal	Decreased
Edema	Mild	Significant
GFR	Decreased	Normal
Hypertension	Yes	No
Hematuria	Yes	No
Pyuria	Yes	No
Casts	RBC	Fatty or none

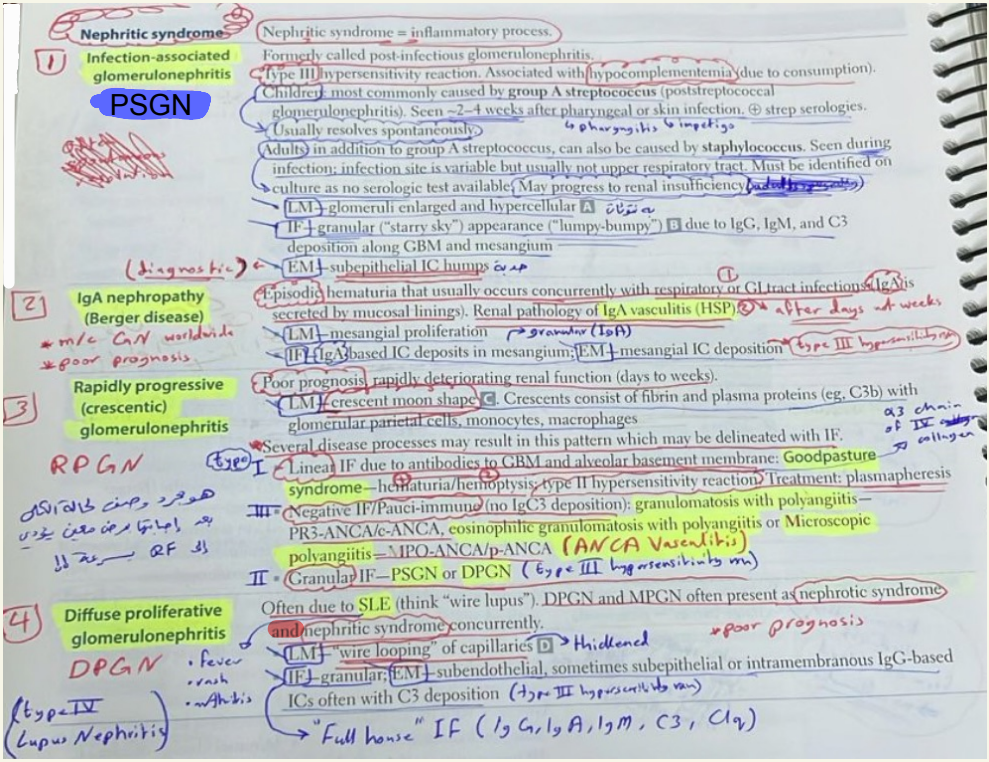
Glomerular vs nonglomerular hematuria

	Glomerular	Nonglomerular
RBC casts	May be seen[1]	Absent
Dysmorphic RBCs	Often present[2]	Rare, usually normal (ie, isomorphic)
Proteinuria[3]	Often ≥1+ (>500 mg/day)	Usually negative or trace (<500 mg/day)
Color	Dark red or brown (cola, tea)	Bright red or pink
Clots	Absent	Possible[1]

Virtually pathognomonic when present.
Acanthocytes highly specific; phase-contrast microscopy often needed for visualization.
Urine dipstick sensitive for albuminuria (ie, glomerular proteinuria).



- Muddy brown granular cast - Acute tubular necrosis
- Red blood cell casts - Glomerulonephritis
- White blood cell casts - Interstitial nephritis and pyelonephritis
- Fatty casts - Nephrotic syndrome
- Broad and waxy casts - Chronic renal failure

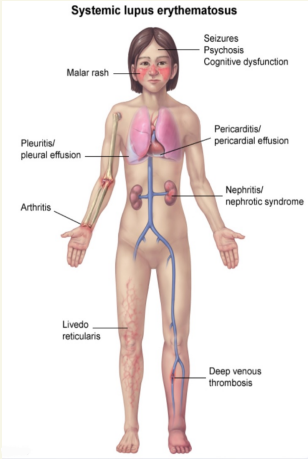


5	Alport syndrome	Type IV collagen mutation → glomerular basement membrane alterations; mostly X-linked dominant. Eye problems (eg, retinopathy, anterior lenticonus), glomerulonephritis, SNHL (can't see, can't pee, can't hear a bee)	Irregular thinning and thickening and splitting of glomerular basement membrane	Initially negative; non-specific staining (usually stays negative)	"Basket-weave" appearance due to irregular thickening and longitudinal splitting of GBM
6	Membrano-proliferative glomerulonephritis	Type I may be 2° to HBV or HCV infection; type II associated with C3 nephritic factor (IgG autoantibody that stabilizes C3 convertase → persistent complement activation → ↓ C3)	Mesangial ingrowth → GBM splitting → "tram-track" on H&E and PAS E stains	Granular	Type I—subendothelial IC deposits Type II—intramembranous deposits, also called dense deposit disease

The absence of dysmorphic RBCs or RBC casts does not exclude glomerular bleeding: both findings can be missed for various reasons (eg, prolonged centrifugation). Bilateral flank pain (vs unilateral suggesting a nonglomerular cause) are consistent with glomerular hematuria.

	IgA Nephropathy	APSGN
Onset	• Several days after upper respiratory tract infection or spontaneous • Most common in young adults	• Weeks after group A *Streptococcus* infection (eg, pharyngitis, impetigo) • Most common in school-aged children
Pathogenesis	• IgA-based immune complex deposition in mesangium	• Immune complex deposition along GBM (ie, subepithelial)
Clinical features	• Gross hematuria (often recurrent) • ± Flank pain, low-grade fever, hypertension • May be asymptomatic	• Gross hematuria • Edema (periorbital or generalized) • Hypertension • May be asymptomatic
Laboratory findings	• Urinalysis: + protein, RBCs, RBC casts • Serum: ◦ Normal C3 & C4 ◦ ↑ Creatinine	• Urinalysis: + protein, RBCs, RBC casts • Serum: ◦ ↓ C3 & CH_{50} ◦ ↓ Or normal C4 ◦ ↑ Creatinine

APSGN = acute poststreptococcal glomerulonephritis; **CH_{50}** = total complement; **GBM** = glomerular basement membrane;



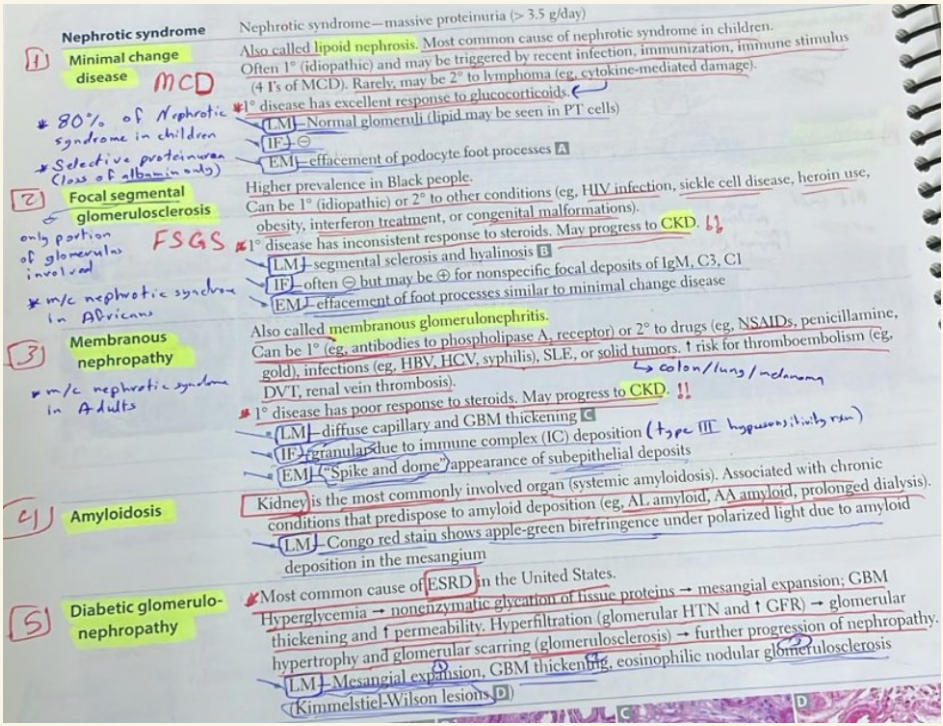
IgA nephropathy	
Clinical features	Onset: spontaneous or several days after URI Episodic gross hematuria ± Flank pain, low-grade fever, ↑ BP Asymptomatic, microscopic hematuria can occur
Laboratory findings	Urinalysis: protein, blood, red blood cell casts Normal serum C3 & C4 ↑ Serum creatinine
Diagnosis	Usually clinical Confirmed by kidney biopsy: mesangial IgA deposition
Prognosis/ risk factors	Often self-resolves End-stage renal disease in some patients Risk factors: ↑ creatinine, ↑ BP, persistent proteinuria Slowly progressive (>10 yr)

Lupus Nephritis	
Epidemiology	• Affects ~50% of patients with SLE • Can be the presenting manifestation of SLE
Pathogenesis	• Loss of immune tolerance to nuclear antigens (eg, nucleosomes) • Renal deposition of circulating ICs (eg, anti-dsDNA bound to DNA) • Complement activation & inflammatory injury
Clinical features(related to site of ICs)	• Mesangial: microscopic hematuria &/or asymptomatic hematuria • Subendothelial: glomerulonephritis ± proteinuria • Subepithelial: nephrotic syndrome
Diagnostic tests	• ANA, anti-dsDNA, anti-Smith • Low serum complement (C3 & C4) • Kidney biopsy

ANA = antinuclear antibody; **ds** = double-stranded; **IC** = immune complex; **SLE** = systemic lupus erythematosus.

MPGN is classically associated with cryoglobulinemic small-vessel vasculitis (eg, palpable purpura, arthralgia). MPGN can be caused by chronic hepatitis C (most common), hepatitis B, and HIV. Therefore, serum cryoglobulin testing should be accompanied by viral serologies.

Thin basement membrane disease is a benign familial condition that presents as microscopic or gross hematuria, which can occur after URI. A family history of hematuria usually exists, and hypertension and/or elevated creatinine is not typically seen.



Although malignancy is often clinically apparent before the onset of MN, MN can sometimes be the presenting feature of occult malignancy. Therefore, patients should undergo age-appropriate cancer screening (eg, colonoscopy, mammography).

Membranous Nephropathy	
Pathogenesis & etiology	• Immune-mediated podocyte injury • Primary: PLA2R autoantibodies (most common) • Secondary: infection (eg, hepatitis B), malignancy, autoimmune (eg, SLE), medication (eg, NSAID)
Clinical features	• Nephrotic syndrome, ↑ thromboembolic risk
Diagnosis	• Microscopy: diffuse GBM thickening, spikes on LM; granular IgG & C3 on IF; subepithelial deposits & podocyte effacement on EM • Laboratory testing: primary (eg, PLA2R studies); secondary (eg, ANA, viruses, cancer screening)
Treatment	• All patients: supportive care (eg, RAAS blockade, loop diuretics) • Primary: monitoring (low risk, spontaneous remission), immunosuppression (higher risk) • Secondary: therapy for underlying cause

Focal Segmental Glomerulosclerosis	
Pathogenesis	• Primary FSGS: circulating factor causing immune injury to podocytes • Secondary FSGS: glomerular hyperfiltration (eg, obesity, solitary kidney, reflux nephropathy), podocyte toxin (eg, heroin), infection (eg, HIVAN)
Clinical features	• Primary FSGS: usually nephrotic syndrome* • Secondary FSGS: proteinuria ± nephrotic syndrome
Diagnosis	• LM: segmental scarring in <50% of glomeruli** • IF: usually negative • EM: podocyte foot process effacement
Treatment	• Renin-angiotensin blockade, loop diuretics • Primary FSGS: immunosuppression • Secondary FSGS: risk factor modification (eg, weight loss, ART)

*Proteinuria >3.5 g/day, generalized edema & hypoalbuminemia.

**Glomerular tuft collapse is also seen in HIVAN.

Renin-angiotensin system inhibitors (eg, ACE inhibitors) reduce proteinuria and help delay kidney dysfunction. Many patients develop end-stage renal disease even with optimal therapy.

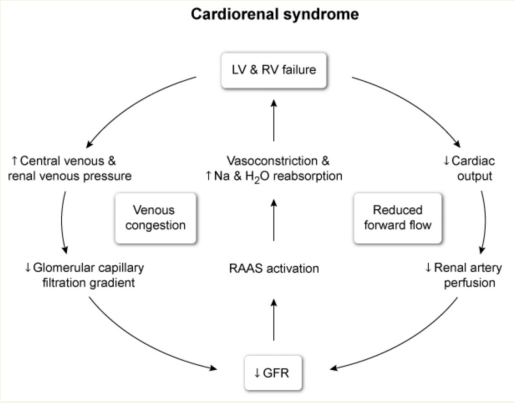
HIV-associated nephropathy (HIVAN) is caused by viral infection of podocytes that leads to nephrotic syndrome and a severe variant of focal segmental glomerulosclerosis (FSGS) with collapsing glomeruli. Suspected HIVAN requires confirmation of collapsing FSGS by biopsy because HIV can injure the kidneys by a variety of mechanisms. Antiretroviral therapy should be initiated or continued in patients with HIVAN to slow the progression of renal failure.

Hepatorenal Syndrome

Hepatorenal syndrome can occur in patients with advanced liver disease. It results from vasoconstriction of renal arterioles, causing prerenal injury with an expected blood urea nitrogen/creatinine ratio >20.

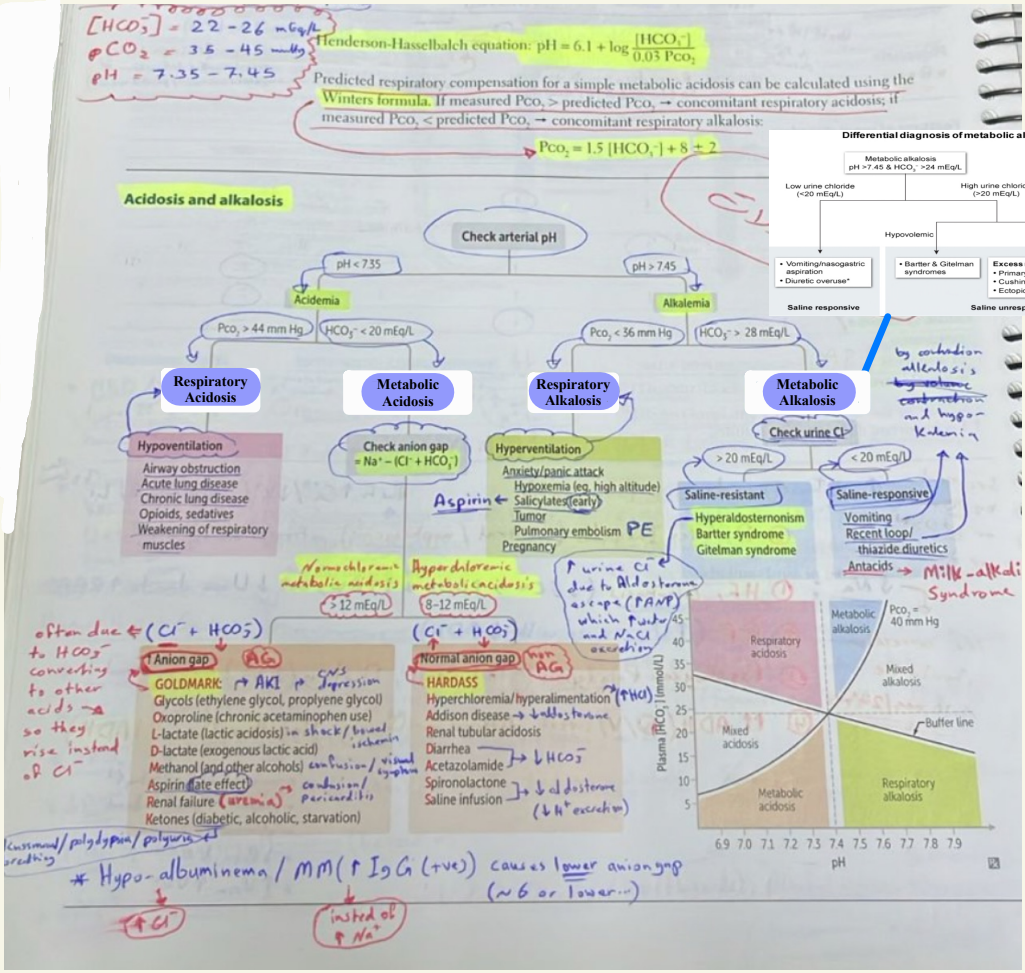
Risk factors	• Advanced cirrhosis with portal hypertension • Acute liver failure, severe alcoholic hepatitis
Pathophysiology	• Splanchnic vasodilation* → renal hypoperfusion → RAASactivation → overwhelming renal vasoconstriction → AKI • Precipitants: gastrointestinal bleed, infection (eg, SBP)
Diagnosis	• Bland urinalysis • Very low urine Na^+ (<10 mEq/L) • Exclusion of other causes of AKI • No improvement with trial of volume expansion
Treatment	• Albumin + splanchnic vasoconstrictors** (temporizing) • Liver transplantation (curative)
*Due to excess local release of vasodilators (eg, nitric oxide). **Terlipressin, norepinephrine, or midodrine plus octreotide.	

Cardiorenal Syndrome



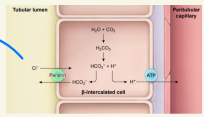
Prerenal acute kidney injury (AKI) can occur in volume-overloaded states. Prerenal AKI in an acute heart failure exacerbation is most likely due to cardiorenal syndrome, which involves elevated central venous and renal venous pressures leading to a reduction in glomerular filtration.

Acid-Base Disturbance



Appropriate compensatory $PaCO_2$ or HCO_3^- changes in acid-base disorders	
Metabolic acidosis (acute or chronic)	Expected $PaCO_2$ = (1.5 × HCO_3^-) + 8 ± 2 (Winters formula)
Metabolic alkalosis (acute or chronic)	~7 mm Hg ↑ in $PaCO_2$ per 10 mEq/L ↑ in HCO_3^-
Respiratory acidosis (chronic only*)	~4 mEq/L ↑ in HCO_3^- per 10 mm Hg ↑ in $PaCO_2$
Respiratory alkalosis (chronic only*)	~4 mEq/L ↓ in HCO_3^- per 10 mm Hg ↓ in $PaCO_2$
*Compensation for respiratory disturbances is minimal in the acute setting. The full level of chronic compensation is achieved after ~72 hr. For simplicity, normal baseline $PaCO_2$ & HCO_3^- should be considered 40 mm Hg & 24 mEq/L, respectively.	

Chronic vomiting leads to volume depletion and metabolic alkalosis, which is initiated by a loss of hydrogen and perpetuated by chloride depletion. Treatment with normal saline restores intravascular volume and replenishes chloride, thereby allowing renal elimination of bicarbonate.



Postictal lactic acidosis commonly occurs following a tonic-clonic seizure. It is a transient anion gap metabolic acidosis that resolves without treatment within 90 minutes following resolution of seizure activity. If the metabolic acidosis has not resolved, other potential causes of anion gap metabolic acidosis (eg, intoxication, sepsis) should be investigated.

Norepinephrine acts as a positive inotrope and vasoconstrictor and is often used in patients with lactic acidosis due to hypotension and poor organ perfusion (eg, sepsis) that persists following fluid resuscitation.

Etiologies of AGMA can be further elucidated by calculating the serum osmolal gap, which is the difference between measured osmolality and calculated osmolality. A high osmolal gap signifies a large amount of an osmotically active substance in the serum, namely a toxic alcohol such as methanol or ethylene glycol.

Serum osmolality (normal: 275-295 mOsm/kg H_2O)	
Calculated serum osmolality	$(2 \times Na^+)$ + (glucose / 18) + (BUN / 2.8) + (ethanol / 4.6)*
Serum osmolal gap	Laboratory-measured osmolality − calculated osmolality (>10 suggests unmeasured substance)

*Ethanol is frequently measured in the laboratory & may be included in the calculated serum osmolality when appropriate.
BUN = blood urea nitrogen.

Toxic alcohol ingestion (methanol or ethylene glycol)	
Typical sources	• Methanol: windshield wiper fluid, contaminated homemade liquor • Ethylene glycol: automotive coolant/antifreeze, brake fluid • Industrial solvents & deicing solutions may contain either toxic alcohol
Clinical features	• Early: CNS sedation & inebriation, osmolar gap • Late: anion gap metabolic acidosis, compensatory tachypnea ◦ Ocular toxicity (methanol) ◦ Urine oxalate crystals, hypocalcemia, AKI (ethylene glycol)
Management	• Fomepizole (inhibits ADHase) is preferred therapy • Ethanol solution (competes for ADHase) if fomepizole unavailable • IV sodium bicarbonate for acidemia (eg, pH <7.3) • Hemodialysis for severe cases (eg, acidosis, end-organ damage)
ADHase = alcohol dehydrogenase; **AKI** = acute kidney injury; **IV** = intravenous.	

Ethylene glycol is a sweet-smelling. Ethylene glycol is metabolized to glycolate, which is directly cytotoxic to the renal tubules (eg, acute kidney injury). Glycolate is further metabolized to oxalate, which contributes to oliguric renal failure by precipitating in the kidneys and forming calcium oxalate crystals that cause tubular obstruction. Urine microscopy typically shows envelope- or dumbbell-shaped calcium oxalate crystals.

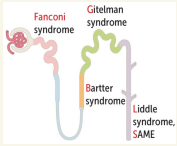
Mixed primary acid-base disorders				
	HCO_3^-	$PaCO_2$	pH	Example
Metabolic acidosis +respiratory acidosis	↓	↑	Very low	Sepsis (lactic acidosis)with respiratory failure
Metabolic alkalosis +respiratory alkalosis	↑	↓	Very high	Hyperemesis gravidarum &hyperventilation of pregnancy
Metabolic acidosis +respiratory alkalosis	↓	↓	Near normal	Salicylate toxicity
Metabolic alkalosis +respiratory acidosis	↑	↑	Near normal	Overdiuresed heart failure& underlying COPD
Metabolic acidosis + **metabolic alkalosis**	↔	↔	Near normal	Diabetic ketoacidosiswith severe vomiting

A mixed acid-base disorder involves ≥2 primary disturbances and may be suggested by either a very abnormal pH (eg, <7.2 or >7.6) or a near-normal pH despite significant abnormalities in serum bicarbonate (HCO3−) and PaCO2.

Acute salicylate (Aspirin) intoxication should be suspected in patients with the triad of tinnitus, fever, and tachypnea. It usually causes a mixed primary respiratory alkalosis and primary metabolic acidosis with arterial pH often within the normal range.

Acute salicylate toxicity usually presents with a mixed acid-base disturbance.

- Primary respiratory alkalosis develops shortly after ingestion because salicylates directly stimulate the medullary respiratory center, resulting in increased ventilation and low PaCO2.
- Primary anion gap metabolic acidosis develops after several hours because toxic salicylate levels inhibit oxidative phosphorylation. This results in the accumulation of unmeasured organic acids (eg, ketoacids, lactate) in the blood, which causes low serum HCO3−.
- Because the 2 primary disturbances shift arterial pH in opposite directions, arterial blood gas often shows a near-normal pH.

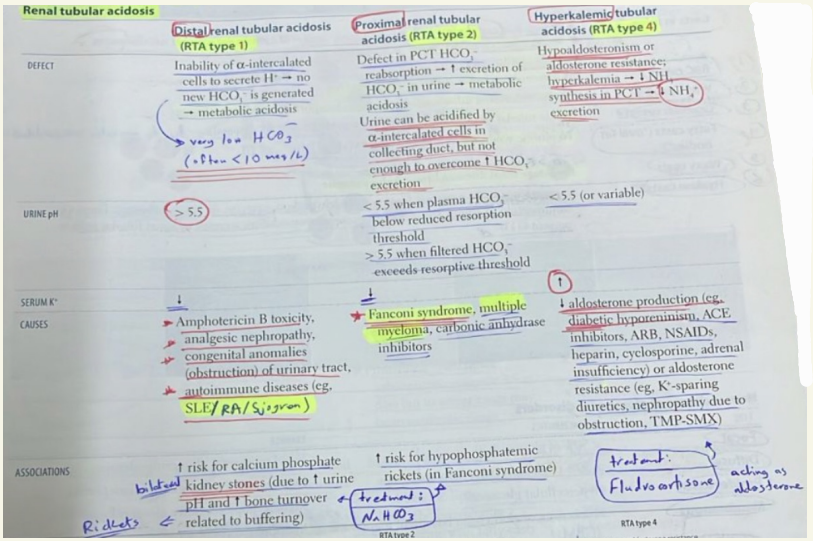


	DEFECTS	EFFECTS	CAUSES	NOTES
Fanconi syndrome	Generalized reabsorption defect in PCT → ↑ excretion of amino acids, glucose, HCO_3^-, and PO_4^{3-}, and all substances reabsorbed by the PCT	Metabolic acidosis (proximal RTA), hypophosphatemia, hypokalemia	Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, drugs (eg, ifosfamide, cisplatin, tenofovir, lead poisoning	Growth retardation and rickets/osteopenia common due to hypophosphatemia Volume depletion also common
Bartter syndrome AR	Reabsorption defect in thick ascending loop of Henle (affects $Na^+/K^+/2Cl^-$ cotransporter)	Metabolic alkalosis, hypokalemia, hypercalciuria	Autosomal recessive	Presents similarly to chronic loop diuretic use
Gitelman syndrome AR	Reabsorption defect of NaCl in DCT	Metabolic alkalosis, hypomagnesemia, hypokalemia, hypocalciuria	Autosomal recessive	Presents similarly to chronic thiazide diuretic use Less severe than Bartter syndrome
Liddle syndrome AD	Gain of function mutation → ↓ Na^+ channel degradation → ↑ Na^+ reabsorption in collecting tubules	Metabolic alkalosis, hypokalemia, hypertension, ↓ serum aldosterone	Autosomal dominant	Presents similarly to hyperaldosteronism, but aldosterone is nearly undetectable Treatment: amiloride
Syndrome of Apparent Mineralocorticoid Excess AR	Cortisol activates mineralocorticoid receptors; 11β-HSD converts cortisol to cortisone (inactive on these receptors) Hereditary 11β-HSD deficiency → ↑ cortisol → ↑ mineralocorticoid receptor activity	Metabolic alkalosis, hypokalemia, hypertension ↓ serum aldosterone level; cortisol tries to be the SAME as aldosterone	Autosomal recessive Can acquire disorder from glycyrrhetinic acid (present in licorice), which blocks activity of 11β-hydroxysteroid dehydrogenase	Treatment: K^+-sparing diuretics (↓ mineralocorticoid effects) or corticosteroids (exogenous corticosteroid ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation)

Autosomal recessive renal tubular channelopathies represent a special case. Bartter syndrome mimics loop diuretic overuse and Gitelman syndrome mimics thiazide diuretic overuse. Although affected patients are chloride depleted, high urine chloride is present because the defect persistently impairs renal Cl- reabsorption.
The metabolic alkalosis is saline unresponsive, and kidney transplantation is the only definitive treatment.

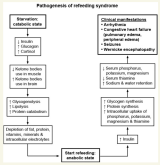
Renal Tubular Acidosis (RTA)

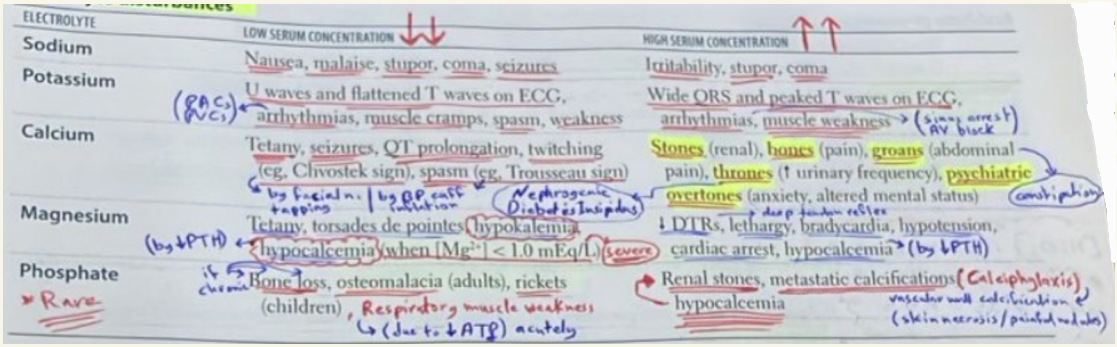
Renal tubular acidosis (RTA) involves a net loss of HCO3− and is a common cause of nonanion gap metabolic acidosis.

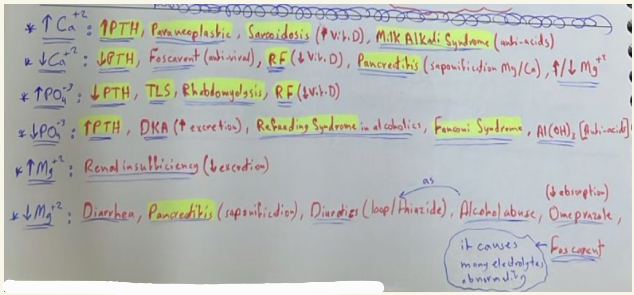


Hyperkalemic RTA is commonly seen in elderly patients who have poorly controlled diabetes with damage to the juxtaglomerular apparatus, which causes a state of hyporeninemic hypoaldosteronism.

Electrolyte Disturbance







Magnesium toxicity	
Causes	• Renal impairment (ie, decreased Mg excretion) • Increased Mg intake (eg, IV Mg sulfate, Mg-based laxatives/enemas)
Clinical features	• Neuromuscular: ↓ reflexes, weakness, paralysis, respiratory failure • Cardiovascular: hypotension, bradycardia, conduction defects • Electrolyte: hypocalcemia
Management	• Discontinue Mg-containing medications • IV fluids ± loop diuretics • IV calcium for neuromuscular & cardiac symptoms • Hemodialysis in severe renal impairment

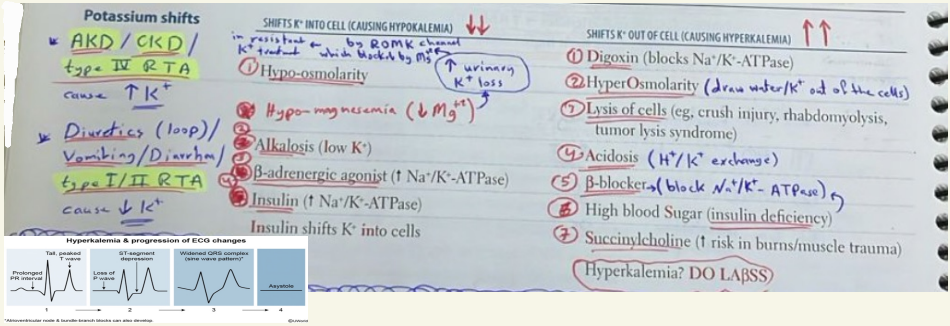
Patients with chronic alcohol use disorder often present with multiple electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypophosphatemia).

Hypomagnesemia can lead to refractory hypokalemia due to removal of inhibition of renal potassium excretion and should be suspected in patients with hypokalemia that is difficult to correct with potassium replacement. Intracellular magnesium is thought to inhibit potassium secretion by renal outer medullary potassium (ROMK) channels in the collecting tubules of the kidney.

Metabolic effects of thiazide diuretics	
Adverse effect	**Mechanism**
Hyponatremia	Inhibition of Na^+/Cl^- cotransporters in the distal convoluted tubule
Hypokalemia	Compensatory rise in renin & aldosterone secretion
Hypercalcemia	Increased reabsorption in distal tubule
Hyperglycemia	Decreased insulin secretion & increased insulin resistance
Hypercholesterolemia	
Hyperuricemia	Increased reabsorption in proximal tubule

Seizures are commonly caused by electrolyte abnormalities, most commonly severe hyponatremia. Hyponatremia is often seen in the setting of thiazide diuretic use, classically in elderly female patients with a low BMI (ie, thiazide-induced hyponatremia). Treatment includes permanent thiazide discontinuation and intravenous fluid administration.

Loop diuretics are frequently administered to cirrhotic patients with volume overload and ascites. Potential side effects include hypokalemia, metabolic alkalosis, and prerenal kidney injury.



Hyperkalemia ,in the outpatient setting, is most often caused by reduced urinary potassium excretion due to renal insufficiency or medications/disorders that impair the renin-angiotensin axis. Less common causes include the movement of potassium from the intracellular to the extracellular space (eg, uncontrolled hyperglycemia, metabolic acidosis) or increased tissue catabolism (eg, trauma, tumor lysis syndrome). Patients with persistent, unexplained hyperkalemia should be evaluated further for hypoaldosteronism with serum renin and aldosterone levels.

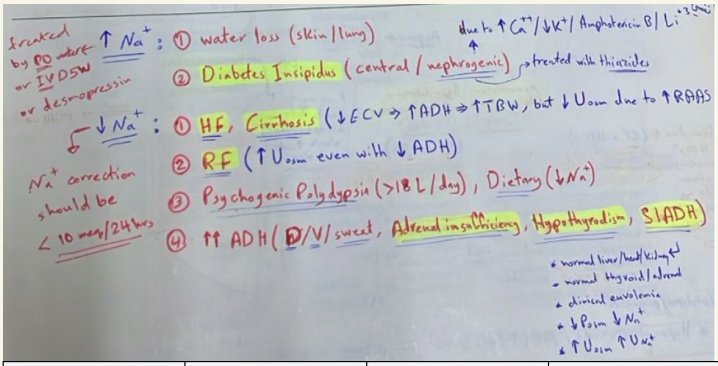
It is generally managed with a low-potassium diet (eg, <40-70 mEq/day) and avoidance of other medications (eg, nonsteroidal anti-inflammatory drugs) that raise serum K.

Definitive treatment of hyperkalemic emergency (ECG changes, potassium ≥6.5 mEq/L) requires removing potassium from the body via the stool (eg, patiromer), kidneys (eg, furosemide), and/or blood (eg, hemodialysis). However, these therapies often take hours to have effect. Because hyperkalemic emergency can rapidly cause death, urgent treatment is indicated. This typically includes administering intravenous calcium (eg, calcium gluconate), which counterbalances the membrane depressive effect of hyperkalemia. In addition, intravenous insulin (often given in combination with glucose to prevent hypoglycemia) should be administered because it moves potassium into cells due to increased activity of the Na+/K+-ATPase in skeletal muscle.

Common medications that cause hyperkalemia

Medication	Mechanism
ACE inhibitor, ARB	Decreases aldosterone secretion (inhibition of AT II/AT II receptor) + inhibits ENaC
Cyclosporine	Blocks aldosterone activity
Digitalis	Inhibits Na^+/K^+-ATPase
Heparin	Blocks aldosterone production
Nonselectiveβ-adrenergic blocker	Interferes with β_2-mediated intracellular potassium uptake
NSAID	Decreases renal perfusion → decreased potassium delivery to the collecting ducts
Potassium-sparing diuretic	Inhibits ENaC or aldosterone receptor
Succinylcholine	Causes extracellular leakage of potassium through acetylcholine receptors
Trimethoprim	Inhibits ENaC

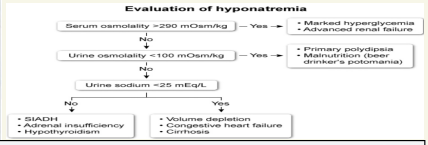
The benefit of renin-angiotensin system inhibitors in patients with CKD generally outweigh the risk of chronic hyperkalemia; therefore, the medication is usually continued and the hyperkalemia is treated separately.



Hypervolemic hyponatremia	
Pathogenesis	• ↓ EABV* → ↓ renal perfusion (↑ RAAS) & hypotension (↑ ADH) • Water reabsorption > salt reabsorption
Associated conditions	• Heart failure • Cirrhosis • Kidney disease (eg, kidney failure, nephrotic syndrome)
Treatment	• Hypervolemia: diuretics • Hyponatremia: no specific therapy** ◦ Minimize hypotension to ↓ ADH

*Kidneys & baroreceptors incorrectly sense that hypovolemia is present.

**Management should focus on minimizing hypotension to decrease ADH. Treatment can be considered in severe hyponatremia (<120 mEq/L) or if the patient is significantly symptomatic (eg, seizures).



Serum osmolality	ECV	Urine findings	Causes
Hypotonic (<275 mOsm/kg)	Hypovolemic	U_{Na} <40 mEq/L	• Nonrenal salt loss (eg, vomiting, diarrhea)
		U_{Na} >40 mEq/L	• Renal salt loss (eg, diuretics, primary adrenal insufficiency)
	Euvolemic	U_{Osm} <100 mOsm/kg	• Primary polydipsia • Malnutrition (eg, beer potomania)
		U_{Osm} >100 mOsm/kg & U_{Na} >40 mEq/L	• SIADH*
	Hypervolemic	Variable	• Heart failure, cirrhosis, nephrotic syndrome
Isotonic	Variable		• Pseudohyponatremia (eg, paraproteinemia, hyperlipidemia)
Hypertonic (>295 mOsm/kg)			• Translocational hyponatremia (eg, hyperglycemia, exogenous solutes like mannitol)

*Hypothyroidism & secondary adrenal insufficiency should be ruled out.

Elevated blood glucose increases plasma osmolality, drawing water out of cells and diluting serum sodium.

Hyponatremia in the hypovolemic state occurs due to nonosmotic stimulation of antidiuretic hormone (ADH) secretion in response to hypovolemia, hypotension, and decreased renal perfusion (via angiotensin II). Restoration of blood volume shuts off nonosmotic stimulation of ADH and corrects the hyponatremia.

Intravascular volume depletion occurs in dehydration and can lead to hyponatremia due to decreased renal perfusion and excess free water retention. The urine sodium concentration should be low (<40 mEq/L) as the kidneys attempt to retain solute in an effort to increase blood volume.

Syndrome of inappropriate antidiuretic hormone	
Etiologies	• CNS disturbance (eg, stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs) • Lung disease (eg, pneumonia) • Ectopic ADH secretion (eg, small cell lung cancer) • Pain &/or nausea
Clinicalfeatures	• Mild/moderate hyponatremia: nausea, forgetfulness • Severe hyponatremia: seizures, coma • Euvolemia (eg, moist mucous membranes, no edema, no JVD)
Laboratoryfindings	• Hyponatremia • Serum osmolality <275 mOsm/kg H_2O (hypotonic) • Urine osmolality >100 mOsm/kg H_2O • Urine sodium >40 mEq/L
Management	• Fluid restriction ± salt tablets • Hypertonic (3%) saline for severe hyponatremia

Patients with SIADH are typically euvolemic; therefore, urine sodium concentration is typically elevated (>40 mEq/L), unlike in patients with hypovolemia where the kidneys attempt to retain solute in an effort to increase blood volume.

Sertraline level is not routinely measured; SIADH can occur at a therapeutic SSRI level.

The symptoms of SIADH depend on the degree of hyponatremia and the rate at which it occurred. Rapid decreases (over <48 hours) in serum sodium concentration lead to profound fluid shifts and severe symptoms. Patients with serum sodium 130-135 mEq/L are usually asymptomatic; those with chronic hyponatremia with serum sodium 120-130 mEq/L may be asymptomatic or display mild symptoms (lethargy, forgetfulness). These patients usually respond to fluid restriction (<800 mL/day), sometimes with the addition of salt tablets.

Patients with serum sodium <120 mEq/L may have severe symptoms (eg, profound confusion, seizures, coma), which signal an increased risk of cerebral edema and brainstem herniation. These patients require an urgent increase in their serum sodium concentration that is best accomplished with administration of hypertonic (3%) saline. Extreme care must be taken with the rate of correction (<8 mEq/L over the first 24 hours), as rapid correction results in excess water being moved by osmosis from the intracellular compartment (neurons and glia) into the extracellular compartment. This in turn leads to disruption of cellular metabolic activity and subsequent cell damage (i.e., central pontine myelinolysis or osmotic demyelination syndrome, a devastating and potentially fatal complication (eg, dysarthria, quadriparesis, coma)). The opposite is true when rapidly correcting a patient with hypernatremia, when cerebral edema can occur.

Management of hypercalcemia	
Severe(calcium >14 mg/dL)or symptomatic	**Short-term (immediate) treatment** • Normal saline hydration plus calcitonin • Avoid loop diuretics unless volume overload (heart failure) exists **Long-term treatment** • Bisphosphonate (zoledronic acid)
Moderate(calcium 12-14 mg/dL)	• Usually no immediate treatment required unless symptomatic • Treatment is similar to that for severe hypercalcemia
Asymptomatic or mild(calcium <12 mg/dL)	• No immediate treatment required • Avoid thiazide diuretics, lithium, volume depletion & prolonged bed rest

Hypercalcemia patients are typically volume depleted due to polyuria and decreased oral intake. Initial treatment includes saline hydration to restore intravascular volume and calcitonin to inhibit bone resorption. The calcium-lowering effect of bisphosphonates is delayed, usually occurring over 2-4 days, and they are typically given after initial administration of saline and calcitonin.

Although loop diuretics can promote diuresis and reduce calcium levels, their routine use in hypercalcemic patients is not recommended as they can worsen the volume depletion. Hemodialysis is an effective treatment for hypercalcemia. However, it is typically reserved for patients with renal insufficiency or heart failure in whom aggressive hydration cannot be administered safely. Glucocorticoids can be used to treat hypercalcemia due to excessive vitamin D intake, granulomatous diseases (eg, sarcoidosis), and certain lymphomas, by inhibiting the formation of 1,25-dihydroxyvitamin D by activated mononuclear cells in the lungs and lymph nodes.

Study sarcoidosis in Pulmonolgy, page 46 & Cardiology, page 13

Sarcoidosis

Sarcoidosis is a multisystem, granulomatous disorder that can manifest with skin findings, including papular lesions and erythema nodosum. Hypercalcemia in sarcoidosis occurs due to extrarenal calcitriol production in the lungs and lymph nodes and is independent of parathyroid hormone (PTH). It is associated with high serum calcitriol, low PTH, and increased urinary calcium.

Pulmonary	Hilar lymphadenopathy* Interstitial infiltrates
Cutaneous	Papules, nodules & plaques Erythema nodosum*
Ophthalmologic	Anterior & posterior uveitis Keratoconjunctivitis sicca
Neurologic	Facial nerve palsy Central diabetes insipidus Hypogonadotropic hypogonadism
Cardiovascular	AV block Dilated or restrictive cardiomyopathy
Gastrointestinal	Hepatosplenomegaly Asymptomatic LFT abnormalities
Other	Hypercalcemia Peripheral lymphadenopathy Parotid gland swelling Polyarthritis* Constitutional symptoms (fever,* malaise)
*Manifestations of Löfgren syndrome.	

Familial hypocalciuric hypercalcemia (FHH)

FHH is a benign autosomal dominant disorder caused by a mutation of the calcium-sensing receptor (CaSR). Normally, high-normal calcium levels suppress PTH secretion by the parathyroid glands, but in FHH, higher calcium concentrations are required to suppress PTH release. Concurrently, the defective CaSR leads to increased reabsorption of calcium in renal tubules.

In the evaluation of hypercalcemia, an elevated (or inappropriately normal) PTH level suggests either primary hyperparathyroidism or FHH. However, patients with primary hyperparathyroidism have increased urinary calcium excretion due to excessive mobilization of calcium from bones, whereas patients with FHH usually have very low urinary calcium levels (typically <100 mg/24 hr).

Urine calcium excretion can be more precisely assessed using the urine calcium/creatinine clearance ratio (UCCR) = (Caurine/Caserum)/(Creaturine/Creatserum) UCCR is usually <0.01 in FHH compared to >0.02 in primary hyperparathyroidism.

Most patients with FHH are asymptomatic, although potential complications include pancreatitis and chondrocalcinosis. In the absence of complications, no specific treatment is required.

UTI

Acute Cystitis

Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency. Systemic signs (eg, high fever, chills) are usually absent.

Risk factors include female sex (short urethra), sexual intercourse, indwelling catheter, diabetes mellitus, impaired bladder emptying.

Causes:

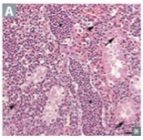
- *E coli* (most common)
- *Staphylococcus saprophyticus*—seen in sexually active young women (*E coli* is still more common in this group)
- *Klebsiella*
- *Proteus mirabilis*—urine has ammonia scent

Labs: ⊕ leukocyte esterase. ⊕ nitrites (indicates presence of Enterobacteriaceae). Sterile pyuria (pyuria with ⊖ urine cultures) could suggest urethritis by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

Treatment: antibiotics (eg, TMP-SMX, nitrofurantoin).

Pyelonephritis

Acute pyelonephritis



Neutrophils infiltrate renal interstitium A. Affects cortex with relative sparing of glomeruli/vessels. Presents with fevers, flank pain (costovertebral angle tenderness), nausea/vomiting, chills.

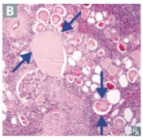
Causes include ascending UTI (*E coli* is most common), hematogenous spread to kidney. Presents with WBCs in urine +/– WBC casts. CT would show striated parenchymal enhancement.

Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy (progesterone-mediated ↓ in ureter tone and compression by gravid uterus).

Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess (with possible posterior spread to adjacent psoas muscle), urosepsis.

Treatment: antibiotics.

Chronic pyelonephritis



The result of recurrent or inadequately treated episodes of acute pyelonephritis. Typically requires predisposition to infection such as vesicoureteral reflux or chronically obstructing kidney stones.

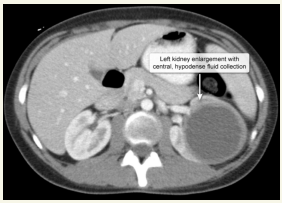
Coarse, asymmetric corticomedullary scarring, blunted calyces. Tubules can contain eosinophilic casts resembling thyroid tissue B (thyroidization of kidney).

Treatment of urinary tract infection in nonpregnant women	
UncomplicatedUTI	• Nitrofurantoin Can be given for pregnant • Trimethoprim-sulfamethoxazole • Fosfomycin (single dose) • Fluoroquinolones only if previous options cannot be used • Urine culture only if initial treatment fails
ComplicatedUTI*	• Outpatient: fluoroquinolones • Inpatient: ceftriaxone, piperacillin-tazobactam, carbapenems (eg, imipenem) • Culture obtained prior to therapy, with adjustment of antibiotic as needed
*Infection above the bladder (eg, pyelonephritis), pelvic pain in men, other signs or symptoms of systemic illness.	

Preferred empiric treatment options include trimethoprim-sulfamethoxazole (3 days), nitrofurantoin (5 days), and fosfomycin (single dose). Intramuscular ceftriaxone with oral doxycycline is often used empirically for treating suspected chlamydial and/or gonococcal infections.

Symptoms suggestive of a complicated UTI include fever, chills or rigors, and flank pain or costovertebral angle tenderness.

Renal Abscess



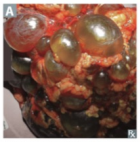
Renal and perinephric abscesses can form in the setting of urologic infection (eg, pyelonephritis, UTI) or through hematogenous spread (eg, bacteremia, endocarditis). Necrosis of infected tissue progresses over time to cavity formation; therefore, manifestations typically develop insidiously (average ~12 days of symptoms) in patients with a history of a predisposing infection in the prior 1-2 months.

Systemic symptoms (eg, fever, fatigue, diaphoresis, weight loss) are common. Because of the localized nature of the process, unilateral flank pain/tenderness and a palpable mass may be present, but UTI symptoms (eg, dysuria, urinary urgency) are often absent. Although urinalysis results often include pyuria, bacteriuria, and proteinuria, findings may be normal if the abscess is not in contact with the collecting ducts.

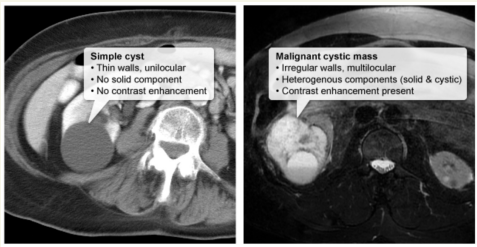
The diagnosis is confirmed with CT scan or ultrasound. Management includes antibiotic therapy and percutaneous drainage.

Renal tuberculosis (due to hematogenous spread of miliary tuberculosis) can result in abscess formation or glomerulonephritis; pyuria, hematuria, urinary casts, and lower urinary tract symptoms are common. In addition, tuberculosis typically occurs in patients with risk factors (eg, incarceration, employment in high-risk health care).

Renal Cyst Diseases: AD Polycystic Kidney & Others

Autosomal dominant polycystic kidney disease 	Numerous cysts in cortex and medulla A causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with combinations of flank pain, hematuria, hypertension, urinary infection; progressive renal failure in ~ 50% of individuals. Mutation in genes encoding polycystin protein: PKD1 (85% of cases, chromosome 16) or PKD2 (15% of cases, chromosome 4). Complications include chronic kidney disease and hypertension (caused by ↑ renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts, diverticulosis. Treatment: If hypertension or proteinuria develops, treat with ACE inhibitors or ARBs.
Autosomal recessive polycystic kidney disease 	Mutation in *PKHD1* encoding fibrocystin. Cystic dilation of collecting ducts B. Often presents in infancy, and may be seen on prenatal ultrasound. Associated with congenital hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.
Autosomal dominant tubulointerstitial kidney disease	Also called medullary cystic kidney disease. Causes tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; smaller kidneys on ultrasound. Poor prognosis.
Simple vs complex renal cysts	Simple cysts are filled with ultrafiltrate (anechoic on ultrasound). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic. Complex cysts, including those that are septated, enhanced, or have solid components on imaging require follow-up or removal due to possibility of renal cell carcinoma.

Characteristics of renal cysts	
Simple renal cyst	**Malignant cystic mass**
Thin, smooth, regular wall	**Thick, irregular wall**
Unilocular	Multilocular
No septae	Multiple **septae**, occasionally thick & calcified
Homogeneous content	Heterogeneous content (solid & cystic)
Absence of contrast enhancement on CT/MRI	Presence of **contrast enhancement** on CT/MRI
Usually asymptomatic	May cause pain, hematuria, or hypertension
No follow-up needed	Requires follow-up imaging & urological evaluation for malignancy



Simple renal cysts are most commonly seen in patients age >50. They are benign and often discovered incidentally by radiological examination.

Percutaneous aspiration may be considered if the cyst is large and painful or infected with purulent material.

Autosomal dominant polycystic kidney disease	
Clinicalpresentation	• Most patients asymptomatic until age 30-40 • Flank pain, hematuria • Hypertension • Palpable abdominal masses (usually bilateral) • Chronic kidney disease (CKD)
Extrarenalfeatures	• Cerebral aneurysms • Hepatic & pancreatic cysts • Mitral valve prolapse, aortic regurgitation • Colonic diverticulosis • Ventral & inguinal hernias
Diagnosis	• Ultrasonography showing multiple renal cysts
Management	• Aggressive control of risk factors for CV & CKD • ACE inhibitors preferred for hypertension • Hemodialysis, renal transplant for ESRD

In ADPKD, Affected patients begin developing asymptomatic kidney cysts early in life. By age 30-40, the cystic changes have often progressed to the point that disease manifestations become clinically apparent. Hypertension is one of the earliest clinical manifestations. It likely results from cyst expansion leading to localized renal ischemia and consequent increased renin production with activation of the renin-angiotensin-aldosterone system. Therefore, the hypertension is best treated with ACE inhibitors (eg, lisinopril). Other complications of ADPKD include nephrolithiasis (most commonly uric acid stones due in part to a tendency toward acidic urine in ADPKD) and cerebral aneurysms.

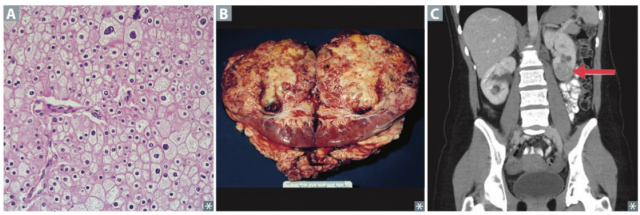
Early in the disease process, patients also develop a urinary concentrating defect (evidenced by low specific gravity on urinalysis), likely due to renal tubular destruction. In effect, a mild nephrogenic diabetes insipidus is created with resulting increased circulating vasopressin levels. The high vasopressin levels may encourage renal cyst growth, and vasopressin-2 receptor antagonists (eg, tolvaptan) have been shown to slow ADPKD progression in some patients. Other treatments for ADPKD are mostly supportive and involve minimizing risk factors for worsening of chronic kidney disease. Renal blood flow (RBF) decreases as cystic structural derangement of the kidneys progresses and damages the renal vasculature. In response, production of prostaglandins increases to attempt to dilate renal afferent arterioles and restore RBF.

Recurrent flank pain and hematuria are common in patients with ADPKD; these symptoms often result from cyst rupture that can be triggered by activities involving bending and exertion (eg, yard work).

Renal Cell Carcinoma (RCC)

Polygonal clear cells A filled with accumulated lipids and carbohydrate. Often golden-yellow B on gross pathology, due to ↑ lipid content.
Originates from PCT → invades renal vein (may develop varicocele if left sided) → IVC → hematogenous spread → metastasis to lung, bone, and liver.
Manifests with flank pain, palpable mass, hematuria (classic triad) as well as anemia, 2° polycythemia (less common), fever, weight loss.
Treatment: surgery/ablation for localized disease. Immunotherapy (eg, ipilimumab) or targeted therapy for metastatic disease, rarely curative. Resistant to radiation and chemotherapy.

Most common 1° renal malignancy C.
Most common in males 50–70 years old, ↑ incidence with tobacco smoking and obesity.
Associated with paraneoplastic syndromes, eg, PTHrP, Ectopic EPO, ACTH, Renin ("PEAR"-aneoplastic).
Clear cell (most common subtype) associated with gene deletion on chromosome 3 (sporadic, or inherited as von Hippel-Lindau syndrome).
RCC = 3 letters = chromosome 3 = associated with VHL (also 3 letters).



- Flank pain, hematuria & a palpable abdominal renal mass
- Scrotal varicoceles (left sided)
- Paraneoplastic symptoms
  - Anemia or erythrocytosis
  - Thrombocytosis
  - Fever
  - Hypercalcemia
  - Cachexia

Most RCC patients are asymptomatic until the disease is advanced. The classic triad of RCC (flank pain, hematuria, and a palpable abdominal renal mass) is found in only 10% of patients; when present, it strongly suggests advanced/metastatic disease.

Hematuria is seen in about 40% of patients and signifies tumor invasion of the collecting system. Scrotal varicoceles (most are left-sided) are observed in about 10% of patients. Varicoceles typically fail to empty when the patient is recumbent due to tumor obstruction of the gonadal vein where it enters the renal vein. Presence of this finding should always raise suspicion for mass obstruction to venous flow, as is seen in RCC. 20% of patients may also have constitutional symptoms such as fever, night sweats, anorexia, weight loss, or easy fatigability. Ectopic production of erythropoietin by the tumor can produce polycythemia, although most advanced tumors are associated with anemia.

CT scan of the abdomen is the most sensitive and specific test for diagnosing RCC and should be obtained when the index of suspicion is high. RCCs are of the clear cell subtype and typically bilateral. They are often preceded by the formation of multiple renal cysts, which are considered a premalignant condition.

Von Hippel-Lindau disease	AD
Etiology	• Mutation in the *VHL* tumor suppressor gene on chromosome 3 • Autosomal dominant inheritance
Manifestations	1 • Cerebellar & retinal hemangioblastomas 2 • Pheochromocytoma 3 • Renal cell carcinoma (clear cell subtype)
Management	◦ Surveillance for associated malignancies ◦ Eye/retinal examination ◦ Plasma or urine metanephrines ◦ MRI of the brain & spine ◦ MRI of the abdomen • Tumor resection

Although the tumors are noninvasive, symptoms occur due to hemorrhage or compression of surrounding tissues. Bleeding from retinal tumors can lead to retinal exudates and impaired vision or, if untreated, retinal detachment with vision loss. Acute hemorrhage in a brain tumor can result in herniation and death.

Renal Vein Thrombosis

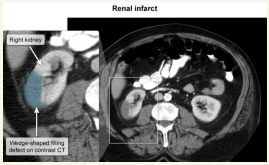
Causes	• Hypercoagulability ◦ Nephrotic syndrome (particularly membranous nephropathy) ◦ Malignancy (particularly renal cell) ◦ Other (eg, inherited thrombophilia, oral contraceptive pills) • Trauma
Clinical features	• Acute: renal infarction symptoms (flank pain, hematuria, ↑ LDH, ↑ kidney size on imaging) • Chronic: renal symptoms typically absent (may cause pulmonary embolus)
Diagnosis	• CT scan or MR angiography • Renal venography
Treatment	• Anticoagulation • Local thrombolysis/thrombectomy (if AKI present)

RVT results in markedly increased glomerular pressure, leading to renovascular congestion, capsular stretch (manifesting as flank pain), and hematuria.

There is significant overlap in the presentation of renal infarction and acute RVT; however, renal infarction most commonly occurs due to cardioembolic disease (eg, atrial fibrillation), resulting in incomplete infarction and a wedge-shaped area of ischemia on imaging. In addition, patients frequently report abdominal pain in addition to flank pain. An acute increase in blood pressure due to renin release is also common.

The renal veins' predisposition to thrombosis may be due to hemoconcentration (ie, higher viscosity) of the postglomerular circulation that results from glomerular fluid loss.

Renal infarction manifestations include flank pain, nausea, and vomiting.
Urinalysis demonstrates hematuria and proteinuria without casts.
A wedge-shaped cortical infarction on CT scan is diagnostic.
Renal infarctions can occur as a sequela of infectious endocarditis, which typically presents with recurrent fever, cardiac murmurs, and leukocytosis.





Step 2

& Relevant Clinical Step 1

Rheumatology

تَذكَّر:

إنَّ الطِّبَّ وسِيلةٌ.. لا غايَةٌ!

Contact & Updates:

Ehab Alroud

Rheumatoid Arthritis (RA)



Clinical presentation	• Pain, swelling & morning stiffness in multiple joints • Small joints (PIP, MCP, MTP); spares DIP joints • Systemic symptoms (fever, weight loss, anemia) • Cervical spine involvement: subluxation, cord compression
Laboratory/imaging studies	• Positive rheumatoid factor & anti–CCP antibodies • C-reactive protein & ESR correlate with disease activity • X-ray: soft tissue swelling, joint space narrowing, bony erosions

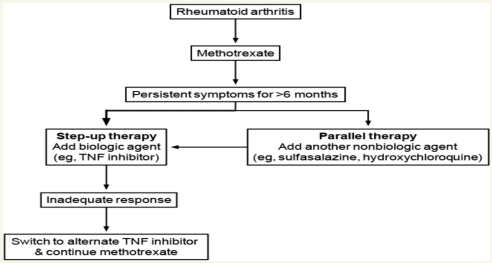
Felty Syndrome	
Clinicalfeatures	• Rheumatoid arthritis ◦ Severe erosive joint disease & deformity ◦ Rheumatoid nodules ◦ Vasculitis (mononeuritis multiplex, necrotizing skin lesions) • Neutropenia (ANC <2000/μL) • Splenomegaly
Diagnosis	• Anti-CCP & RF are positive in >90% of patients • Markedly elevated ESR, often >85 mm/hr • Peripheral smear & bone marrow biopsy to rule out other causes of neutropenia

Extraarticular manifestations of rheumatoid arthritis	
Systemic	• Fever • Weight loss • Fatigue
Pulmonary	• Fibrotic lung disease • Pleural effusions • Lung nodules (Caplan syndrome) • Pulmonary hypertension
Cardiovascular	• Atherosclerosis • Vasculitis
Musculoskeletal	• Osteopenia/osteoporosis
Dermatologic	• Rheumatoid nodules
Hematologic	• Anemia
Neuropsychiatric	• Depression • Neuropathy
Other	• Sjögren syndrome • Raynaud phenomenon • Scleritis, episcleritis

RA can cause exudative pleural effusions characterized by low glucose, very high LDH, and (often) low pH and is associated with interstitial lung disease.

All patients diagnosed with RA should be started on disease-modifying antirheumatic agents (DMARDs) as soon as possible as joint damage begins early in its course.

Patients on methotrexate (MTX) should have regular monitoring with complete blood counts and hepatic function markers. They also should be tested for hepatitis B and C before starting therapy. MTX should not be used in patients who are pregnant or are planning to become pregnant in the near future and those with severe renal insufficiency, liver disease, or excessive alcohol intake. Patients should avoid alcohol intake while on treatment. The toxicity of MTX (including hepatotoxicity) can be mitigated by the administration of folic acid, which does not reduce the effectiveness of the drug. NSAIDs or glucocorticoids should be used for initial temporary symptomatic relief while awaiting response to DMARD therapy.



Disease-modifying antirheumatic drugs

Agent	Mechanism	Adverse effects
Methotrexate	• Folate antimetabolite	• Hepatotoxicity • Stomatitis • Cytopenias
Leflunomide	• Pyrimidine synthesis inhibitor	• Hepatotoxicity • Cytopenias
Hydroxychloroquine	• TNF & IL-1 suppressor	• Retinopathy
Sulfasalazine	• TNF & IL-1 suppressor	• Hepatotoxicity • Stomatitis • Hemolytic anemia
TNF inhibitors(eg, adalimumab, certolizumab,etanercept, golimumab, infliximab)		• Infection • Demyelination • Congestive heart failure • Malignancy

Rheumatoid factor [RF] (low specificity) & cyclic citrullinated peptide antibodies [anti-CCP] (high specificity) are the primary serologic markers for RA. Patients who have negative assays for both markers (seronegative RA) may have a more favorable prognosis.

Rheumatologic diseases & commonly associated autoantibodies		
	Sensitivity (%)	**Specificity (%)**
Rheumatoid arthritis	RF: 70-80	Anti-CCP: 95
Systemic lupus erythematosus	ANA: 95	Anti-dsDNA/anti-Sm: 96
Drug-induced lupus	ANA: 95	Antihistone: 95
Diffuse systemic sclerosis	ANA: 95	Anti–Scl-70: 99
Limited systemic sclerosis	ANA: 95	Anticentromere: 97
Polymyositis/dermatomyositis	ANA: 75	Anti–Jo-1: 99
ANA = antinuclear antibodies; **anti-CCP** = anti–cyclic citrullinated peptide; **anti-dsDNA** = anti–double-stranded DNA; **anti–Scl-70** = anti–topoisomerase I; **anti-Sm** = anti-Smith; **RF** = rheumatoid factor.		

Osteoarthritis vs rheumatoid arthritis		
	Osteoarthritis	**Rheumatoid arthritis**
Age of onset	>40; increases with age	40-60; often younger
Joint involvement	• Knees & hips • DIP joint • First CMC joint	• MCP joint • PIP joint • Wrists
Morning stiffness	None/brief	Prolonged
Systemic symptoms	Absent	• Fever • Fatigue • Weight loss
Examination	• Hard, bony enlargement of joints	• Soft/spongy, warm joints
X-ray	• Narrowed joint space (Asymmetric) • Osteophytes Subchondral Sclerosis & Cysts	• Periarticular erosions

Osteoarthritis (OA)

Age of onset	• >40; prevalence increases with age
Jointinvolvement	• Knees • Hips • Distal interphalangeal joints • 1st carpometacarpal joint
Morningstiffness	• None/brief (<30 min)
Systemicsymptoms	• Absent
Examinationfindings	• Hard, bony enlargement of joints • Reduced range of motion with crepitus

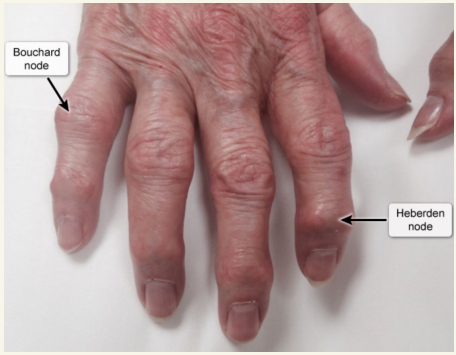
Risk factors for osteoarthritis	
Modifiable	**Nonmodifiable**
• Sedentary lifestyle • Obesity • Occupational joint loading • Diabetes mellitus	• Advanced age • Female sex • Family history • Abnormal joint alignment • Prior joint trauma

OA presents in adults age >40 with progressive pain that is worsened by activity and relieved by rest. The pain is typically felt in the groin, buttock, or lateral hip (trochanteric) region and can radiate to the lower thigh or knee. The joint is not tender, and systemic symptoms are absent.

OA of the hands is primarily a clinical diagnosis; imaging (eg, x-ray) is less sensitive than examination findings and is usually unnecessary for diagnosis or management.

Initial management of hand osteoarthritis includes stretching and strengthening exercises. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, diclofenac) are beneficial for most patients; oral NSAIDs are also effective but carry a greater risk for toxicity (eg, peptic ulcer).

Hand osteoarthritis	
Clinical presentation	• Age >40 • Chronic, progressive hand pain & stiffness • DIP & PIP joints; 1st carpometacarpal joint
Diagnosis	• Examination: bony enlargement (Heberden & Bouchard nodes), crepitus with range of motion • X-ray: joint space narrowing, subchondral sclerosis, periarticular osteophytes
Initial management	• Stretching & strengthening exercises • Topical or oral NSAIDs



SLE

Systemic lupus erythematosus (SLE) is a multisystem, inflammatory disease that often affects young, African American women. Arthritis and arthralgias affect 95% of patients with SLE and tend to be migratory, symmetric, polyarticular, accompanied by brief morning stiffness (much shorter in duration than rheumatoid arthritis [RA]). Lymphadenopathy often occurs as a primary manifestation (~50% of cases).

X-rays usually reveal no evidence of joint destruction or erosion (unlike other inflammatory arthritides such as RA).

Lumbar puncture is useful when CNS involvement of SLE is suspected. CSF findings may be normal or reflect mild inflammation (eg, slight elevation in CSF leukocytes, lymphocytosis).

RASH OR PAIN:





- **R**ash (malar **A** or discoid **B**)
- **A**rthritis (nonerosive)
- **S**erositis (eg, pleuritis, pericarditis)
- **H**ematologic disorders (eg, cytopenias)
- **O**ral/nasopharyngeal ulcers (usually painless)
- **R**enal disease
- **P**hotosensitivity
- **A**ntinuclear antibodies
- **I**mmunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid)
- **N**eurologic disorders (eg, seizures, psychosis)

Laboratoryfindings	• Hemolytic anemia, thrombocytopenia & leukopenia • Hypocomplementemia (C3 & C4) • Antibodies: ◦ Antinuclear antibodies (sensitive) ◦ Anti-dsDNA & anti-Smith (specific) • Renal involvement: proteinuria & elevated creatinine

Features of drug-induced lupus erythematosus

Clinical features*	Acute onset of: • Constitutional symptoms (eg, fever, malaise) • Arthralgias • Serositis (eg, pleuritis, pericarditis) • Rash (less common compared with SLE)
Risk factors	• High drug dose, prolonged use (>3 months) • Slow acetylator status
Laboratory findings	• Antihistone antibodies (>90%) • Antinuclear antibodies (>95%)
Implicated drugs	• Most common: procainamide, hydralazine, penicillamine • Others: minocycline, TNF-α inhibitors (eg, etanercept, infliximab), isoniazid

*No minimum number of SLE criteria is needed for diagnosis.

Osteonecrosis is a common complication of systemic lupus erythematosus, and the risk is increased with long-term glucocorticoid use. It causes pain in the groin, thigh, or buttocks that is worsened by activity. Early examination findings are often mild or normal, and x-rays are often unremarkable; MRI is more sensitive and the more appropriate test.

Treatment includes stopping the causative medication and treating symptoms (eg, nonsteroidal anti-inflammatory drugs). Cyclophosphamide is reserved for patients with significant renal or central nervous system problems. However, hemorrhagic cystitis and bladder cancer are caused by acrolein, a bladder-toxic metabolite of cyclophosphamide. Drinking plenty of fluids, voiding frequently, and taking mesna are all helpful in preventing these complications.

Antiphospholipid Antibody Syndrome (APS)	
Clinical features	**Venous or arterial thromboembolic disease** • Deep vein thrombosis • Pulmonary embolism • Ischemic stroke/transient ischemic attack **Adverse pregnancy outcomes** • Unexplained embryonic or fetal loss • Premature birth due to placental insufficiency or preeclampsia
Laboratory findings	• Lupus anticoagulant effect: paradoxical activated PTT prolongation not reversed on plasma mixing studies • Presence of specific antiphospholipid antibodies ◦ Anticardiolipin antibody ◦ Anti–β2-glycoprotein I antibody

In patients with APS, a false positive RPR test is not uncommon as the syphilis antigen used in RPR testing contains cardiolipin.

The biggest risk factor for APS is SLE; APS occurs in up to 40% of these patients. A minority of healthy individuals may develop transient antiphospholipid antibodies, so all positive serology for APS should be repeated at 12 weeks to confirm diagnosis.

Patients with APS often require anticoagulation for life (heparin product or warfarin) as the risk of recurrent thrombus is high. For those with concomitant SLE, hydroxychloroquine is also added.

Mixed Connective Tissue Disease

Definition	• Autoimmune disorder with variable features of: ◦ Systemic lupus erythematosus ◦ Systemic sclerosis ◦ Polymyositis ◦ Rheumatoid arthritis
Clinical features	• Raynaud phenomenon* • Hand/finger swelling* • Arthritis/synovitis* • Inflammatory myopathy* • Pulmonary hypertension • Malar or discoid rash • Mild CNS &/or kidney disease
Laboratory findings	• Anti–U1 ribonucleoprotein (anti-U1RNP) • Antinuclear antibody • Rheumatoid factor, anti–cyclic citrullinated peptide • Elevated creatine kinase • Anemia/cytopenia
*Diagnostic criteria.	

Raynaud Phenomenon

	Primary	Secondary
Etiology	• Idiopathic response to cold or stress • Risk factors include CVD, smoking	• Vasoconstriction due to vascular pathology • Causes: autoimmune disease (eg, systemic sclerosis), drugs (eg, amphetamines), trauma (eg, frostbite)
Clinicalpresentation	• Young; predominantly female • Symmetric attacks • Normal examination & laboratory results	• Older (>40); male & female • Asymmetric attacks • Examination/laboratory results: tissue injury (eg, digital ulcers), abnormal nail fold capillaries, autoimmune antibodies (eg, ANA)
Management	• Nonpharmacologic: warming techniques, smoking cessation, stress reduction • Medication: CCB (first-line), PDE-5 inhibitor (second-line)	• Evaluate & treat underlying disorder • Same medications as for primary RP • Consider aspirin if increased risk for digital ulceration

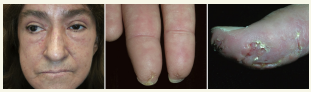
Episodes can also involve tingling, numbness, and pain with skin color changes of pallor (white attack) or cyanosis (blue attack).

IgG4-related Disease

IgG4-related disease: Immune-mediated spectrum of conditions, characterized by fibrosis and lymphoplasmacytic infiltrate, that can affect multiple organs. Patients usually have elevated serum IgG4 levels.

Most common IgG4-related conditions are:

- Sialadenitis and dacryoadenitis
- Riedel thyroiditis
- Autoimmune pancreatitis
- Autoimmune aortitis (may lead to thoraco/abdominal- aortic aneurysms)
- Retroperitoneal fibrosis (may affect the ureters and present with signs of AKI/ CKD and/or hydronephrosis)



Systemic Sclerosis (SSc)

Pathogenesis	• Progressive tissue fibrosis • Vascular dysfunction
Clinical features	• Skin: telangiectasia, sclerodactyly, digital ulcer, calcinosis cutis • Extremities: arthralgia, myalgia, contracture • Gastrointestinal tract: esophageal dysmotility, dysphagia, acid reflux • Lungs: dyspnea, dry cough • Vascular system: Raynaud phenomenon
Autoantibodies	• Antinuclear • Anti–topoisomerase type I (anti–Scl-70) (diffuse SSc) • Anticentromere (limited SSc)
Complications	• Lungs: interstitial lung disease, pulmonary arterial HTN • Kidneys: HTN, scleroderma renal crisis (severe HTN, AKI, MAHA) • Heart: myocardial fibrosis, pericarditis, pericardial effusion

Limited cutaneous	• Scleroderma on head & distal upper extremities • Prominent vascular manifestations ◦ Raynaud phenomenon ◦ Cutaneous telangiectasia ◦ Pulmonary arterial hypertension • CREST syndrome • Anticentromere antibodies • Better prognosis
Diffuse cutaneous	• Scleroderma on trunk & upper extremities • Prominent internal organ involvement ◦ Scleroderma renal crisis ◦ Myocardial ischemia & fibrosis ◦ Interstitial lung disease • Anti–Scl-70 (topoisomerase type I) antibodies • Anti–RNA polymerase III antibodies • Worse prognosis

CREST = **C**alcinosis, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly & **T**elangiectasia.

SSc can cause atrophy and fibrosis of the smooth muscle in the lower esophagus. This leads to decreased peristalsis and decreased tone in the lower esophageal sphincter. Esophageal dysmotility with gastroesophageal reflux is commonly seen in both subtypes. In addition, Raynaud phenomenon is common in both subtypes.

Limited SSc is more common to be complicated with pulmonary arterial HTN. However, diffuse SSc is more common to be complicated with interstitial lung disease (ILD).

Antinuclear antibodies (ANA) are present in almost all patients but are nonspecific. Anti-topoisomerase I (anti-Scl-70) and anti-RNA polymerase III are less sensitive but more specific and are associated with extensive disease.
Anticentromere antibodies may also be seen, primarily in patients with limited disease.

Scleroderma renal crisis (SRC) is characterized by the acute onset of HTN & AKI in patients with systemic sclerosis. Renal vascular injury (due in part to collagen deposition) leads to renal ischemia, which results in activation of the renin-angiotensin-aldosterone system (RAAS). The mainstay of therapy is ACE-i (typically captopril), which reduce renin-angiotensin-aldosterone system hyperactivity, improve renal function, and normalize blood pressure. An elevated serum creatinine level is not a contraindication for ACE inhibitors in this population, and slight elevations in creatinine are common during drug initiation. Glucocorticoids are a major risk factor for the development of SRC and should be avoided in patients with SSc.

Sjogren Syndrome

Exocrinefeatures	• **Keratoconjunctivitis sicca** • Dry mouth, salivary hypertrophy • Xerosis
Extraglandularfeatures	• **Raynaud phenomenon** • Cutaneous vasculitis • Arthralgia/arthritis • Interstitial lung disease • Non-Hodgkin lymphoma
Diagnosticfindings	• Objective signs of **decreased lacrimation** (eg, Schirmer test) • Positive **anti-Ro** (SSA) &/or **anti-La** (SSB) • Salivary gland biopsy with focal lymphocytic sialoadenitis • Classification: primary if no associated CTD, secondary if comorbid CTD (eg, SLE, RA, scleroderma)

Autoimmune sialoadenitis in Sjogren Syndrome (SS) causes enlargement of the salivary glands visible on MRI or ultrasound.
Biopsy of salivary glands can confirm the diagnosis of SS if other evaluations are nondiagnostic. However, samples are usually taken from the minor glands of the lip.

Age-related dry eye syndrome vs Sjögren syndrome		
	Age-related dry eye syndrome	**Sjögren syndrome**
Prevalence	• Common	• Uncommon to rare
Age of onset	• 50s-80s	• 30s-60s
Clinicalfeatures	• Mild to moderate mucosal dryness	• Mucosal dryness often severe • Parotid enlargement • Comorbid autoimmune disease (eg, scleroderma, rheumatoid arthritis)
Diagnosticfeatures	• Normal ESR and autoimmune markers* • Secretory function objectively normal/near-normal (eg, normal Schirmer test)	• Abnormal ESR and autoimmune markers* • Secretory function objectively decreased (eg, abnormal Schirmer test)
∗Examples: antinuclear antibody, anti-SSA (Ro), anti-SSB (La).		

ARDES is more common in women, with increased risk in patients with diabetes mellitus or thyroid disorders. Concurrent dry mouth symptoms are also common.

Seronegative spondyloarthritis

Arthritis without rheumatoid factor (no anti-IgG antibody).
Strong association with HLA-B27 (MHC class I serotype).
Subtypes ([PAIR]: Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, and Reactive arthritis) share variable occurrence of inflammatory back pain (associated with morning stiffness, improves with exercise), peripheral arthritis, enthesitis (inflamed insertion sites of tendons, eg, Achilles), dactylitis (“sausage fingers”), uveitis.

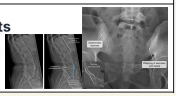
Psoriatic Arthritis

Arthritis	• Affects peripheral and axial skeleton • Causes prolonged (≥30 min) morning stiffness • Varied patterns: oligoarthritis, symmetric polyarthritis, spondylarthritis (eg, sacroiliitis), distal arthritis (eg, DIP joint) • Severe and deforming disease possible (eg, arthritis mutilans)
Soft tissue & nail involvement	• Enthesitis (inflammation at tendon insertion site) • Dactylitis (sausage digits) of toe or finger • Nail pitting & onycholysis • Pitting edema of hands or feet 
Skin lesions	• Typically precedes onset of arthritis • May also occur with or after onset of arthritis

Achilles tendinopathy	
Risk factors	• Athletic activity, increase in activity • Systemic disorders: psoriasis, ankylosing spondylitis • Medications: glucocorticoids, fluoroquinolones
Clinicalfeatures	• Swelling, warmth, pain at posterior heel • Tendon rupture: "popping" sensation & acute pain following rapid acceleration/direction change
Examinationfindings	• Swelling, tenderness 2-6 cm proximal to tendon insertion • Rupture: positive Thompson test*
Diagnosis	• Clinical findings • Ultrasound: swelling, neovascularization • MRI
Management	• Acute: activity modification, ice, NSAIDs • Chronic: eccentric resistance exercises

*With the patient prone and feet off the end of the table, squeeze the calf muscles; the absence of plantar flexion indicates tendon rupture.

Ankylosing Spondylitis

Inflammatory back pain	• Insidious onset at age <40 • Symptoms >3 months • **Relieved with exercise** but not rest • Nocturnal pain
Examination findings	• Arthritis (sacroiliitis) • Reduced chest expansion & spinal mobility • Enthesitis (tenderness at tendon insertion sites) • Dactylitis (swelling of fingers & toes) • Uveitis
Complications	• Osteoporosis/vertebral fractures • Aortic regurgitation • Cauda equina syndrome
Laboratory	• Elevated ESR & CRP • **HLA-B27** association
Imaging	• **X-ray of sacroiliac joints**  • MRI

Although ankylosing spondylitis (AS) has a male:female ratio of 2:1, it should be considered in any young patient with progressive low back pain and stiffness lasting >3 months. The incidence peaks in individuals age 20-30.

Sacroiliitis is characteristic on X-ray. Whereas >90% of patients with AS have HLA-B27, only 5% of patients with HLA-B27 have AS; therefore, HLA-B27 is not specific for AS and testing for it is not necessary for diagnosis.

Nonpharmacologicmeasures	• Exercise (postural exercises, ROM/stretching exercises) • Physical therapy
Initial treatment	• NSAIDs (eg, ibuprofen, naproxen) • COX-2 inhibitors (eg, celecoxib)
Treatment failure/disease progression	• TNF-α inhibitors (eg, etanercept, infliximab) • Anti–IL-17 antibodies (eg, secukinumab)

Reactive Arthritis	“Can’t see, can’t pee, can’t climb a tree.”
Preceding infection	• Genitourinary: *Chlamydia trachomatis* • Gastrointestinal: *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Clostridioides difficile*
Musculoskeletal	• Asymmetric oligoarthritis • Enthesitis • Dactylitis
Extraarticular symptoms	• Ocular: conjunctivitis, anterior uveitis • Genital: urethritis, cervicitis, prostatitis • Dermal: keratoderma blennorrhagicum, circinate balanitis • Oral ulcers 
Diagnostic evaluation	• Elevated inflammatory markers (eg, erythrocyte sedimentation rate, C-reactive protein) • Synovial fluid: elevated white blood cell count (2,000-4,000/mm^3), negative Gram stain and culture

Reactive arthritis (ReA) is an immune-mediated spondyloarthritis that can occur 1-4 weeks following certain genitourinary or gastrointestinal infections. It is self-limited (eg, resolving within 6 months), and treatment is largely supportive. Arthralgia usually improves with NSAIDs (eg, ibuprofen, naproxen). If treatment for circinate balanitis is desired, low-potency topical corticosteroids (eg, 1% hydrocortisone) are often adequate.

Unlike in circinate balanitis, Chancroid is extremely painful, which is a rare sexually transmitted infection caused by Haemophilus ducreyi. It manifests as an ulcerating pustule with irregular margins and tender inguinal lymphadenopathy.

Herpes simplex infection presents with grouped vesicles on an erythematous base with subsequent ulceration. these lesions are typically painful.

Syphilis presents with a painless ulcer with a raised border at the inoculation site (ie, chancre). Untreated cases may progress to secondary syphilis, characterized by a variety of skin lesions, including a diffuse papular rash, alopecia, and condylomata lata.

Viral Arthritis

Viral arthritis due to parvovirus B19 usually seen in adults, whereas erythema infectiosum due to parvovirus B19 is more common in children. This arthritis usually associated with brief morning stiffness, normal ESR, and exposure to small children.
Treatment is symptomatic, primarily with NSAIDs.

Parvovirus B19 infection	
Signs & symptoms	• Most patients are asymptomatic or have flulike symptoms • **Erythema infectiosum** (fifth disease): Fever, nausea & "slapped cheek" rash (more common in children) • Acute, symmetric **arthralgia/arthritis**: Hands, wrists, knees & feet (resembles RA) • Transient **pure red cell aplasia**; aplastic crisis in patients with underlying hematologic disease (eg, sickle cell)
Diagnosis	• Acute infection ◦ B19 IgM antibodies in immunocompetent patients ◦ NAAT for B19 DNA in immunocompromised patients • Previous infection: B19 IgG antibodies (documents immunity) • Reactivation of previous infection: NAAT for B19 DNA

Septic Arthritis

Risk factors	• Advanced age • Joint abnormality (eg, OA, RA, prosthesis) or trauma • Immunocompromised (eg, diabetes mellitus) • Bacteremia (eg, intravenous drug use)
Clinical features	• Hot, swollen joint with ↓ ROM • Fever • ↑ ESR & CRP
Diagnosis	• Synovial fluid analysis ◦ Leukocytosis (>50,000/mm^3) ◦ Gram stain (sensitivity ~30%-50%) & culture • Blood cultures
Initial treatment	• Intravenous antibiotics • Joint irrigation & drainage (eg, arthroscopy, open arthrotomy)

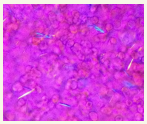
In patients with gout, synovial crystals may be seen between flares, so the presence of these crystals alone does not rule out septic arthritis.

Disseminated gonococcal infection	
Manifestations	• Purulent monoarthritis OR • Triad of tenosynovitis, dermatitis, migratory polyarthralgia
Diagnosis	• Detection of *Neisseria gonorrhoeae* in urine, cervical, or urethral sample • Culture of blood, synovial fluid (less sensitive)
Treatment	• 3rd-generation cephalosporin intravenously

Disseminated gonococcal infection can present with fever and chills. Regarding dermatitis; most often 2-10 pustular/vesiculopustular lesions on the distal extremities. Although symptoms of gonococcal urethritis (eg, dysuria, purulence) are often absent, most cases are presumptively diagnosed by genitourinary nucleic acid amplification testing (NAAT).

Joint fluid characteristics				
	Normal	**Noninflammatory (eg, OA)**	**Inflammatory (eg, crystals, RA)**	**Septic joint**
Appearance	Clear	Clear	Translucent or opaque	Opaque
WBCs (mm^3)	<200	200-2,000	2,000-100,000	50,000-150,000
PMNs	<25%	25%	Often >50%	>80%-90%

Gout



Gout typically presents as an acute monoarticular arthritis (80% occurring in 1st MTP joint or knee) that quickly progresses to maximum intensity within 12-24 hours. Recurrent attacks that typically develop overnight or early in the morning. A gout attack can be precipitated by conditions that cause increased production or decreased elimination of uric acid, or an acute change in uric acid levels. Medications that raise (eg, thiazide diuretics, cyclosporine) or lower (eg, allopurinol) uric acid levels. Higher consumption of coffee (but not tea) is associated with lower uric acid levels and a decreased risk of gout attack.

Patients generally respond to NSAIDs (eg, indomethacin), colchicine, or steroids (systemic or intraarticular). Long-term prophylactic medications (eg, allopurinol) are indicated for patients with recurrent attacks.

Causes of gout	
Increased urate production	• Primary gout (idiopathic) • Myeloproliferative/lymphoproliferative disorders • Tumor lysis syndrome • Hypoxanthine-guanine phosphoribosyltransferase deficiency
Decreased urate clearance	• Chronic kidney disease • Thiazide/loop diuretics

Gout initially causes an episodic monoarthritis typically affecting the first MTP joints and knees. Persistent hyperuricemia can lead to tophaceous gout, which is characterized by excessive monosodium urate deposition, leading to chronic inflammation and nodular deformity. Tophi commonly involve the joints of the hands and feet; soft tissue involvement may also occur, including the ears, tendons, and olecranon bursa.

Risk factors for gout	
Increased risk	• **Medications** (eg, diuretics, low-dose aspirin) • Surgery, trauma, recent hospitalization • Volume depletion • **Diet**: High-protein foods (meat, seafood), high-fat foods, fructose or sweetened beverages • Heavy **alcohol** consumption • Underlying medical conditions (eg, hypertension, obesity, chronic kidney disease, organ transplant)
Decreased risk	• Dairy product intake • Vitamin C (≥1,500 mg/day) • Coffee intake (≥6 cups/day)

Medications (e.g., Losartan)

Prevention of future gout attacks
• Weight loss to achieve BMI <25 kg/m^2 • Low-fat diet • Decreased seafood & red meat intake • Protein intake preferably from vegetable & low-fat dairy products • Avoidance of organ-rich foods (eg, liver & sweetbreads) • Avoidance of beer & distilled spirits • Avoidance of diuretics when possible

Lesch-Nyhan syndrome: genetic enzyme deficiency of hypoxanthine-guanine phosphoribosyltransferase. It is characterized by self-injurious behaviors and neurologic disability. It is associated with overproduction of uric acid but is usually diagnosed in childhood.

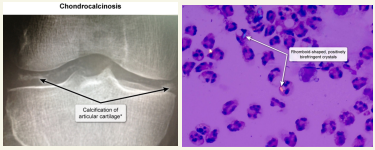
X-rays characteristically show soft tissue opacification (if tophaceous) and punched-out lytic lesions with a rim of overhanging bone (rat-bite lesion). Definitive diagnosis is obtained via aspiration & microscopy synovial fluid analysis, which demonstrates a white, chalky material, with high levels of inflammatory cells and needle-shaped, negatively birefringent monosodium urate crystals (appear yellow when lying parallel to the polarizing axis, and blue when lying perpendicular). Compared to urate crystals, CPPD crystals are smaller, rhomboid-shaped, and weakly positively birefringent.

Pseudogout (CPPD)

Acute calcium pyrophosphate crystal arthritis (pseudogout)	
Symptoms	• Acute mono- or oligoarticular arthritis • Peripheral joints (knee most common)
Diagnosis	• Inflammatory effusion (eg, synovial fluid WBC 15,000-30,000/mm^3) • CPPD crystals (rhomboid shape, positive birefringence) • Chondrocalcinosis (calcification of articular cartilage and/or menisci)
Treatment	• Intraarticular glucocorticoids • Nonsteroidal anti-inflammatory drugs • Colchicine

CPPD = calcium pyrophosphate deposition; **WBC** = white blood cell.

Attacks of pseudogout often occur in the setting of trauma/overuse, surgery, or diseases (e.g., Hemochromatosis, or Hyperparathyroidism).



Acute monoarthritis			
	Gout	**Acute CPPD arthritis***	**Septic arthritis**
Risk factors	• Male sex • Obesity, CVD • ↑ Alcohol & purine intake • Medications (eg, diuretics)	• Age ≥65 • Hyperparathyroidism • Preexisting arthritis (eg, OA) • Recent illness or surgery	• Immune suppression (eg, T2DM) • IVDU • Joint prosthesis, indwelling catheter • Recent joint injection, surgery
Affected joints	• Initial: 1st MTP; knee • Recurrent: upper extremity, ankle	• Knee • Upper extremities (eg, wrist, shoulder) • Ankle	• Knee • Hip • Ankle
Diagnostic findings	• Synovial fluid: needle-shaped, negatively birefringent crystals • Tophi, preexisting hyperuricemia	• Synovial fluid: rhomboidal, weakly positively birefringent crystals • X-ray: chondrocalcinosis	• Synovial fluid: positive Gram stain & culture

Vasculitides



Vasculitis: an inflammation of blood vessels with leukocytes in their walls. It is a group of large, medium, and small vessel diseases characterised by palpable (non-blanchable) purpura and systemic manifestations (e.g., arthralgia, fever, fatigue). Treatment: mainly systemic glucocorticoids +/- Cyclophosphamide.

Large-vessel vasculitis:

- Takayasu arteritis

Takayasu arteritis	
Risk factors	• Female • Asian • Age 10–40
Symptoms	• Constitutional (eg, fever, weight loss, fatigue) • Arteriooclusive (eg, claudication, ulcers) in upper extremities • Arthralgias/myalgias
Examination findings	• Blood pressure discrepancies • Pulse deficits • Arterial bruits
Diagnosis	• Elevated inflammatory markers (eg, ESR, CRP) • Chest x-ray: aortic dilation, widened mediastinum • CT/MR angiography: wall thickening, narrowing of lumen
Treatment	• Systemic glucocorticoids

- Giant cell (temporal) arteritis [GCA]: occurs in females > 50 years old, characterised by unilateral headache, possible temporal artery tenderness, and jaw claudication. It may lead to sudden painless irreversible blindness due to anterior ischemic optic neuropathy (carotid artery branches), which can develop in up to 20% of patients. Therefore, treat with high-dose glucocorticoids prior to temporal artery biopsy to prevent blindness. Another recognized complication, which has been noted in 10%-20% of patients, is aortic aneurysm due to large-vessel involvement. Patients with aortic aneurysm are typically followed with serial imaging studies.
GCA is well-known to be associated with polymyalgia rheumatica.

Medium-vessel vasculitis:

- Buerger disease (thromboangiitis obliterans): occurs in heavy tobacco smoker males < 40 years old, presented with intermittent claudication. May lead to gangrene, autoamputation of digits, andsuperficial nodular phlebitis. Treated primarily by smoking cessation.

- Kawasaki disease: usually occurs in Asian children < 4 years old. It is characterised by “CRASH and burn”: bilateral nonexudative bulbar Conjunctivitis, Rash (polymorphous desquamating), Adenopathy (cervical), Strawberry tongue (oral mucositis) , Hand-foot changes (edema, erythema), and fever (≥ 5 days). It may develops coronary artery aneurysms; thrombosis or rupture can cause death. Treatment: IV immunoglobulin and aspirin (on of the rare indications for Peds)!

- Polyarteritis nodosa (PAN): usually affects middle-aged males “SKIN”: Skin, kidneys (Innumerable renal microaneurysms and spasms on arteriogram [string of pearls appearance]), Intestines, and Nerves. Additionally, there is a hepatitis B seropositivity in 30% of patients.

Behçet disease	
Epidemiology	• Young adults • Turkish, Middle Eastern, or Asian descent
Clinicalfindings	• Recurrent, painful oral aphthous ulcers • Genital ulcers • Eye lesions (eg, uveitis) • Skin lesions (eg, erythema nodosum, acneiform lesions) • Thrombosis
Evaluation	• Pathergy: Exaggerated skin ulceration with minor trauma (eg, needlestick) • Biopsy: Nonspecific vasculitis of different sized vessels

Cryoglobulinemia*		
	Type I	Mixed = type II or III
Associateddiseases	• Plasma cell dyscrasias (eg, Waldenström, multiple myeloma)	• Chronic viremia (eg, HCV, HIV) • Autoimmunity (eg, SLE, Sjögren syndrome)
Pathogenesis:cryoglobulin	• B-cell lineage malignancy: monoclonal IgM	• B-cell hyperactivation: IgM RF** bound to polyclonal IgG
Clinicalfindings	• Cryoprecipitates → **vascular occlusion** (eg, livedo reticularis, retiform purpura, digital ischemia) • High cryocrit → **hyperviscosity** (eg, blurred vision, vertigo, ataxia)	• Immune complexes → **vasculitis** (eg, palpable purpura, GN, arthralgia, neuropathy) • Viral hepatitis → hepatomegaly
Laboratoryfindings	• + Cryocrit, normal complement • ↑ Erythrocyte sedimentation rate • + Monoclonal spike on SPEP	• + Cryocrit, ↓ C4 • + RF autoantibodies • + Viral or antinuclear antibodies

*Immunoglobulins that precipitate at <37 C (98.6 F).

Monoclonal RF (type II), polyclonal RF (type III).GN** = glomerulonephritis; **HCV** = hepatitis C virus; **RF** = rheumatoid factor; **SLE** = systemic lupus erythematosus; **SPEP** = serum protein electrophoresis.

Small-vessel vasculitis:

- Behçet syndrome

- Mixed cryoglobulinemia: small-vessel vasculitis that causes palpable purpura, glomerulonephritis, arthralgias, and peripheral neuropathy. Laboratory abnormalities include cryoglobulins, rheumatoid factor, and hypocomplementemia. Chronic hepatitis C infection is the most common cause, and serologies should be checked in all patients.

- Immunoglobulin A vasculitis [HSP]: (**H**enoch-**S**chönlein **P**urpura) is m/c childhood systemic vasculitis, which often follows URI. It is associated with IgA nephropathy (Berger disease). Classic triad: **H**inge pain (arthralgias), **S**tomach pain (abdominal pain associated with intussusception), and **P**alpable purpura on buttocks/ legs. Treatment: supportive.

ANCA-vasculitis: (may be associated with pauci-immune glomerulonephritis):

- MPO-ANCA/p-ANCA — Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome): asthma, sinusitis, peripheral neuropathy, and high IgE level.

- PR3-ANCA/c-ANCA — Granulomatosis with polyangiitis [GPA] (Wegener's granulomatosis): Upper respiratory (e.g., nasal septum perforation, chronic sinusitis) + Lower respiratory (hemoptysis/SOB).

- MPO-ANCA/p-ANCA — Microscopic polyangiitis: similar to GPA but without granuloma or nasopharyngeal involvement.

Fibromyalgia

Fibromyalgia most commonly presents in young to middle-aged women with widespread pain, fatigue, and cognitive/mood disturbances.
Patients have point muscle tenderness in areas such as the mid trapezius, lateral epicondyle, costochondral junction in the chest, and greater trochanter.
It is diagnosed clinically using the widespread pain index and symptom severity score, which emphasize cognitive problems, fatigue, and severity of somatic symptoms.

Patients perceive that their pain and fatigue worsen acutely after exercise, although a regular, incremental, low-impact exercise regimen (eg, fast walking, swimming, water aerobics) can improve pain and provide long-term benefit.

Medications (eg, duloxetine, tricyclic antidepressants) reserved for patients who fail initial measures.

	Clinical features	Diagnosis
Fibromyalgia	• Young to middle-aged women • Chronic widespread pain • Fatigue, impaired concentration • Tenderness at trigger points (eg, midtrapezius, costochondral junction)	• ≥3 months of symptoms with widespread pain index or symptom severity score • Normal laboratory studies
Polymyositis	• Proximal muscle weakness (eg, increasing difficulty climbing stairs) • Pain mild/absent	• Elevated muscle enzymes (eg, creatine kinase, aldolase, AST) • Autoantibodies (anti–Jo-1, ANA) • Biopsy: endomysial infiltrate, patchy necrosis
Polymyalgia rheumatica	• Age >50 • Systemic signs & symptoms • Stiffness > pain in shoulders, hip girdle, neck • Association with giant cell (temporal) arteritis	• Elevated ESR, C-reactive protein • Rapid improvement with glucocorticoid therapy

Polymyalgia Rheumatica

Clinicalfeatures	• Rapid-onset pain & stiffness in shoulders & hips ± neck involvement • Fatigue, weight loss, low-grade fever • ~10% associated with GCA (eg, headache, jaw claudication, visual symptoms)
Diagnostictesting	• Elevated acute phase markers (eg, ESR, CRP) • Temporal artery biopsy if symptoms of GCA normal CPK
Treatment	• Very rapid response to oral glucocorticoids

Polymyalgia Rheumatica (PMR) characterised by acute onset of symptoms (eg, 2 weeks) at age ≥50

There are no specific serologic tests for PMR

PMR involves periarticular structures (eg, bursae, tendons), but the muscle tissue itself is unaffected and remains histologically normal. Therefore, objective muscle strength is preserved, although range of motion can be limited due to pain and stiffness.

Polymyositis & Dermatomyositis



Muscle weakness	• Proximal, symmetric • Weakness in UE = LE
Skin findings — for Dermatomyositis	• Gottron sign/papules • Heliotrope rash • "Shawl & face" rash 
Extramuscular findings	• Interstitial lung disease • Dysphagia • Myocarditis
Diagnosis	• ↑ CPK, aldolase, LDH • Anti-Mi2, anti-Jo-1 • Diagnostic uncertainty: EMG/MRI, biopsy (skin/muscle)
Management	• High-dose glucocorticoids **plus** glucocorticoid-sparing agent • Screening for malignancy

CPK = creatine phosphokinase; **EMG** = electromyography; **LDH** = lactate dehydrogenase; **LE** = lower extremity; **UE** = upper extremity.

The classic autoantibodies associated with dermatomyositis are anti-Mi-2 (against helicase) and anti-Jo-1 (antisynthetase antibody, found more commonly in polymyositis).

In dermatomyositis, over 15% of adult patients will have or develop a malignancy, most commonly adenocarcinomas. Therefore, regular age-appropriate cancer screening is essential.

Neuromuscular paraneoplastic syndromes		
	Involved site	**Clinical features**
Myasthenia gravis	Acetylcholine receptor in postsynaptic membrane	• Fluctuating muscle weakness ◦ Ocular (ptosis, diplopia) ◦ Bulbar (dysphagia, dysarthria) ◦ Facial, neck & limb muscles • Normal deep tendon reflexes
Lambert-Eaton syndrome	Presynaptic membrane voltage-gated calcium channels	• Proximal muscle weakness • Autonomic dysfunction (eg, dry mouth) • Cranial nerve involvement (eg, ptosis) • Diminished or absent deep tendon reflexes
Dermatomyositis & polymyositis	Muscle fiber injury	• Symmetric & more proximal muscle weakness • ILD, Raynaud phenomenon • Polyarthritis • Dysphagia • Skin findings (eg, Gottron papules, heliotrope rash) in dermatomyositis

Other Related Topics

Differential diagnosis of myopathy

	Weakness	Pain & tenderness	ESR	Creatine kinase	Other features
Glucocorticoid-induced myopathy	Yes	No	Normal	Normal	• Prominent atrophy • Lower extremities most affected
Polymyalgia rheumatica	No	Yes	↑	Normal	• Stiffness of shoulders & hips with restricted motion • Often coexists with GCA • Rapid improvement with glucocorticoids
Polymyositis & dermatomyositis	Yes	Uncommon	Normal or ↑	↑	• Multisystem involvement (arthritis, rash, ILD) • ↑ Malignancy risk
Statin-induced myopathy	Variable	Yes	Normal	Normal or ↑	• Additive risk with fibrates
Hypothyroid myopathy	Yes	Yes	Normal	↑	• Delayed DTRs; myoedema • Hypothyroid symptoms & abnormal thyroid test results

Myotonic Dystrophy

Pathogenesis	• Autosomal dominant CTG trinucleotide repeat expansion • Longer repeat length correlating with earlier & more severe disease
Presentation	• Classic (adult): myotonia & weakness (eg, face, hands, ankles) • Childhood: cognitive & behavioral difficulties (classic symptoms develop over time) • Infantile: hypotonia, respiratory failure, inverted V–shaped upper lip
Associated findings	• Cardiac: arrhythmias, cardiomyopathy • Gastrointestinal: dysphagia, constipation • Respiratory: pharyngeal weakness, hypoventilation • Nonmuscular: insulin resistance, hypogonadism, cataracts, frontal balding, excessive daytime sleepiness
Diagnosis & treatment	• Genetic testing • Supportive management

CTG = cytosine-thymine-guanine.

Myotonic dystrophy classically involves muscle weakness, pain, and atrophy, particularly in the distal (eg, hands, feet) and facial (eg, long & narrow face, sagging jaw, hollow cheeks) muscles; footdrop may result in frequent falls & an unsteady gait.
Myotonia is a characteristic feature and can be elicited by percussion of the thenar eminence, which results in thumb abduction followed by delayed relaxation (percussion myotonia), or by sustained muscle contraction after the release of a handshake (grip myotonia).



Osteoporosis

Osteoporosis: failure of normal bone resorption due to defective osteoclasts, leading to thickened, dense bones that are prone to fracture. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. Overgrowth of cortical bone fills marrow (BM) space, leading to pancytopenia & extramedullary hematopoiesis. It can result in cranial nerve impingement & palsies due to narrowed foramina. Labs are normal.
X-rays show diffuse symmetric sclerosis (bone-in-bone, “stone bone”).
BM transplant is potentially curative as osteoclasts are derived from monocytes.

Osteoporosis risk factors	
Nonmodifiable	• Advanced age • Postmenopausal • Low body weight • White or Asian • Malabsorption disorder • Hypercortisolism, hyperthyroidism, hyperparathyroidism • Inflammatory disorder (eg, rheumatoid arthritis) • Chronic liver or kidney disease
Modifiable	• Smoking • Excessive alcohol intake • Sedentary lifestyle • Medications (eg, glucocorticoids, anticonvulsants) • Vitamin D deficiency, inadequate calcium intake • Estrogen deficiency (eg, premature menopause, oophorectomy)

Screening for osteoporosis with dual-energy x-ray absorptiometry [DEXA] is recommended in all women age >65 and for younger women with history of fragility fracture/ an equivalent risk of osteoporotic fracture (FRAX fracture risk >10%).

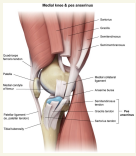
If DEXA T-score ≤-2.5, osteoporosis confirmed, treated with Bisphosphonate (e.g., Alendronate). Whereas osteopenia (milder bone density loss) T-score is between -1 and -2.5, and treated with Calcichew (1000 mg Ca & Vit D).

Osteomalacia mainly caused by vit D deficiency, which reduces intestinal calcium absorption, leading to 2° hyperparathyroidism & renal phosphate wasting. The resulting hypophosphatemia causes impaired mineralization of newly deposited osteoid matrix (vs normally meniralized bone density loss in osteoporosis). Although bone contours are generally normal, the newly formed bone is weak & prone to fracture. Initially, patients may be asymptomatic or have nonspecific arthralgias & myalgias only, but chronic deficiency can lead to proximal muscle wasting, gait abnormality, and deformity of weight-bearing bones.

Clinical features of osteomalacia	
Causes	• Malabsorption • Intestinal bypass surgery • Celiac disease • Chronic liver disease • Chronic kidney disease
Symptoms/signs	• May be asymptomatic • Bone pain & muscle weakness • Muscle cramps • Difficulty walking, waddling gait
Diagnosis	• ↑ Alkaline phosphatase, ↑ PTH • ↓ Serum calcium & phosphorus, ↓ urinary calcium • ↓ 25(OH)D levels • Imaging ◦ Cortical thinning & reduced bone density ◦ Bilateral symmetric pseudofractures (Looser zones)

Vitamin D deficiency should be confirmed with a serum 25-hydroxyvitamin D level, which reflects total body vitamin D stores. In contrast, 1,25-dihydroxyvitamin D primarily reflects parathyroid hormone levels and renal function and is not an accurate marker for deficiency.

Pes anserinus Bursitis



Pes anserinus pain syndrome presents with localized pain and tenderness over the medial tibial condyle. It is often associated with overuse; risk factors include obesity, diabetes mellitus, knee osteoarthritis, and angular deformity of the knee. The diagnosis is based on clinical features, although x-ray can exclude concurrent osteoarthritis. Management includes quadriceps strengthening exercises and nonsteroidal anti-inflammatory drugs

Patellofemoral Pain Syndrome



Patellofemoral pain syndrome (PFPS) is a common cause of chronic anterior knee pain in women. Diagnosis is based on clinical findings; symptoms are typically reproducible with isometric quadriceps contraction (eg, squatting). Treatment includes strengthening the quadriceps and hip abductors. The diagnosis of PFPS is based on clinical findings, although no individual feature has high predictive value. Running, negotiating stairs, and prolonged sitting often aggravate the pain. Atrophy or weakness of the quadriceps or hip abductors is common, and rotational or varus/ valgus malalignment may be noted.

Carpal Tunnel Syndrome



The carpal tunnel is bounded by the carpal bones and transverse carpal ligament. It contains the median nerve, along with the tendons of the flexor digitorum profundus and superficialis and the flexor pollicis longus. Compression of the nerve causes carpal tunnel syndrome (CTS), which is characterized by pain and paresthesia that may involve all or part of the first 3½ digits. Symptoms are often intermittent and worse at night and may be provoked by repetitive or forceful hand and wrist use. Patients may report relief from shaking the hand. They may also have referred pain to the lateral palm, forearm, or even upper arm. However, because the palmar cutaneous branch of the median nerve passes outside the carpal tunnel, sensation over the thenar eminence typically remains intact (vs Median nerve compression in the forearm [Pronator teres syndrome]).

The diagnosis of CTS is usually made on clinical grounds. Provocative maneuvers (eg, Phalen and Tinel tests) often reproduce the symptoms but have limited sensitivity and specificity. If examination findings are inconclusive, diagnosis can be confirmed with nerve conduction studies, which have high sensitivity and specificity for CTS. Typical findings: slowed conduction velocities in the median nerve across the wrist.

Acute & Chronic Back Pain

Causes of chronic low back pain	
Mechanical(eg, muscle strain,disk degeneration)	• Normal neurologic examination • Paraspinal tenderness
Radiculopathy(eg, herniated disc)	• Radiation below the knee • Positive straight-leg raising test • Neurologic deficits
Spinal stenosis	• Pseudoclaudication • Relief with leaning forward
Inflammatory(eg, spondyloarthropathy)	• Worse with rest, better with activity • Sacroiliitis
Metastatic cancer	• Age >50 • Worse at night • Unrelieved with rest
Infectious(eg, osteomyelitis, discitis)	• Recent infection or IVDU • Fever, focal spine tenderness

Management of chronic nonspecific lower back pain (mechanical)	
Clinical features	• Pain >12 weeks • No evidence of specific etiology (eg, malignancy, infection, fracture)
Nonpharmacologic measures	• Maintain normal activity as tolerated • Stretching & strengthening exercise program • Heat • Address maladaptive coping (eg, CBT, mind-body interventions)
Medication	• Intermittent NSAID or acetaminophen • Duloxetine, tricyclic antidepressants, or tramadol • Nonbenzodiazepine muscle relaxants

Prolonged activity restriction in patients with uncomplicated low back pain is associated with increased long-term pain and stiffness. Patients should be counseled to maintain normal activity. Acetaminophen is less effective but can be considered for patients with NSAIDs contraindications (eg, CKD).

Lumbosacral Strain (LSS)	
Causes	• Strain of paraspinal muscles, tendons, intervertebral ligaments • Sudden or unbalanced muscle contraction (eg, lifting, twisting) • Risk factors: obesity, spinal deformity or degeneration, muscle weakness
Clinical features	• Pain in lumbar area; may radiate to buttocks, hips, thighs (above knee) • Paraspinal tenderness • No neurologic deficits; negative straight-leg raising test
Management	• Moderate activity • Nonsteroidal anti-inflammatory drugs • Nonbenzodiazepine muscle relaxants

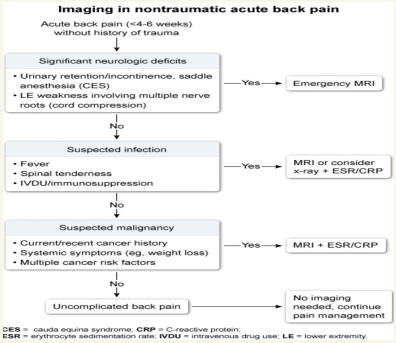
LSS is the most common cause of back pain. It can occur after lifting a heavy object, and the pain is often worse with ambulation. However, the pain and tenderness are typically in the paraspinal area without significant midline tenderness (as in vertebral compression fractures).

LSS pain is in the lumbar paravertebral muscles that does not radiate below the level of the knee. In contrast, the pain in lumbosacral radiculopathy, which is most commonly caused by a herniated intervertebral disc, classically radiates down the posterolateral leg to the foot (Sciatica). It usually follows an inciting event, and lumbar flexion makes the pain worse.

Acute Lumbosacral Radiculopathy

Causes	• Herniated intervertebral disc (most common) • Degenerative spondylosis • Malignancy • Epidural abscess
Signs &symptoms	• Pain in low back radiating down posterior leg to foot • Positive straight-leg or crossed straight-leg raising test • Dermatomal sensory loss & myotomal weakness
Evaluation	• Diagnosis based primarily on clinical features • MRI recommended for: ○ Significant/progressive or bilateral neurologic deficits ○ Evidence of bladder/bowel dysfunction, saddle anesthesia ○ Suspected malignancy or epidural abscess
Management	• Activity modification (not bed rest) • First 1-2 weeks: NSAIDs • After 2 weeks: consider physical therapy, oral glucocorticoids • After 4-6 weeks: obtain MRI & assess for surgical indication

High-risk features in back pain
Consider MRI if any of the following is present:
Cauda equina syndrome
Acute urinary retention
Saddle anesthesia
Epidural abscess/spinal infection
Fever
Immunosuppression
Intravenous drug use
Malignancy
Current/recent malignancy
Unexpected weight loss
Other
Severe/bilateral/progressive weakness
Focal spine tenderness
Coagulopathy
Age >50



Lumbosacral radiculopathy (LSR) is due to nerve root compression, most commonly by a herniated disc. The diagnosis is based primarily on clinical findings; neuroimaging (eg, MRI) is not recommended unless there are high-risk features. The prognosis in uncomplicated cases is good, and symptoms are typically self-limiting.

Lumbar spinal stenosis (SS) is a common cause of back pain in patients age >60. SS is caused by narrowing of the spinal canal, leading to compression of one or more spinal roots. It is primarily seen in degenerative arthritis with osteophyte formation affecting the facet joints (spondylosis). However, other factors may contribute, including hypertrophy of the ligamentum flavum, bulging of the intervertebral discs, and spondylolisthesis (displacement of one vertebral body relative to another).
The symptoms of SS are posture-dependent. Extension of the lumbar spine (eg, standing, walking upright) further narrows the spinal canal and worsens the symptoms, whereas lumbar flexion (eg, walking uphill, leaning on a cane) relieves the pain.
The diagnosis of SS can be confirmed on MRI of the spine. Most patients are treated conservatively with physical therapy & exercise. Surgical intervention may be required.

	Neurogenic claudication (pseudoclaudication)	**Vascular claudication**
Symptoms	• Posture-dependent pain • Lumbar extension worsens pain (eg, walking downhill) • Lumbar flexion relieves pain (eg, walking while bent forward) • Lower extremity numbness & tingling • Lower extremity weakness • Low back pain	• Exertionally dependent pain • Pain relieved with rest but not with bending forward while walking • Lower extremity cramping/tightness • No significant lower extremity weakness • Possible buttock, thigh, calf, or foot pain
Examination	• Normal pulses • Frequently normal examination	• Decreased pulses • Cool extremities • Decreased hair growth • Pallor with leg elevation
Diagnosis	• MRI of the spine	• Ankle-brachial index

The onset of pain with walking is referred to as "neurogenic claudication" which is postural (vs exertional in vascular claudication), relieved by walking while leaning forward ("shopping cart sign"), and exercise with the spine flexed (eg, cycling) does not incite symptoms.





Step 2

& Relevant Clinical Step 1